ALKYLATION

OF

4- AND 5-SUBSTITUTED BENZIMIDAZOLES

A report submitted in part fulfillment of the requirements for the degree of

MASTER OF SCIENCE

by

JOHN REGINALD HOWELL

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Department of Chemistry,
School of General Studies,
Australian National University
STATEMENT

All the work described in this thesis was carried out by myself except where specific reference is made to the contribution of others.

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The factors which determine alkylation patterns for anionic 5- and 4-substituted benzimidazoles in dimethylformamide were found to be distinctly different. For the 5-substituted compounds, the direction of alkylation depends on through bond substituent effects which lead to small reactivity differences between the competing nucleophilic sites. In contrast, the alkylation preference in 4-substituted benzimidazoles is dominated by through space substituent effects and, as a result, varies greatly in magnitude and direction.

The interpretation of experimental findings was facilitated by the use of a conceptual model for the reaction transition state structures. Also the effects of certain parameters on the alkylation process were theoretically calculated.
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Introduction

Although the benzimidazole nucleus (1) seldom occurs in nature, it still plays an important role in biological systems. For instance, as the 5,6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole (2), it is an integral part of vitamin B₁₂. The significance of this function, and of the discoveries made in imidazole chemistry, has prompted considerable research on benzimidazoles with the aim of synthesising pharmacologically useful compounds. A number of benzimidazole derivatives which
have gained widespread use as pharmaceuticals, veterinary anthelmintics and fungicides are listed in a recent publication. The most successful of these have been 2-(4-thiazolyl) benzimidazole (thiabendazole) (3a) and one of its derivatives (bendazole) (3b) which have found use as anthelmintic agents.

\[
\begin{array}{c}
\text{3a } R=H, \quad 3b \quad R=\text{NHCO}_2\text{CH(CH}_3\text{)}_2 \\
\end{array}
\]

Some nonbiological fields have also benefited from benzimidazole technology. The textile industry has made extensive use of benzimidazole compounds and, to a lesser extent, so too have the photographic and rubber industries.

At present benzimidazole research is still expanding and though there are many directions in which this expansion may occur it is essential that existing work be consolidated.

Before developing the theme of this project further it might be appropriate to first consider the numbering scheme in benzimidazole derivatives. Conventionally, benzimidazole compounds are numbered so that the substituent bearing nitrogen atom, \( \text{N-R} \), is numbered 1 and the other heterocyclic nitrogen is numbered 3 - as shown in structure (1). Therefore, if the nitrogen substituent is a hydrogen, which is exchangeable between the two nitrogens, then both the numbering pattern and
the name of the compound will change depending on the tautomeric form\textsuperscript{2}. In benzimidazole itself the forms are equivalent, so no such problem arises. However, if a substituent is asymmetrically attached to one of the benzene ring carbons then the tautomeric structures are different, for example the substitution at C\textsuperscript{4}(C\textsuperscript{7}) shown in Figure 1. In such a situation the position numbering differs between the tautomers so that the same atom may have a different positional value in each tautomer. As the name of the compound depends on the position of the substituent it also differs. In order to facilitate the comparison of tautomers and of their derivatives, the numbering scheme in this thesis has been simplified.

In contrast to traditional numbering procedures, the reference position in this study has been the benzene ring substituent rather than the substituent bearing nitrogen, >N-R. The benzene substituent is not in position 1 but is described by the lowest number possible in counting from one nitrogen
directly through the other. Thus, in Figure 1 the two tautomers would be named as $N^1$-H and $N^3$-H tautomers of a 4-substituted-benzimidazole system.

If the nitrogen substituent, $\geq N\text{-}R$, is a less mobile group than hydrogen then two distinct, isomeric compounds are possible. The revised numbering system also applies to and is exemplified in this study by these compounds (Figure 2).

One of the most common methods for producing new benzimidazoles for pharmacological screening is the substitution of the nitrogen born hydrogen, $\geq N\text{-}H$, by fixed groups. This often takes the form of an alkylation reaction. If the benzimidazole is asymmetrically substituted in the benzene ring then the two nitrogen atoms will be distinguishable and two products may form upon alkylation. In the present study all of the benzimidazoles are substituted in this manner and the
affect that this has on the alkylation will be of special interest.

For the unionised benzimidazoles alkylation has been found to occur on the pyridine-like nitrogen. If both tautomers are present then the two possible isomeric products will be produced. The proportions of these will depend directly on the relative reactivity of the two pyridine nitrogen sites, the tautomeric ratio and the rate constant for tautomeric interconversion.

If the reacting system is the conjugate base of the benzimidazole, i.e. the benzimidazole anion, then tautomeric considerations are irrelevant. The proportions of the isomeric products are then dependent, only, on the reactivity of the related nitrogen atoms. This project concentrates on the alkylation of benzimidazole anions which are more reactive than, and whose alkylation patterns are more amenable to interpretation than the corresponding protonated forms.

Because benzimidazole anions have two positions at which N-alkylation may occur, such anions are termed ambident nucleophiles and, as such, should be subject to the rules that govern these types of compounds. These rules have been derived from observations of many distinct ambident nucleophilic systems and in general have proved widely applicable. The rules constitute the theory behind ambident nucleophilic reactivity which identifies and attempts to explain the factors which affect the preference for alkylation sites. This explanation has often been facilitated by the borrowing and adapting of new methods developed for visualising reactions. Some of these new concepts have been employed in this study and
will be discussed in the first chapter. Also presented in that section will be some recently developed concepts which have not yet had any significant application to ambident nucleophilic systems.

Although ambident nucleophilic theory should encompass the alkylation of benzimidazoles, the theory may be difficult to apply. This is due to the basic differences between the benzimidazoles and the ambident nucleophilic systems upon which the theory is largely based. In the former, the alkylation sites are both nitrogen atoms and hence only differentiated by their individual relationships with the rest of the molecule. In the asymmetric benzimidazole molecule it is the substituent that causes this distinction between the two nitrogen atoms. The electronic and steric characteristics of the substituent may affect the two nitrogen atoms differently and hence change their relative susceptibility to alkylation. These differences may not be very large, particularly if the substituent is remote from the nucleophilic centre.

On the other hand, current ambident nucleophilic theory was generally derived from models whose reaction sites were composed of different types of atoms. In particular a great proportion of this work was drawn from enolate compounds where carbon and oxygen alkylation are in competition. In such systems the electronic and steric differences between alkylation centres are very marked and so conclusions reached may not be readily applicable to the benzimidazoles.

Hence it is more appropriate to utilize the theory as modified by application to benzimidazole related systems. The extensive work on the alkylation of various heterocycles
by H. Tieckelmann\textsuperscript{9} and L.W. Deady\textsuperscript{10} is very useful in this context. A still further refinement is the study on the ambident nucleophilic character of cinnolines (4) and indazoles (5) by M.H. Palmer\textsuperscript{11}. Although this work is not as comprehensive as that of Tieckelman and Deady the subject compounds are benzo-derivatives of heterocycles with nitrogen atoms as both alkylation sites, and so are more closely related to benzimidazoles.

However, even the last examples are not good representations of the benzimidazole nucleus. In the latter the nitrogen atoms are separated from one another as well as being positioned symmetrically in the molecule. Thus if the differentiating substituent is remote there should be little difference in alkylation preference for either site. Consequently an alteration in reactants or conditions should produce only a small change in the alkylation pattern. If discernible, the changes may indicate subtle influences on ambident nucleophile activity which are not apparent in conventional systems. This insensitivity may especially be the case if the results are compared with those of benzimidazoles.
where the same substituent is in a less remote position.

Adenine (Figure 3) is structurally related to benzimidazoles and so would be expected to undergo alkylation in a similar manner. Recently, work has been done on the alkylation of the anions of adenine\(^1\) and its N\(^6\)-acyl derivatives\(^2\) as well as on unionised adenine\(^3\) itself. The investigations made extensive use of the Loose/Tight Transition State Theory\(^4\) to interpret the results. The conclusions reached were that steric as opposed to electronic factors are decisive in directing the alkylation pattern away from the N7 position. It is expected that additional information will be obtained from the benzimidazole system as it is not complicated by the presence of pyrimidine nitrogens and is more versatile with respect to type and position of substituents.

Although a large number of alkylations on substituted benzimidazoles have been reported\(^5,6,7,8,9\), there has been very little collation and interpretation of the results. This is, in part, due to the great diversity of the reactants, reaction conditions, methods of analysis and results that
constitute the published material. Also doubt has arisen as to the validity of the results and the nature of some of the reactions studied.

The majority of the work done has been on the alkylation of 5-substituted benzimidazoles. Recent reports\textsuperscript{3,19,20} have concluded that for C\textsubscript{5} substituents there is little difference in preference for either site. These deductions were based on observed or estimated tautomeric ratios for the neutral benzimidazoles and, in the case of 5-nitrobenzimidazole, also on alkylations performed using a range of experimental conditions. In the case of 5-nitrobenzimidazole the N\textsubscript{1} site was slightly more reactive and for 5-methoxybenzimidazole the N\textsubscript{3} site was favoured. Work\textsuperscript{11d} on the related system of indazole has also revealed the minimal affect of isolated (though conjugated) substituents in influencing alkylation ratios.

In the case of the 4-substituted benzimidazoles very few alkylations\textsuperscript{21,22} have been performed. The research that has been done indicates that steric interactions at the N\textsubscript{3} site result in very little, if any, alkylation at this position. Hence N\textsubscript{1} alkylation predominaates. In contrast, estimates of the tautomer ratios for benzimidazoles with NO\textsubscript{2},\textsuperscript{3} I, Br, Cl and F\textsuperscript{23} as 4-substituents point to N\textsubscript{3} as being the favoured protonation site. This is thought to be due to hydrogen bonding and implies that the negative environment in the vicinity of N\textsubscript{3} is greater than that of N\textsubscript{1}. However this feature does not seem to be translated into greater reactivity for N\textsubscript{3} or, if it is, then the enhanced reactivity is outweighed by steric considerations.

Research in the related cinnoline\textsuperscript{11a} and indazole\textsuperscript{11d}
systems has also revealed the dominance of steric factors in determining alkylation patterns when a NO₂ group is placed adjacent to a reaction site.

The published results on the alkylation of 5- and 4-substituted benzimidazoles will be discussed in greater depth in chapters 2 and 3 respectively.

However, research into the benzimidazole field is far from complete. It is apparent from the brief observations already made here that much investigation is still required, with a definite emphasis on the interpretation and explanation of results. In this project, an attempt is made to do just that by systematically performing a series of alkylations and interpreting the results. Chapter 1 describes the approach taken which is based on that used in the previously mentioned works on alkylation in adenine and related systems. It is hoped that this procedure will again produce useful information and hence in a much wider sense the procedure may be recognized as a useful tool for chemical systems in general.
Mechanism

On deprotonation of a benzimidazole its nitrogens become more effective nucleophiles and readily undergo a substitution reaction in the presence of an alkylating agent. In dipolar aprotic solvents this substitution probably takes place by an $S_N^2$ mechanism (Figure 4) since, due to auto-ionisation difficulties, $S_N^1$ reactions are uncommon in such media.\textsuperscript{15} As the reaction is $S_N^2$ there is just one transition state (t.s.), the energy of which will help determine the reaction rate.

![Figure 4]  

In the benzimidazole anion both nitrogens compete for alkylation and, as they are similar nucleophiles and react under the same conditions, it seems reasonable to assume that they follow a similar reaction pathway.

Reaction conditions were designed to ensure that the reverse reaction could not occur, (as was subsequently found to be the case), and this prevents the thermodynamic stabilities of the products having any direct bearing on the alkylation pattern. Had the reverse reaction been established the products, due to differing thermodynamic stabilities, would
probably have reverted to the reactants at rates different from those at which they formed. The product proportions would then deviate from those obtainable from a pure forward reaction, the results of which are the main concern of this project.

All of the above points give rise to a relationship upon which interpretation of all the alkylation reactions is based. This is that the alkylation site preferences will depend on the relative energies of the corresponding transition states and will be reflected in the alkylation product ratio.

The potential energy diagram (Figure 5) displays some of the characteristics associated with the reaction. Initially the alkylation sites have the same energy since they are on the same molecule, but, as interaction with the alkylating agent progresses, they become differentiated until, in their t.s. structures, the potential energy difference is $\delta \Delta V(R)^\neq$. As shown, the t.s. of both alkylations does not
necessarily occur at the same place on the reaction co-ordinate. In a macroscopic system this potential energy difference can be translated into a free energy difference, between the t.s. species, of $\delta AG^\#$ per mole (Figure 6). The value of $\delta AG^\#$ determines the relative proportions of the two t.s. complexes and hence the product ratio of the alkylation.

It is quite probable that $\delta AV(R)^\#$ will not have the same value as the potential energy difference of the products ($AV(R)_P$) and, extrapolating further, that they could have different signs. In such a situation the potential energy plots of the two reactions must be equal at some point on the reaction co-ordinate and the crossover is shown in Figure 5. In free energy terms, $\delta AG^\#$ and the product free energy difference ($AG_P$) would also have opposite signs in this situation, which leads to the least thermodynamically stable product being formed in the greatest amount. Conversely, the most stable product would form in the smallest amount. This feature is also displayed in Figure 5 and particularly emphasizes the distinction between kinetic and thermodynamically controlled reactions. Although its presence would be very informative it need not appear at all in this series of experiments.

Experimental Factors Affecting Alkylation Site

There are a number of experimental factors capable of influencing the alkylation pattern in benzimidazoles. These factors, other than the structure of the nucleophile itself, are listed below as described by Le Noble.6

1. Solvent,
2. Counterion,
3. Additives or catalysts,
4. Concentrations,
5. Temperature,
6. Pressure,
7. Leaving group,
8. Alkalinity,

Due to time limitations it was decided to concentrate on the two parameters most likely to show appreciable and unambiguous results. The two subjects chosen for this study were the structure of the ambident nucleophile (a benzimidazole), and the structure of the alkylating agent, which would affect the relative nature of the two substitution sites and the specificity of the alkylating agent respectively. As will be related in the next section, variations in the structure of the two factors would also alter that of the reaction t.s.

Optimum conditions for the other parameters were chosen and kept constant throughout this experiment.

A systematic approach was adopted in investigating benzimidazole ambident nucleophilic character using the previously mentioned variables. Firstly, following the synthesis of a substituted benzimidazole, a series of independent alkylations was carried out and, secondly, a different benzimidazole was synthesised and alkylated with the same series of reagents. In this manner a great range of alkylation could be performed and an extensive amount of data obtained.

Interpretation of these results depended on the t.s. structure for each reaction. The following two concepts
were employed to help visualise the t.s. structures:

Early/Late and Loose/Tight Transition State Structures

There are a great number of possible t.s. structures for $S_N^2$ reactions and it would be useful to be able to classify them. One method would be to describe the activated complex in terms of bond formation and bond breakage as independent variables. However, it was found more useful to employ the concepts of early/late$^{25}$ and loose/tight$^{15}$ character to represent a transition state structure. These two concepts have seldom been used together before, despite the fact that they seem naturally to complement each other.

Although both methods of classification cover the range of possible t.s. structures, the individual variables in the latter case can each be linked to changes in the structures of the reactants. As a result, a particular combination of reactants can be more readily identified with a certain t.s. structure thus simplifying the interpretation of results. This facility has led to the early/late and loose/tight system being adopted for the present study. Both variables are incorporated in Figure 7 which is a natural development of the diagrams of More O’Ferrall$^{26}$ and Jencks$^{27}$.

The early/late quality of a t.s. structure involves a combination of both bond making and bond breaking, acting as a single variable (as does loose/tight). In fact, experimentally, it would be difficult to divorce the one effect from the other. In this case the bond formation is directly proportional to bond breakage. Therefore, a small amount of bond making between the nucleophile (N) and the
active carbon centre \( (C_\alpha) \) will be matched by an equal amount of bond breaking between \( C_\alpha \) and the leaving group \( (X) \). This is termed an early t.s. structure because, as the \( C_\alpha-X \) bond is covalent and the \( N-C_\alpha \) mainly electrostatic, the complex is similar in makeup to the reactants. The late t.s. complex, on the other hand, displays product-like characteristics with strong covalent bonding between \( N \) and \( C_\alpha \).

The early/late character will be controlled, for this series of experiments, by changing the availability of negative charge on the nitrogens. It has been suggested\(^{28}\) that a nucleophile with electron donating substituents should have an earlier t.s. than one without. Conversely an electron withdrawing substituent should make the t.s. later.

In the loose/tight classification of t.s. structures, there is an inverse relationship between bond making and bond
breaking. In a loose t.s. the reacting centres are bound by electrostatic forces since charge is localised and so this structure is reactant-like. The Cα possesses a positive charge and, if the alkylating agent contains substituents capable of generating negative charge at this atom, the loose arrangement will be favoured. The ether oxygen of benzyl chloromethyl ether has this ability and thus produces a loose t.s. structure.

In the tight t.s., the structure is similar to that of the product since charge is dispersed and the bonding is covalent. As the charge on the Cα is negative in this case, the tight t.s. will be favoured if the accessible substituents (to the Cα) of the alkylating agent are also electron withdrawing. Phenacyl chloride provides an example since its strongly electron withdrawing carbonyl group is adjacent to the Cα.

The importance of the loose/tight variable in determining the t.s. structure will depend on the position of the latter along the reaction co-ordinate (the degree of early/late character). If the t.s. is predominantly early or late its structure is already well defined and is less liable to be changed by the loose/tight variable. However, if the t.s. structure is more intermediate between early and late situations then the loose/tight variable will have much more influence.

Thus, for any variation of reactants in a benzimidazole alkylation, an estimate can be made of the resulting t.s. structure. Further, by controlling the electron donating abilities of relevant substituents in the nucleophile, and the alkylating agent, the early/late and loose/tight
characteristics of the t.s. structure, respectively, can be controlled. However, the effects of reactant manipulation are not solely restricted to one variable or the other and there may be some overlap.

Relative Transition State Stabilities

The stability of each t.s. depends both on its susceptibility to, and the magnitude of, certain factors. The degree of susceptibility depends on the t.s. structure and, as this varies, a particular factor may become more or less important in determining t.s. stability. The absolute and relative magnitudes of these influences can differ between alkylation sites and are a function of the nature and position of the benzimidazole substituent. Thus, a change in the t.s. structure may alter the reliance on a particular influencing factor and the alkylation site at which this factor is most dominant will be most affected. Therefore, the relative reactivities and t.s. stabilities of the alkylation sites may vary with the t.s. structure. In this system the influencing factors are electrostatic interactions, polarizability and proximity interactions. These three factors are not usually all used in conjunction but seem to adequately represent the alkylation selectivity process.

As the reacting species approach each other they interact with a consequent redistribution of energy. Figure 5 shows the whole process in terms of potential energy changes. This diagram considers the energy characteristics of both bond formation and bond breakage as well as of other aspects of the reaction. For the purposes of this study, the bond formation component is of most interest as it directly
involves the nucleophilic variable. Any change in the nature of the nucleophile should be most evident in the interaction energy of the developing bond. The electrostatic, polarizability and proximity factors determine the N-C$_{\alpha}$ interaction energy and an attempt to relate these to N-C$_{\alpha}$ distance is shown graphically in Figure 8*. For large N-C$_{\alpha}$ separations corresponding to early or loose reaction complex structures, the interaction energy is largely electrostatic. Consequently, the stabilisation of the reaction complex will depend on the magnitude and localisation of negative charge on the nucleophile. The electrostatic interaction energy should

* An adaption of similar plots$^{29}$ constructed to depict protonation of the three membered nitrogen heterocycle aziridine.
monotonically increase until just before the $N-C_\alpha$ covalent bond forms at which stage it may level off or even diminish. However at closer approach distances the other stabilising effects also develop. The first of these superimposed on the electrostatic interactions are those of polarization. As the reactants converge they are mutually polarized the extent of which depends on the innate polarizability of each participant. The consequent energy lowering should be less than that achieved by the electrostatic factor and, being more distance dependent than the latter, should increase more rapidly as $N$ and $C_\alpha$ closely approach each other. Like the electrostatic interaction plot, the polarizability one should level off and diminish, however, in this case, after the covalent bonding distance is reached. Note that as more considerations are involved in the polarizability factor its magnitude may be difficult to predict.

When the $N-C_\alpha$ interatomic distance is small, as in the case of a late or tight reaction structure, partial covalent bonds form between these centres. The stabilising (destabilising) forces that develop have been collectively called proximity interactions. These forces include non-bonded steric affects, $\pi$-bonding patterns, charge transfer effects among others. The proximity interactions increase rapidly for small reactant separations and usually become greater than those of electrostatic origin. Just before bonding distance is achieved the interaction curve should flatten out and then decrease. As the proximity effects involve a number of components its interaction plot may vary greatly in magnitude and shape.

Therefore it is apparent that, as the separation between $N$ and $C_\alpha$ diminishes, the three main interactions become
superimposed. The plots of these three may be sum-totalled to give the overall interaction of the complex for any N-Cα distance. Such an N-Cα Interaction Curve can be constructed for each reaction site in an ambident nucleophile. The difference between these curves would then determine the relative stabilities of the corresponding reaction complexes. As the curves should be somewhat different in shape, particularly where polarizability and proximity factors are concerned, the relative stabilities of their complexes may vary quite irregularly, both in direction and magnitude, with N-Cα distance. For large N-Cα separations, the relative stabilities should be mainly dependent on the magnitude of the negative charge associated with each nucleophilic site. At intermediate distances, electrostatic, polarizability and perhaps even proximity factors may all determine the relative complex stabilities the direction of which could be difficult to predict. Toward the other extreme, closely approaching the N-Cα covalent bond length, the relative stabilities should, in fact, reflect the thermodynamic stabilities of the products.

The relative stabilities of the reaction complexes will be translated into an alkylation ratio wherever the reaction t.s. structure corresponds to a certain N-Cα distance. In this project the t.s. structure for a particular ambident nucleophile will be varied by altering the alkylating agent used. Therefore, the trend in alkylation results obtained with a range of alkylating agents will reflect changes in the interaction energy differences between the competing isomeric reactions. Because of the irregularity of these changes, the alkylation trend would be expected to be quite rough. This effect would be enhanced if the number of alkylating agents used was limited and if these differed
markedly in steric and polar properties.

In the discussion of early/late and loose/tight t.s. character, it was indicated that these terms could be roughly used to estimate the t.s. structure for any set of reactants in a benzimidazole alkylation. A knowledge of the t.s. structure for a reaction together with the actual results from that reaction allow the mechanism that connects the two to be investigated. Specifically, the relative importance of the factors that influence alkylation site reactivities can be determined. An attempt has also been made to estimate the importance of these factors on theoretical grounds, as is outlined in the following section.

Molecular Electrostatic Potential and Protonation Energy

In conjunction with the experimentation, a number of theoretical calculations\(^{30}\) (see Appendix 1) have also been performed on the benzimidazole system. The principal calculations involved the construction of molecular electrostatic potential (M.E.P.) maps\(^{31}\) for benzimidazole anions and the estimation of protonation energies leading to the uncharged benzimidazoles. The purpose of these analyses was to obtain relative theoretical reactivities of the alkylation sites under a number of different circumstances.

The M.E.P. calculation is an estimate of the interaction energy of a point positive charge (proton), at a particular position, with the total electrostatic field generated by a molecule. This is a much more realistic approach than just the consideration of the charge on the two atoms directly concerned. If the M.E.P. values are calculated for a number of positions around the molecule, a
contour picture may be constructed. Such an M.E.P. map will have negative minima in positions where the proton would most likely be situated. For substituted benzimidazoles, a deep minima would be expected near each nitrogen and these should differ in magnitude and shape due to the asymmetric influence of the substituent. It was anticipated that the relative reactivities of the two nitrogens would reflect the minima differences if the t.s. occurs when the positive charge is at a relatively large distance from the molecule. When the positive charge is close to the molecule the minima are distorted by polarization, charge transfer and exchange effects which are not included in this calculation. Thus, the relative reactivities of the two alkylation sites should be predictable from M.E.P. theory for reactions having loose or early t.s. structures.

The fact that the calculations are performed for a theoretical gaseous reaction should not prevent them from correlating well with the corresponding experimental reaction in solution. The solvent chosen, dimethylformamide, should not interact significantly with the negatively charged nitrogens and so their relative reactivities should be estimatable from the calculated minima. Bonaccorsi, in fact, has used the M.E.P. approach to predict the preferred protonation and alkylation sites in purines and pyrimidines with remarkable accuracy.

In the situation where the t.s. is late or tight, the reacting species are close together and the M.E.P. picture is not appropriate. In these circumstances a more accurate method of predicting favoured reaction sites is through the calculation of their protonation energies. The
figures obtained in this manner in fact describe the thermodynamic stabilities of the benzimidazole tautomeric structures and hence give an idea of those of the corresponding alkyl products. However, in extrapolating to the alkyl species, consideration must be given to the effects of steric interactions on the thermodynamic stabilities.

In addition to the above calculations, other less elaborate ones were performed; e.g. Mullikan population analysis\textsuperscript{33} and determination of the coefficients of the highest occupied molecular orbital\textsuperscript{34}. These calculations were used to evaluate whether the degree of sophistication involved in the M.E.P. approach was really necessary. In fact, the positive correlation of the M.E.P. predictions with these alternate calculations was poor and they were also not found to be useful in explaining the experimental results. Consequently, excepting the calculation of total negative charge on the nucleophilic atom (q\textsubscript{tot.}), they have not been utilized further in this study. The q\textsubscript{tot.} calculations were performed because they are conventionally used to predict the direction of an electrostatically controlled reaction.

Thus the assessment of a reaction in terms of early/late and loose/tight character can be translated into an estimate of the relative nucleophilicities of the reaction sites. If the predictions of product preference then agree with the experimental results, the theoretical methods used in visualising the reaction will be shown to be appropriate.

The actual application of the concepts and molecular orbital calculations described in this chapter to interpret the results of this project are described in the following chapters.
The 5-substituted benzimidazoles (6) were alkylated first because they constitute a simpler ambident nucleophilic system than do the 4-substituted compounds. In the latter case the substituent is adjacent to one of the alkylation sites and so direct, as well as through bond, interactions may occur between the two. For the 5-substituted benzimidazoles the effects of the relatively remote substituent should be mainly through bond and so the alkylation results should be easier to interpret. If this is achieved the information obtained may then be extended to the 4-substituted benzimidazole system to help explain its alkylation pattern.

In examining the alkylation processes in 5-substituted benzimidazoles a fairly large body of literature can be drawn upon. However, this material is diverse in nature and only in recent years has any systematic study been performed.

As well as the actual alkylation results, measurements of benzimidazole tautomeric ratios are also of interest. Except for differences in the size of the N-substituent, the
tautomers are good structural models of the corresponding alkyl isomers. However, since steric interactions between the nitrogen substituent and that of the benzene ring should be minimised in 5-substituted benzimidazoles, the tautomeric ratio should correlate well with the relative thermodynamic stabilities of the related N-alkyl compounds. Consequently, in an alkylation reaction where the t.s. structure is tight or late, the tautomeric ratio of the parent material should be a good indication of the preferred site of attack.

In 1960 Ridd and co-workers published the results of an investigation on the mechanisms of N-substitution in imidazole and benzimidazole derivatives. One aspect of the work involved the determination of the pK\textsubscript{A} values for the N\textsuperscript{1} and N\textsuperscript{3}-methyl isomers of 5-nitrobenzimidazole, 2-methyl-5-nitrobenzimidazole, 5-chlorobenzimidazole and 5-chloro-2-methylbenzimidazole. These measurements of basicity were subsequently used to estimate the tautomeric ratio for the corresponding N-unalkylated compounds. The N\textsuperscript{1} to N\textsuperscript{3} tautomeric ratios were found to differ very little from unity and for the compounds listed above were 1.85, 0.90, 1.00 and 1.00 respectively. Ridd also concluded, from the alkylation of imidazole, that the relative nucleophilic reactivities of the two nitrogens were in the same direction as the basicities but of reduced magnitude. This conclusion together with the values determined for tautomeric ratios (relative basicities), indicate that for 5-substituted benzimidazoles, there should be very little differentiation of the nucleophilic sites towards alkylation. In conjunction with the measurements of basicity some alkylations were, in fact, performed to test this proposition. Both the ionised and unionised benzimidazoles
were separately reacted with methyl sulphate as the alkylating agent. In the unionised experiment 5-nitrobenzimidazole, 2-methyl-5-nitrobenzimidazole and 5-bromobenzimidazole were each alkylated using a slight excess of the methyl sulphate as solvent. The \( \text{N}^1 \) compound was found to constitute 55\%, ca 50\% and 60-70\% respectively of the total N-alkyl product. 5-Nitrobenzimidazole and 2-methyl-5-nitrobenzimidazole were also deprotonated and alkylated in water to give effectively the same results again. Thus, the alkylation pattern is largely consistent with the estimates of nucleophilicity and indicates that the nitrogen atoms are very nearly equal in this regard. Ridd suggests that this equivalence is probably due to the \( \text{C}^2 \) bridge which gives the nitrogens similar conjugative accessibility to the substituent.

A number of other research groups, in studying \( \text{pK}_A \) values, have also obtained information on tautomeric ratios. Rabiger and Joullié have attempted to correlate Hammett sigma values with the \( \text{pK}_A \) measurements for 5-(F-,Cl-,Br-,I-)benzimidazoles. Their inability to do so was presumed to result from a marked variation of tautomeric ratios from compound to compound. Such a conclusion, if correct, suggests that the two imidazole nitrogens may be well differentiated.

Recently, however, in a more thorough investigation, such relationships were in fact established for the 5-(H-,CH\(_3\)-,F-,Cl-,Br-,CF\(_3\)-,NO\(_2\)-)benzimidazole series. From the excellent correlations the authors deduced that the tautomers are nearly equivalent in thermodynamic stability. In a similar study, another group of workers also reached the same conclusions. In addition, the same
Researchers have examined the relationship between Hammett para and meta sigma constants and the rate of 2-chloro substitution in 2-chloro-5-(H-,CH$_3$-,CH$_3$O-,Cl-,NO$_2$-)benzimidazoles. The good correlation achieved was also considered to be an indication of equality in the tautomeric populations.

Thus, it seems obvious that in 5-substituted benzimidazoles very little differentiation between the two nitrogens occurs. This is in agreement with similarly substituted cinnolines (4) and indazoles (5) for which it was suggested that a substituent remotely positioned in the benzene ring should have a minor electronic affect on the nucleophilic sites.

A. Alkylation of 5-Nitrobenzimidazole Anion

The most extensive study specifically on the alkylation of 5-nitrobenzimidazoles (7) has been that carried out by Reddy and Rao. Not only have these authors performed their own series of experiments but they have also compiled the results of previous publications on the subject. The tabulation of the latter, for the reactions of both ionised and unionised 5-nitrobenzimidazoles, reveals such a diverse alkylation pattern as to be uninterpretable. The experiments
undertaken by the authors were aimed at clarifying the situation. To this end 2-(H,CH₃,C₆H₅)-5-nitrobenzimidazoles were alkylated under two different sets of conditions. In the first set, methyl iodide was the alkylating agent and the reaction was carried out in refluxing acetone with potassium carbonate present. In the second series of experiments, a slight excess of benzyl chloride, the alkylating agent, was used as solvent. Also sodium acetate and iodine were present and the reactions performed at 170-180°C. In nearly all the reactions the N¹ product was slightly preferred. However, because the exact natures of these reactions are in doubt, the specific results are not very useful. Ostensibly the reactions in acetone involved the unionised benzimidazole but the presence of potassium carbonate, in all probability, has produced some deprotonation. As the benzimidazole anion reacts many times faster than the parent compound, a substantial proportion of the product could have been derived in the former manner.

In the benzylation reactions deprotonation should not be a problem. However, the temperature is such that a reverse reaction should occur. The presence of dialkylated material supports this hypothesis. In such a situation the results would tend to rely to a certain extent on the thermodynamic stabilities of the products.

Therefore, the reactions of Reddy and Rao can only be used to make a general comment to the effect that the two alkylation sites have similar reactivities.

Recently some alkylation results have been reported on 5-nitrobenzimidazole and its anion under unambiguous conditions. However, the reports only stated, in
each case, that the two products were formed in roughly equal proportions.

Therefore, previous studies in this field strongly indicate that the imidazole nitrogens have comparable reactivities but the alkylation preference cannot be refined any further with certainty.

Alkylation Results. Variation of Alkylation Agent

In Table 1 are displayed the results of reacting the 5-nitrobenzimidazole anion with various alkylation agents. The procedure followed was to dissolve the benzimidazole in N,N-dimethylformamide (DMF) and then deprotonate by the addition of a 5% excess of sodium hydride. After stirring for 1 hour a 95% stoichiometric amount of alkylation agent was added and the solution stirred at 30°C for 18 hours before analysis.

The results indicate that there is, in fact, little difference in the nucleophilic strength of the imidazole nitrogens and that the N1 alkylation is slightly preferred. However, surprisingly, the magnitude of this preference does not vary with the alkylation agent used. Although it is difficult to detect such changes when the nitrogens are almost equivalent, it still seems fairly certain the N1 alkylation is preferred in each alkylation. In reacting with the nucleophile, the alkylation agents should provide a gradation in t.s. structure from relatively loose (chloromethyl methyl ether) through to fairly tight (phenacyl chloride). As the factors controlling the alkylation preference change with these t.s. structures, it is not expected that the preference should remain relatively constant. One explanation
Table 1
Reaction of 5-Nitrobenzimidazole Anion
with Various Alkylating Agents

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>P.m.r. A Signal</th>
<th>N¹ Alkylation B (%)</th>
<th>N³ Alkylation B (%)</th>
<th>N¹:N³ Ratio</th>
<th>δΔG# C (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂H₅CH₂Cl</td>
<td>CH₂</td>
<td>54.0±3</td>
<td>46.0</td>
<td>1.17</td>
<td>0.10</td>
</tr>
<tr>
<td>C₆H₅CH₂Cl</td>
<td>CH₂ D</td>
<td>55.0±3</td>
<td>45.0</td>
<td>1.22</td>
<td>0.12</td>
</tr>
<tr>
<td>C₆H₅COCH₂Cl</td>
<td>CH₂</td>
<td>55.0±3</td>
<td>45.0</td>
<td>1.2</td>
<td>0.12</td>
</tr>
</tbody>
</table>

A. Proton magnetic resonance signal used to analyse the proportion of each product.

B. % component of the total N¹- and N³-alkyl products. Values rounded off to the nearest 0.5%. Errors derived as shown in the experimental section.

C. Difference, per mole, in the activation free energies of the N¹ and N³ alkylation processes. Calculated using the equation

\[
N¹:N³ \text{ ratio} = e^{-\frac{\delta\Delta G^\#}{RT}}
\]

D. The C²H indicated a 56.0±4% preference for N¹.

for the invariance is that the t.s. structure is too early or too late for alterations in the loose/tight character to have an effect. However, the alkylation results of other benzimidazoles suggest that this is not the case. For instance, the alkylation pattern of 4-nitrobenzimidazole, whose early/late t.s. behaviour should be comparable with that of 5-nitrobenzimidazole, is greatly dependent on the nature of the alkylating agent. Consequently, the t.s.
structure of 5-nitrobenzimidazole, as well as that of 4-nitrobenzimidazole, is estimated to be intermediate between early and late.

To obtain a more satisfactory explanation it is necessary to dissect out the contributions made by each selectivity factor in specific reactions. As mentioned in chapter 1, these factors are electrostatic effects, polarizability and proximity effects. The electrostatic preference dominates loose t.s. structures and, as the latter tightens, first polarizability and then proximity preferences become superimposed upon the electrostatic one. For a very tight t.s. structure, the combined alkylation preference of the three, in fact, reflect the relative thermodynamic stabilities of the corresponding alkylation products.

In the reaction with chloromethyl methyl ether the resulting loose t.s. should engender electrostatic control. Thus, the preference for N^1 alkylation indicates that this nitrogen has the greater electron density but not by far.

The reaction of the benzimidazole anion with benzyl chloride should display a markedly tighter t.s. structure the stabilisation of which would probably be aided by polarization. As indicated in the first chapter, the magnitude of the polarization interaction should be inferior to that of the electrostatic one. Consequently, in this simple ambident nucleophilic system, the alkylation preferences of the polarizability factor would also be expected to be less than the electrostatic preferences. Therefore, for this reaction the alkylation preference should mainly reflect electrostatic differences, particularly if the polarization interactions have not fully developed at this stage. It
should be noted that the direction of the polarizability preference is as yet uncertain.

The polarizability factor and possibly the proximity one should also be involved in the tight t.s. structure corresponding to the phenacyl chloride reaction. If both are fully developed the alkylation preference in this situation would mirror the relative thermodynamic stabilities of the alkyl products. If such were the case, then the proximity interactions should be quite large and the alkylation ratio would be expected to differ from the values obtained in the previous reactions. As this did not occur, the implication is that proximity effects are only partly established in the phenacylation reaction and so electrostatic interactions still determine the alkylation pattern.

In order to check the above conclusion an attempt was made to experimentally determine the relative product thermodynamic stabilities. To gain this measure the two products of 5-nitrobenzimidazole benzylation (chosen for convenience) were separated and dissolved in DMF containing a 10% excess of benzyl chloride. The solutions were then heated at 120°C with the object of forming some dibenzylated material. On formation this should readily decompose to form the monobenzyl products and thereby establish a reversible pathway between these products. The proportion of each monobenzylated compound present when an equilibrium was reached could then provide a measure of their relative thermodynamic stabilities.

The two reactions were performed starting from each product, to improve accuracy and to ensure that equilibrium was achieved. Samples from both solutions were analysed.
periodically until well after both product ratios were coincident (21 days). The results (Table 2) indicate that the N<sup>1</sup> product is again favoured and to a greater degree than was previously the case.

### Table 2

**Benzylation of 5-Nitrobenzimidazole, N<sup>1</sup>-Benzy1-5-nitrobenzimidazole and N<sup>3</sup>-Benzy1-5-nitrobenzimidazole**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>P.m.r. Signal</th>
<th>N&lt;sup&gt;1&lt;/sup&gt; Alkylation (%)</th>
<th>N&lt;sup&gt;3&lt;/sup&gt; Alkylation (%)</th>
<th>N&lt;sup&gt;1&lt;/sup&gt;:N&lt;sup&gt;3&lt;/sup&gt; Ratio</th>
<th>ΔG (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-nitrobenzimidazole</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>42.5±3</td>
<td>57.5</td>
<td>1:1.35</td>
<td>A</td>
</tr>
<tr>
<td>N&lt;sup&gt;1&lt;/sup&gt;-benzy1-5-nitrobenzimidazole</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>61.5±4&lt;sup&gt;B,C&lt;/sup&gt;</td>
<td>38.5</td>
<td>1.60</td>
<td>0.29&lt;sup&gt;D&lt;/sup&gt;</td>
</tr>
<tr>
<td>N&lt;sup&gt;3&lt;/sup&gt;-benzy1-5-nitrobenzimidazole</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>63.0±3&lt;sup&gt;B,C&lt;/sup&gt;</td>
<td>37.0</td>
<td>1.70</td>
<td>0.32&lt;sup&gt;D&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>62.0±4&lt;sup&gt;-4&lt;/sup&gt;-5</td>
<td>38.0</td>
<td>1.63</td>
<td>0.30</td>
</tr>
</tbody>
</table>

A. The free energy difference has no relevance to any specific chemical property.

B. The % value is calculated for 30°C as converted from 120°C using the equation

\[
N^1:N^3 \text{ ratio} = e^{-\left(\frac{\Delta G}{RT}\right)}
\]

C. 20% of total material was dialkyl product.

D. Free energy difference between the two benzyl products.

This result seems to suggest that the thermodynamic involvement in the anion reaction may not be great and, consequently, neither will be that of the proximity factor. It also indicates that the proximity interactions favour alkylation...
at the N₁ site.

Therefore, electrostatic and proximity factors favour N₁ alkylation and the direction of the polarizability preference is uncertain. As the reaction t.s. structure tightens, and each of these factors comes into play, the alkylation ratio would be expected to change. That this change does not occur is probably due to the weakness of the polarizability preferences as well as an inability to fully develop the proximity ones. This allows the electrostatic interactions to dominate the alkylation preferences for the present reactions. These interactions, themselves, should alter with t.s. structure but the change is less marked and may be obscured by the errors associated with the alkylation results.

In addition to the dialkylation reaction a number of other experiments were undertaken to further elucidate the 5-nitrobenzimidazole alkylation process. One of these involved the benzylation of 5-nitrobenzimidazole in its unionised form. The experiment followed the standard alkylation procedure except that no base was used and the reaction time was extended to 168 hours. Alkylation of the unionised compound occurs at the pyridine-like nitrogen and the product proportions depend on both the relative reactivities of these atoms and their relative availabilities as determined by the tautomer ratio. The results of this reaction (Table 2) show the first preference for N₁ alkylation and indicate that the tautomeric ratio primarily determines

* The rate of tautomeric interconversion need not be considered as it should be very much faster than the rate of reaction.
the alkylation pattern. As the tautomeric ratio reflects the thermostabilities of the corresponding N-alkyl compounds the N₁ tautomer should be favoured. Consequently, the associated N³ pyridine-like atom will be more available for reaction. However, the N₁ pyridine-like atom, though less prevalent, should be more reactive than the N³ equivalent. The preference for N³ alkylation in the result shows that the tautomeric factor outweighs the opposing reactivity one. Ridd³ has obtained similar results for the alkylation of 4-substitutedimidazoles and concluded that basicity differences are greater than nucleophilicity differences though in the same direction. However, the result of Ridd's³ alkylation of unionised 5-nitrobenzimidazole disagrees with that obtained in the present work. He found that the N₁ product was present in a slightly greater amount and this preference increased for the reaction of the anionic compound. These results are strangely at variance with his conclusions on basicity and nucleophilicity.

Thus, for the unionised 5-nitrobenzimidazole alkylation, the interpretation of the alkylation pattern indicates that the N₁ tautomer is favoured and, consequently, that the N₁-alkyl compound is the most thermodynamically stable.

Alkylation Results. Variation of Solvent

Another experimental condition that was varied for the alkylation of 5-nitrobenzimidazole anion was the choice of solvent. A series of benzylation were performed following the standard alkylation procedure except that different solvents were used in place of DMF. The effect of such
changes should be manifested in the nature and magnitude of the solvation experienced by the reactants, products and t.s. complex. An increase in the solvation of the reactants will tend to diminish their resemblance to the t.s. complex and hence make the complex later in character. Conversely, a decrease in reactant solvation should make the t.s. structure earlier. For the products an increase (decrease) in solvation should result in a decrease (increase) in the late character of the t.s. complex. The affect of solvation on the t.s. species will depend on its precise nature but may result in a loosening or tightening of its structure. Therefore a change of solvent can alter the mode of reaction quite significantly. The results (Table 3) again display a fine

### Table 3

**Benzylation of 5-Nitrobenzimidazole Anion**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>P.m.r. Signal</th>
<th>(N^1) Alkylation (%)</th>
<th>(N^3) Alkylation (%)</th>
<th>(N^1:N^3) Ratio</th>
<th>(\Delta G^\ddagger) (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>(CH_2)</td>
<td>55.0±3</td>
<td>45.0</td>
<td>1.22</td>
<td>0.12</td>
</tr>
<tr>
<td>Hexamethylphosphor-triamide (HMPA)</td>
<td>(CH_2)</td>
<td>56.0±3</td>
<td>44.0</td>
<td>1.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Acetonitrile(^A)</td>
<td>(CH_2)</td>
<td>56.0±3</td>
<td>44.0</td>
<td>1.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Ethanol</td>
<td>(CH_2)</td>
<td>54.0±3</td>
<td>41.0</td>
<td>1.44</td>
<td>0.22</td>
</tr>
<tr>
<td>Methanol</td>
<td>(CH_2)</td>
<td>55.5±3</td>
<td>44.5</td>
<td>1.25</td>
<td>0.13</td>
</tr>
<tr>
<td>Formamide</td>
<td>(CH_2)</td>
<td>43.5±3</td>
<td>56.5</td>
<td>1:1.33</td>
<td>-0.17</td>
</tr>
</tbody>
</table>

A. The sodium salt was not completely soluble.

disregard for the experimental conditions. The only exception is the alkylation pattern obtained in formamide and this is
explained later in terms of "selective solvation". Therefore, these results are a further indication of the insensitivity of the alkylation preference to certain t.s. structural changes. Again the dominance of such t.s. complexes by electrostatic interactions could explain this invariance.

A similar series of reactions on the 2-benzyl-5-nitrobenzimidazole anion has been reported in the literature. The alkylating agent was 1-chloro-3-diethylaminoethane and a number of different solvents were used. The alkylation ratios (Table 4) in this work vary markedly and so are inconsistent with the results obtained in the present work. The most divergent results were obtained in the non-polar solvents.

Table 4

Alkylation of 2-Benzyl-5-nitrobenzimidazole Anion in Various Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature °C</th>
<th>N^1 Alkylation (%)</th>
<th>N^3 Alkylation (%)</th>
<th>N^1:N^3 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol/water</td>
<td>60</td>
<td>50</td>
<td>50</td>
<td>1.00</td>
</tr>
<tr>
<td>Ethanol</td>
<td>60</td>
<td>50</td>
<td>50</td>
<td>1.00</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>25</td>
<td>19</td>
<td>81</td>
<td>1:4.26</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>60</td>
<td>25</td>
<td>75</td>
<td>1:3.00</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>100</td>
<td>26</td>
<td>74</td>
<td>1:2.85</td>
</tr>
<tr>
<td>Carbontetrachloride</td>
<td>60</td>
<td>65</td>
<td>35</td>
<td>1.86</td>
</tr>
<tr>
<td>Benzene</td>
<td>60</td>
<td>51</td>
<td>49</td>
<td>1.04</td>
</tr>
</tbody>
</table>


The article indirectly indicated that in the dioxan reaction the benzimidazole salt was insoluble and this could also be
the case for the other nonpolar solvents. The presence of this feature could possibly be an explanation for the unexpected results in these solvents. The affect of heterogeneous conditions on alkylation patterns is uncertain but in some cases it has been reported to cause a complete inversion of results. Some work in this project showed, in fact, that the 5-nitrobenzimidazole salt was insoluble in dioxan which led to very small yields on alkylation and a marked preference for the N\(^3\) product. Therefore, the doubtful homogeneity in this literature work prevents it from being seriously compared with the present study.

The only irregular result in the present solvent study was that produced by the reaction in formamide where the alkylation preference was reversed. This affect may be explained in terms of "selective solvation".\(^{39}\) Formamide, being a good hydrogen bonding solvent, readily solvates the nucleophilic sites and does so preferentially. The favoured sites are those with the highest charge and also the ones which form the most stable N substituted products. The latter factor is important because a nucleophilic site which partially accepts a hydrogen becomes structurally similar to the N substituted compound. As N\(^1\) satisfies both requirements it is preferentially solvated. During the alkylation process the concomitant displacement of solvating molecules will be most difficult from the preferentially solvated site and will result in a higher t.s. energy for that site. Therefore, in this case, the N\(^1\) alkylation will be less energetically favoured and the N\(^3\) product should predominate.

Recently a study\(^{12}\) of solvent influence on alkylation patterns has been carried out on the adenine (8) anion.
The anion was reacted with a number of different alkylating agents in hexamethylphosphortriamide, dimethylsulphoxide, DMF, ethanol, methanol and formamide. It was found that in formamide the results were markedly different from those in the other solvents. In agreement with the present work formamide caused an increase in the alkylation at the least negatively charged sites. Similar results were also obtained by Tieckelmann\textsuperscript{9c} when he alkylated the anion of 2-methyl-4-hydroxypyrimidine (9) in DMF, methanol and formamide as well as other solvents.

Thus, the effect of preferential solvation may be important where solvent variation is involved. However, in this project DMF was nearly always used and it is a solvent which should minimise preferential solvation. Therefore electrostatic, polarizability and proximity factors will generally dictate the alkylation pattern.

**Theoretical Calculations**

One of the aims of this thesis was to determine the importance and mode of operation of the factors controlling
alkylation preference. To a certain extent this can be achieved through the analysis of experimental results but the process may be facilitated by appropriate theoretical calculations. To this end molecular electrostatic potential (M.E.P.) maps were prepared and protonation energies (P.E.) calculated for the imidazole nitrogens in the 4- and 5-(nitro-, cyano-, amino-)benzimidazole anions.

In a loose or early t.s. it was considered that the M.E.P. would be a good guide for predicting the preferred alkylation site. The M.E.P. map for 5-nitrobenzimidazole is shown in Figure 9 and is constructed in the molecular plane as the absolute M.E.P. values are maximised therein. The greatest (absolute) minima are associated with the imidazole nitrogens with less important ones around the nitro oxygens. The values of the nitrogen minima (Table 5) are in fact equivalent within the accuracy of the calculation. Thus M.E.P. predicts that the nitrogen reactivities are the same for an electrostatically controlled reaction. The preference actually displayed in the experimental results is thus probably too small for the method to discern.

<table>
<thead>
<tr>
<th>Nucleophilic Atom</th>
<th>M.E.P. Minima (kcal/mole)</th>
<th>$q_{tot.}$</th>
<th>P.E. (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N^3$</td>
<td>-205.5</td>
<td>-7.3750</td>
<td>-417.75</td>
</tr>
<tr>
<td>$N^1$</td>
<td>-205.4</td>
<td>-7.3794</td>
<td>-418.22</td>
</tr>
</tbody>
</table>
Figure 9

As described in the text, reaction of the nucleophile sites were only slightly differentiated. In the 5-alkylbenzimidazole reaction, a consequence, it was decided to greatly change the nature of the 5-substituent when pursuing the study of these compounds. The anilino group,

(Contours every 10 kcal)
For reactions controlled by electrostatic factors, the relative charge densities on the nucleophilic atoms are conventionally used to predict the direction of alkylation. The $q_{\text{tot.}}$ values should be reasonable substitutes for these densities if the nucleophilic centres are the same type of atom. The calculations of $q_{\text{tot.}}$ indicate the $N^1$ atom should be alkylated as it has a greater negative charge. Thus, for this system, the values of $q_{\text{tot.}}$ are in agreement with the alkylation preferences.

As previously discussed, the relative protonation energies of the nucleophilic nitrogens may be employed to estimate the relative thermodynamic stabilities of the corresponding N-alkyl compounds. Therefore P.E. values should be most applicable in examining reactions with tight or late t.s. structures. In the case of 5-nitrobenzimidazole the P.E. calculated for each site is effectively equal. However, indirect measurements of tautomeric proportions, and direct ones of the corresponding N-alkyl thermodynamic stabilities, indicate that the $N^1$ site is favoured. Thus for this system, all three calculations indicate the near equivalence of the nucleophilic sites and $q_{\text{tot.}}$, even predicts the slight preference found for $N^1$.

B. Alkylation of 5-Methoxybenzimidazole Anion

As described in the last section the nucleophilic sites were only slightly differentiated in the alkylation of the 5-nitrobenzimidazole anion. As a consequence, it was decided to greatly change the nature of the 5-substituent when pursuing the study of these compounds. The methoxy group,
as a π-electron donor, was considered to be an appropriate replacement for the π-electron withdrawing nitro moiety.

In contrast to 5-nitrobenzimidazole very little work has been published on the alkylation pattern in 5-methoxybenzimidazole (10). The only report of relevance involves the determination of the tautomeric ratio in 2-chloro-5-methoxybenzimidazole. The ratio was measured by low temperature (−93°C) p.m.r. using tetrahydrofuran as solvent. The low temperature was required to fix the N\(^1\) and N\(^3\) tautomeric forms, the proportions of which could then be measured directly. On extrapolation of these values to 30°C, there were found to be present 41 and 59% of the N\(^1\) and N\(^3\) tautomers respectively. As the presence or absence of the C\(^2\) chlorine should not appreciably alter these figures, it appears again that there is little differentiation between the nucleophilic nitrogens. However, in this case, the preference of alkylation site may be reversed with respect to that of the 5-nitrobenzimidazole.
Alkylation of 5-Methoxybenzimidazole Anion

The anion of 5-methoxybenzimidazole was reacted in the same manner and with the same alkylating agents as was that of 5-nitrobenzimidazole. The results obtained (Table 6) show that the $N^3$ alkylation is favoured as was anticipated.

Table 6

<table>
<thead>
<tr>
<th>Alkylation Agent</th>
<th>Solvent</th>
<th>P.m.r. Signal</th>
<th>$N^1$ Alkylation (%)</th>
<th>$N^3$ Alkylation (%)</th>
<th>$N^1:N^3$ Ratio</th>
<th>$\Delta G^\ddagger$ (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{OCH}_2\text{Cl}$</td>
<td>DMF</td>
<td>$\text{CH}_3$</td>
<td>48.0±3</td>
<td>52.0</td>
<td>1:1.08</td>
<td>-0.05</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$</td>
<td>DMF</td>
<td>$\text{C}^2\text{H}$</td>
<td>46.0±2</td>
<td>54.0</td>
<td>1:1.17</td>
<td>-0.10</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$</td>
<td>DMF</td>
<td>$\text{CH}_3$</td>
<td>46.5±2</td>
<td>53.5</td>
<td>1:1.15</td>
<td>-0.08</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$</td>
<td>Formamide</td>
<td>$\text{C}^2\text{H}$</td>
<td>56.5±3</td>
<td>43.5</td>
<td>1.30</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Thus the nature of the 5-substituent determines the direction of alkylation but the changes made are quite small in magnitude.

The alkylation results are seen to be insensitive to the alkylating agents used and hence to the loose/tight t.s. character. Such was also the case in the reactions of the 5-nitrobenzimidazole anion and the explanation used then may also apply to the methoxy compound. It was suggested that the alkylation ratios of the sample reactions were largely determined by electrostatic preferences because polarizability preferences were too weak and those of the proximity factor were encountered only when partially developed. The thermodynamic equilibrium between the benzyl products of 5-nitrobenzimidazole was then used to estimate the alkylation
preference for an extremely tight reaction t.s. structure. The enhanced preference for the \( N^1 \) compound thereby observed was ascribed to the proximity factor being fully developed and favouring this product. Such an explanation also suits the methoxy compound, particularly since the tautomeric equilibrium described earlier (simulating the \( N\)-alkyl thermodynamic one) shows increased preference for the \( N^3 \) material. Thus for 5-methoxybenzimidazole the electrostatic and proximity factors are seen to favour \( N^3 \) alkylation but the latter only has an affect for very tight t.s. structures.

It should be noted that the charge transfer component probably dictates the alkylation preference of the proximity factor as is indicated by theoretical calculations\(^{29,41,42} \). The important steric component would be expected to be identical for either site. The other major influence in the proximity effects, the \( \pi \)-bond pattern, has been suggested\(^3 \) to have small energy differences between the two products.

The alkylation preference for one site over another signifies that the favoured site has a lower t.s. energy. If, as in the case of 5-nitrobenzimidazole and 5-methoxybenzimidazole, that preference is displayed throughout the range of t.s. structures then the potential energy diagram corresponding to the reaction will always appear as in Figure 10. The diagram indicates that the reaction complex for the preferred site is always lower in energy than that of the other site. This is not only the case for a movement along the reaction co-ordinate but also for one orthogonal to it (out of the plane of the page). A change in the latter corresponds to a variation in the loose/tight character of the
reaction and may be represented by a series of diagrams as in Figure 10.

The benzylation of the 5-methoxybenzimidazole anion was also performed in formamide. As in the previous formamide reaction preferential solvation occurred although this time at the N³ site. This suggests that the N³ site has the highest negative charge as was already concluded on other grounds. The affect resulted in a higher t.s. energy for N³ alkylation and so a greater proportion of the N¹ product.

Theoretical Calculations

Though it was not possible to perform calculations on 5-methoxybenzimidazole some were done on 5-aminobenzimidazole, a compound that should be very similar in alkylation site preference. The results (Table 7) show that N³ alkylation is specified by all three calculations. Also the magnitudes of the preferences are all considered to be meaningful this time.

Therefore, in the case of 5-methoxybenzimidazole, the
Table 7
Theoretical Calculations for the 5-Aminobenzimidazole Anion

<table>
<thead>
<tr>
<th>Nucleophilic Atom</th>
<th>M.E.P. minima (kcal/mole)</th>
<th>$q_{\text{tot.}}$</th>
<th>P.E. (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N^3$</td>
<td>-225.0</td>
<td>-7.4015</td>
<td>-434.68</td>
</tr>
<tr>
<td>$N^1$</td>
<td>-223.9</td>
<td>-7.3966</td>
<td>-433.39</td>
</tr>
</tbody>
</table>

The theoretical results correspond well with those obtained experimentally.

C. Summary

In agreement with recent literature studies it has been shown that, for benzimidazole compounds, the remote 5-substituent does not greatly differentiate the imidazole nitrogens towards alkylation. As well as the magnitude of the differentiation the 5-substituent was also seen to determine its direction. However, even with the consideration of both affects for such dissimilar 5-substituents as $\text{CH}_3$ and $\text{NO}_2$ the product ratio only changes by a factor of $ca$ 1.4 ($ca$ 0.2 kcal in free energy terms) for alkylation of the corresponding compounds. If the product thermodynamic preference is considered for each compound the difference increases but still only alters by a factor of 2.5 ($ca$ 0.5 kcal) between them.

The insensitivity of the results to the alkylating agent or solvent used was thought to derive from an electrostatic dominance of alkylation preference. The most
negatively charged nucleophilic site was preferentially alkylated and by a similar degree despite variation in the above conditions. Studies of product thermodynamic equilibria showed that proximity preferences become important only for very tight t.s. structures and are directionally the same as the electrostatic ones. This suggests that a direct relationship may exist between a nitrogen's negative charge and its charge transfer ability (the component which mainly determines the alkylation preference of the proximity factor).

For the 5-substituted benzimidazoles the calculation of $q_{tot}$ has consistently proven to best predict the preferred alkylation site. This also appeared to be the case for the 5-cyanobenzimidazole calculations although they are yet to be verified by experimental results. At this stage the calculations of M.E.P. and P.E. only seem to be able to make a more general comment about the alkylation potentials of the sites.

Another calculation performed on this nucleophilic system has been the determination of highest occupied molecular orbital (H.O.M.O.) coefficients. However, not only did these calculations fail to predict the preferred alkylation site but in some cases the general equivalence of the sites was not even indicated.

Therefore, in the 5-substituted benzimidazole system, the nitrogen having the greatest negative charge should be preferentially alkylated under most circumstances.
Chapter 3. Alkylation of 4-Substitutedbenzimidazoles

The conclusions reached in the last chapter should also apply to the 4-substitutedbenzimidazoles (11) although the greater proximity of the substituent to the imidazole ring may introduce additional complications. One result of the substituent's nearer position should be to make the alkylation preference more disproportionate. Also there exists the possibility of direct interaction between the substituent and the adjacent nucleophilic site.

In this chapter a number of benzimidazoles have been studied with differing 4-substituents. The compounds, 4-(NO₂-,CH₃OCO-,HOCO-,CH₃-,CH₃O-,NH₂-,CH₃CONH-)benzimidazole, are presented roughly in order of increasing π-electron donating ability of the 4-substituent. However, before going on to further discuss the alkylations performed in this project it is appropriate to generally describe the work previously undertaken in this area.

In the 5-substitutedbenzimidazole system tautomeric ratios were found to be a useful tool in predicting the direction and magnitude of alkylation preferences. Although the relationships are not clear in this system they may be resolved by a consideration of the relevant literature work.
It has been reported\textsuperscript{23} that a correlation exists between the pK\textsubscript{A} values of 4-(F-,Cl-,Br-,I-)benzimidazole and Jaffé's meta sigma constants for the corresponding substituents. It was the author's contention that the loss of the acidic proton from the N\textsuperscript{1} position was strongly favoured thereby leaving the N\textsuperscript{3} tautomer predominant. Proton loss from the N\textsuperscript{3} position was thought to be inhibited by electrostatic attraction to the peri halogen. As further evidence of this the article cited the ability of the 4-fluorobenzimidazole to sublime and the inability of the 5-fluoro compound to do so. In the former the intramolecular interactions presumably reduced those occurring between molecules and thus allowed more facile disruption of the crystal structure.

In his previously mentioned work Ridd\textsuperscript{3} also estimated the tautomeric ratio for 4-nitrobenzimidazole by using the pK\textsubscript{A} values of the two N-methyl-4-nitrobenzimidazole isomers. The ratio was found to be approximately 4 to 1 in favour of the N\textsuperscript{3} tautomer. This is consistent with the existence of an electrostatic interaction between the N\textsuperscript{3} hydrogen and the adjacent 4-nitro group. A study\textsuperscript{43} of the physical properties (including acid/base strength and ultraviolet spectral data) of 4-nitrobenzimidazole have, in fact, demonstrated this interaction to be internal hydrogen bonding.

In contrast, another group of researchers\textsuperscript{36} has concluded that the tautomeric ratios for 2-chloro-4-(NO\textsubscript{2}-,Cl-,CH\textsubscript{3}-,CH\textsubscript{3}O-)benzimidazole are not far from unity. This conclusion was reached because the rate of 2-chloro substitution correlated well with an equation relying equally on both ortho and meta sigma constants.

Some tautomeric measurements\textsuperscript{44} (Table 8) for
substituted purines (Figure 11) have also failed to indicate the presence of favourable internal electrostatic interactions.

![Figure 11](image)

Figure 11

It was found that the N7 tautomer was more preferred in purine (X = H) than in the compound where these interactions would be expected (X = OCH₃).

<table>
<thead>
<tr>
<th>6-Substituent</th>
<th>N⁷ Tautomer (%)</th>
<th>N⁹ Tautomer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>SCH₃</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>OCH₃</td>
<td>32</td>
<td>68</td>
</tr>
<tr>
<td>NH₂</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

In summarising the information on tautomerism in 4-substitutedbenzimidazoles, Elguero² has concluded that the substituent exerts a remote tautomeric perturbation unless an
unusual (attractive or repulsive) interaction occurs between it and the $N^3-H$. Thus hydrogen bonding and favourable and adverse electrostatic interactions may occur but the circumstances are not certain. However, if they are in evidence then the tautomeric ratio will give a better indication of alkylation direction for loose t.s. reactions than for those that are tight.

Very few alkylations have been performed on this system and those that have suggest that the $N^3$ position is strongly hindered. The specifics of these alkylations will be discussed in the section on the relevant 4-substituted-benzimidazole. Steric and not electronic effects have also been found to dominate the alkylation preference in cinnolines and indazoles where a substituent is adjacent to one reaction site.

The exact influence of the 4-substituent is examined in the following series of alkylations.

A. Alkylation of 4-Nitrobenzimidazole Anion

Only two literature articles could be found that reported the product proportions obtained from a 4-nitrobenzimidazole (12) alkylation. In one investigation
Pappalardo and co-workers\textsuperscript{22} have methylated the 4-nitrobenzimidazole anion and acetylated the parent compound. The methylation reaction was undertaken in alcoholic KOH using methyl iodide. The main product was that of N\textsuperscript{1} alkylation with the N\textsuperscript{3} compound only evident through proton magnetic resonance analysis. This result was rationalised by steric effects hindering the N\textsuperscript{3} site. In the acetylation (acetic anhydride/pyridine) the 4-nitrobenzimidazole was unionised and so the complete absence of the N\textsuperscript{3} product could be due to an N\textsuperscript{3} tautomeric preference as well as the greater steric demands of the acetyloyating agent.

Another group of workers\textsuperscript{21} has alkylated the anion of 2,6-dimethyl-4-nitrobenzimidazole using isopropyl bromide and NaOH in tetrahydrofuran. No N\textsuperscript{3} product was observed, presumably due to steric control. The investigators also attempted the preparation of this compound by oxidation of 4-amino-2,6-dimethyl-N\textsuperscript{3}-propylbenzimidazole and by other means. They were unsuccessful and therefore concluded that steric interaction between the N\textsuperscript{3} alkyl and the 4-substituent made the appropriate t.s. very unfavourable for these reactions.

Therefore, in the 4-nitrobenzimidazole system, it is evident that the steric component of the proximity factor may be decisive in hindering alkylation at the congested N\textsuperscript{3} site.

**Alkylation Results**

In this project the 4-nitrobenzimidazole anion was reacted with a wide range of alkylating agents and the results of these reactions appear in Table 9. As expected the imidazole nitrogens in 4-nitrobenzimidazole are well
Table 9
Alkylation of 4-Nitrobenzimidazole Anion

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>P.m.r. Signal</th>
<th>N¹ Alkylation (%)</th>
<th>N³ Alkylation (%)</th>
<th>N¹:N³ Ratio</th>
<th>δΔG² (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅CH₂OCH₂Cl</td>
<td>NCH₂</td>
<td>38.5±6</td>
<td>61.5</td>
<td>1:1.60</td>
<td>-0.28</td>
</tr>
<tr>
<td>(CH₃)₃CCOCH₂Cl</td>
<td>n.a.</td>
<td>100⁺⁰⁻²</td>
<td>-</td>
<td>&gt;49</td>
<td>&gt;2.36</td>
</tr>
<tr>
<td>4-CH₃OC₆H₅CH₂Cl</td>
<td>CH₂</td>
<td>65.0±4</td>
<td>35.0</td>
<td>1.86</td>
<td>0.38</td>
</tr>
<tr>
<td>2-CH₃OC₆H₅CH₂Cl</td>
<td>CH₂</td>
<td>61.0±4</td>
<td>39.0</td>
<td>1.56</td>
<td>0.27</td>
</tr>
<tr>
<td>C₆H₅CH₂Cl</td>
<td>CH₂</td>
<td>67.0±3</td>
<td>33.0</td>
<td>2.03</td>
<td>0.40</td>
</tr>
<tr>
<td>4-NO₂C₆H₅CH₂Cl</td>
<td>CH₂</td>
<td>66.0±5</td>
<td>34.0</td>
<td>1.94</td>
<td>1.08</td>
</tr>
<tr>
<td>C₆H₅COCH₂Cl</td>
<td>CH₂</td>
<td>86.0⁺²⁻⁴</td>
<td>14.0</td>
<td>6.14</td>
<td>0.08</td>
</tr>
</tbody>
</table>

b

<table>
<thead>
<tr>
<th></th>
<th>C²H</th>
<th>53.5⁺³⁻²</th>
<th>46.5</th>
<th>1.15</th>
<th>0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃I</td>
<td>C²H</td>
<td>64.0±4</td>
<td>36.0</td>
<td>1.78</td>
<td>0.34</td>
</tr>
<tr>
<td>CH₃CH₂Br</td>
<td>n.a.</td>
<td>100⁺⁰⁻²</td>
<td>-</td>
<td>&gt;49</td>
<td>&gt;2.36</td>
</tr>
<tr>
<td>(CH₃)₂CHBr</td>
<td>n.a.</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>(CH₃)₃CB₃C</td>
<td>n.a.</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

A. The first time this reaction was performed 90.0% N¹ alkylation and 10.0% N³ alkylation was obtained. It was thought that excess alkylation agent caused dialkyl products to form and initiated a reverse reaction.

B. Other analyses were also used which confirmed these results (see Experimental section).

C. No alkylation products were obtained.
differentiated towards alkylation and, depending on alkylation agent, are found to be so to various extents. This dependence of alkylation pattern on alkylation agent leads to two important conclusions. Firstly, the t.s. structure for these reactions must be between early and late. If the t.s. structure was at one extreme or the other the variation of alkylation agent would have little effect on product ratios. Secondly, the alkylation rules established for the 5-substituted-benzimidazoles will require modification if they are to apply to the 4-nitrobenzimidazole system. For the alkylation of a particular 5-substitutedbenzimidazole it was found that reaction was always favoured at the same site. In the present system this is obviously not the case as the direction of preference relies on the alkylation agent.

In Table 9a the alkylation agents, from benzyl chloromethyl ether to phenacyl chloride, are listed in order of the increasingly tight character of their reaction t.s. structures. However, in Table 9b the order is based on increasing bulk starting from methyl iodide. Each of these series also displays a roughly parallel enhancement in the amount of N¹ alkylation.

The reaction of benzyl chloromethyl ether with 4-nitrobenzimidazole anion should proceed by a relatively loose t.s. structure, the stability of which depends upon electrostatic interactions. The latter must very markedly favour the N³ site for the N³ product to predominate despite adverse steric effects. At this stage it is not evident whether the electrostatic preference for N³ is due to electron density considerations or to the presence of nearby electronegative atoms (or both).
When the alkylating agent is chloromethyl pivalate the reaction t.s. structure is somewhat tighter than it is with benzyl chloromethyl ether and the alkylation pattern relies less on electrostatic interactions. The complete absence of $N^3$ product in this case is unexpected and is inconsistent with the trend of results established by the other alkylating agents. Despite repeated attempts at this reaction the result remained unchanged. As the pivaloylmethyl group is easily hydrolysed it is possible that this has preferentially occurred at the $N^3$ site during the preparation procedure for p.m.r. analysis. A precedent exists for such selective hydrolysis in the $N^7$- and $N^9$-pivaloylmethyl products of adenine (equivalent to the $N^3$ and $N^1$ benzimidazole compounds). However, analysis of the product mixture without the normal preparatory procedure indicated that this was not the case here.

In the reaction with chloromethyl pivalate it is conceivable that dialkylation has occurred and this would lead to preferred removal of the $N^3$ product. Such a problem arose when benzyl chloromethyl ether was first reacted with the 4-nitrobenzimidazole anion and was prevented by using less than the stoichiometric amount of alkylating agent. Such a precaution was also adopted for the pivaloylmethylation reactions to no effect. As a consequence this unusual result cannot be adequately explained at this stage.

As alkylating agents the ring substituted benzyl chlorides should have a reaction t.s. complex which is intermediate in loose/tight character. Also within the series there is a marked gradation in the latter from 4-methoxybenzyl chloride (the loosest) to 4-nitrobenzyl
chloride (the tightest). This feature is of particular interest since the steric bulk of the agents remains constant for attack at the nucleophilic sites. Therefore any change in alkylation results for these alkylating agents will be due solely to the alteration of t.s. structure. The invariance of the results obtained is surprising and suggests that any overall alkylation trends observed may be due to the change in steric demands between alkylating agents. That this is not entirely the case is seen by comparing the alkylation ratios produced by the reactions of benzyl chloromethyl ether (larger alkylating agent) and of methyl iodide (smaller alkylating agent). However, before further considering these results it is advisable to first examine the reactions of the alkyl halides which proceed by a similar t.s. structure to the benzyl chlorides.

The series of alkyl halides from methyl iodide through to tert-butyl bromide shows an increase in both size and the looseness of the reaction t.s. structure. The increase in N1 alkylation for the corresponding reactions indicates that the steric considerations are more important than those concerned with the nature of t.s. structure. Also the strong steric dependence suggests that proximity factors primarily determine the relative N1/N3 reactivities in a t.s. region previously associated with electrostatic and polarisable control.

In the reactions with the substituted benzyl chlorides the proximity factor should, therefore, largely dictate the alkylation preferences. As indicated with the alkyl halides, steric changes are of great importance and their absence in the benzyl chloride series may in part
explain the invariance of the alkylation results. Also the gradation in loose/tight character within the series may not be large and any alkylation trend thus produced could be distorted by the errors inherent in the analysis method. In addition it was suggested in the first chapter that the alkylation patterns obtained could be quite irregular.

The reaction with phenacyl chloride should involve a tight t.s. structure with the concomitant strong contribution of the proximity factor to alkylation preference. The results show that this is in fact the case with the less sterically congested N¹ product being strongly favoured.

The switch in preference between N³ and N¹ alkylation observed for the series of reactions suggests that there is a crossover in the potential energy curves for the N³ and N¹ reaction complexes. For the loose t.s. structure this crossover occurs after the t.s. position, thus electrostatic factors dominate the alkylation preference and favour N³ (see Figure 12). However, if the t.s. structure is tight the crossover takes place before the t.s. complex forms and

![Figure 12](image1.png)

![Figure 13](image2.png)
steric factors are paramount. In this situation the $N^1$ alkylation takes precedence (see Figure 13).

Although the factors primarily determining the alkylation pattern have been identified it still remains to investigate the mode of their operation and the roles played by other selectivity factors. The measurement of product thermodynamic stabilities and examination of data from theoretical calculations may facilitate this process.

In order to determine the relative thermodynamic stabilities of the 4-substituted $N$-alkyl products an attempt was made to establish a reaction equilibrium between them. To this end the unseparated products of the benzylation reaction were dissolved in a small amount of DMF and 0.3 equivalents of benzyl chloride added. The reaction was fixed at 125°C and at periodic intervals a sample was removed and analysed. It was thought that the dibenzyl compound would form from, and decompose to, both monobenzyl compounds and thus eventually establish an equilibrium between the latter two. Figure 14 shows the potential energy diagram that is considered to describe the main features of the reaction. The monobenzyl starting materials should have different potential energies with the $N^3$ compound having the greater. The relative rates of attack on the $N^1$ and $N^3$ sites of the $N^3$ and $N^1$ products respectively will depend on the position of the t.s. complexes on the reaction co-ordinate. If the t.s. structures are very early then $N^3$ benzylation will be more rapid and if very late $N^1$ benzylation will be faster. It is thought that as the t.s. character varies from the first extreme to the second the corresponding $\delta AV(R)^7$ will change from a negative value and approach the value for the
potential energy difference of the reactants ($\Delta V(R)_R^R$). As the reactant benzimidazoles are neutral, the associated t.s. structures should be later than those for the anionic reaction and hence $N^1$ benzylation should occur more rapidly. However the difference in reaction rates should not be too disparate although greater than the ca 2:1 ratio observed in the anionic reaction.

On formation the dibenzyl compound should readily decompose back to both benzimidazole starting materials. Thus it seems reasonable that both products will react and move towards an equilibrium with each other. After 26 days, analysis of the reaction solution showed that the relative proportions of the monobenzyl products had stabilised and hence equilibrium was presumed to have been reached. The results of 88% $N^1$ and 12% $N^3$ product appeared to show what was considered to be an insufficient preference for the $N^1$ compound so this reaction and similar ones for other 4-substituted benzimidazoles were reappraised.

It seems that the dibenzyl product is more stable
than was previously thought and certainly more so than the N\textsuperscript{3} monobenzyl product (as seen by p.m.r. analysis). Consequently, in all such alkylations the N\textsuperscript{3} product readily converts to the dibenzyl one and apparently continues to do so until either it or the alkylation agent is exhausted. The role played by the N\textsuperscript{1} product was difficult to assess because of both the slowness of its reaction and the removal of the available alkylation agent. However, it is evident that an equilibrium may not be present between the two monobenzyl species.

To obtain more meaningful information on such reactions would necessitate an independent approach to equilibrium starting from each monobenzyl product as was performed with benzylated products of 5-nitrobenzimidazole.

### Theoretical Calculations

For the calculations performed the nucleophilic nitrogens in 4-nitrobenzimidazole anion are well differentiated (Table 10). The difference in the N\textsuperscript{1}/N\textsuperscript{3} M.E.P. minima calculated for the latter is, in fact, more than 100 times greater than that for the 5-nitro compound.

#### Table 10

<table>
<thead>
<tr>
<th>Nucleophilic Atom</th>
<th>M.E.P. Minima (kcal/mole)</th>
<th>q\textsubscript{tot} \textsuperscript{A}</th>
<th>P.E. (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N\textsuperscript{3}</td>
<td>-220.6 (-213.2)\textsuperscript{A}</td>
<td>-7.3643 (-7.3816)</td>
<td>-425.22 (-425.6)</td>
</tr>
<tr>
<td>N\textsuperscript{1}</td>
<td>-206.7 (-209.8)</td>
<td>-7.3807 (-7.3842)</td>
<td>-418.70 (-422.5)</td>
</tr>
</tbody>
</table>

A. Bracketed figures show results for calculations on the 4-cyanobenzimidazole anion.
Although the direction of this preference agrees with the experimental findings it is much more disproportionate than the latter would indicate. This may be due to a combination of factors. For instance the M.E.P. calculation employs a proton electrophile, the charge and optimum approach distance of which should accentuate electrostatic differences between N¹ and N³. Also, although the calculation is most applicable to a loose t.s. structure for which steric effects should be negligible they may not be for the present compound*. However, possibly the most important reason for the discrepancy between experimental and theoretical results is that the latter are qualitative rather than quantitative.

The M.E.P. map (Figure 15) indicates that the great N³ preference is due to an overlap of the electrostatic potential of the nitro oxygen with that of the N³ site. Further support for this conclusion is given by the fact that the N³ nitrogen is calculated to have a lower total negative charge than that calculated for N¹. Presumably this is due to electrostatic repulsion of electrons away from N² in response to the nearby presence of the negatively charged nitro oxygen. Thus, it would seem that M.E.P. calculations give a far better indication of electrostatic alkylation preferences than does the more conventional q_tot parameter.

An instance in the literature where electron density does not seem to be an adequate predictive tool is in the methylation (diazomethane/diethyl ether) of nitro

* A comparison between the 4-nitro and 4-methoxybenzimidazole results in Section E of this chapter comments further on this point.
substituted benzenesulfonyl thioamides (figure 10). For the change of the nitro substituent from the 5 to the

Figure 15

On page 46 the charge transfer effects were indicated to be the main component of proximity interactions where steric considerations are not important.
substituted benzoxazole-2-thione anions (Figure 16). For the change of the nitro substituent from the 6 to the 4 position, a great enhancement of N alkylation occurred over that at S despite increased steric requirements for the N of the 4-nitro compound. However, the corresponding change in the relative N/S electron densities was only slight and the result could have been better explained in M.E.P. terms.

The calculated P.E. values show that protonation will be strongly preferred at the N³ site, which is not unexpected in the light of the M.E.P. calculations. However, it is interesting that the preference in the former is less than that in the latter. This pattern was displayed by the calculations done on all 4-substituted benzimidazoles and suggests that polarizability and/or charge transfer* effects constantly oppose the M.E.P. preference. The charge transfer effects should be the larger of the two and together they would be expected to contribute less than half of the protonation energy (most of the remainder being provided by electrostatic interactions).

* On page 46 the charge transfer effects were indicated to be the main component of proximity interactions where steric considerations are not important.
In the previous chapter it was suggested that a direct relationship existed between a nitrogen's negative charge \(q_{\text{tot.}}\) and its charge transfer ability, which may also occur with 4-substituted compounds. In the latter, \(q_{\text{tot.}}\) is always found to display the opposite preference to that of M.E.P. and, if the above relationship holds, so should the charge transfer show the opposite preference. Consequently, the charge transfer interaction may diminish the effect of the M.E.P. preference in the P.E. calculations.

A number of articles\(^\text{29,41,42,46}\) have commented on the significance of electrostatic potential, polarizability and protonation energy calculations with respect to the protonation processes of particular organic compounds. However, the relationships, where found, seemed to depend very much upon the nature of the compound studied and the method of calculation. Consequently, despite these investigations, the alkylation preferences defined by the polarizability and charge transfer effects are specified no further than they were above.

In the 4-substituted benzimidazole, system the P.E. values are not good representations of the relative thermodynamic stabilities of the corresponding N-alkyl compounds. This is because the alkyl group and a proton have very dissimilar steric requirements as is consistent with the lack of correlation between the P.E. values and the alkylation results for reactions with tight t.s. structures.

Together the experimental and theoretical results provide a fairly clear picture of the processes dictating the alkylation patterns of the 4-nitrobenzimidazole anion. The presence of an oxygen atom near the \(N^3\) nucleophilic site adds
very much to the negative environment around that site. As a consequence, protonation occurs preferentially at \( N^3 \) and so does alkylation if the corresponding t.s. structure is sufficiently loose.

As the t.s. structure becomes tighter it is stabilised increasingly by polarization. This effect would not be expected to significantly alter the alkylation preference as dictated by the electrostatic factor. However, because the \( N^3 \) site is strongly sterically congested the steric component of the proximity factor becomes rapidly important and causes this site to be hindered with respect to alkylation. As the t.s. becomes still tighter this favouritism would be expected to grow even more pronounced, irrespective of the appearance of other proximity effects.

Thus the two main effects which dominate the alkylation pattern in 4-nitrobenzimidazole system are electrostatic and steric interactions. These are both through space substituent effects and become superimposed on and dominate the through bond effects which determined alkylation in the 5-substitutedbenzimidazoles.

B. Alkylation of 4-Carboxymethylbenzimidazole Anion

![Chemical Structure](image-url)
4-Carboxymethylbenzimidazole (13) has a structure very similar to 4-nitrobenzimidazole and was investigated in order to compare it with the latter compound. The carboxymethyl and nitro groups have almost identical steric requirements for reaction purposes, particularly if the ester methyl is remote from the imidazole ring. However, the carboxymethyl has a lower electron-withdrawing ability and lower oxygen electrostatic potential.

A literature search did not reveal any studies on tautomerism or alkylation of 4-carboxymethylbenzimidazole, although work done on the similar 4-nitro compound should be relevant.

Alkylation Results

In this system (and some others) reactions were carried out with only three different alkylating agents; benzyl chloromethyl ether, benzyl chloride and phenacyl chloride. These agents were selected because they were considered to provide good spread in loose/tight reaction t.s. character. The results of the alkylations with these agents appear in Table 11.

The reactions of the 4-carboxymethylbenzimidazole anion with benzyl chloromethyl ether and benzyl chloride produce a very similar alkylation pattern to that obtained for the corresponding 4-nitro reactions and further indicate the similarity between these benzimidazoles. Presumably the interpretation used for the 4-nitro compound also applies to that of the carboxymethyl.
Table 11
Alkylation of the 4-Carboxymethylbenzimidazole Anion

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>P.m.r. Signal</th>
<th>$N^1$ Alkylation (%)</th>
<th>$N^3$ Alkylation (%)</th>
<th>$N^1:N^3$ Ratio</th>
<th>$\delta \Delta G^\circ$ (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_6H_5CH_2OCH_2Cl$</td>
<td>NCH$_2$</td>
<td>32.5±2</td>
<td>67.5</td>
<td>1:2.08</td>
<td>-0.44</td>
</tr>
<tr>
<td>$C_6H_5CH_2Cl$</td>
<td>CH$_2$</td>
<td>72.0±2</td>
<td>28.0</td>
<td>2.57</td>
<td>0.56</td>
</tr>
<tr>
<td>$C_6H_5COCH_2Cl$</td>
<td>CH$_2$</td>
<td>67.5$^+4$</td>
<td>32.5</td>
<td>2.08</td>
<td>0.44</td>
</tr>
</tbody>
</table>

In the phenacylation reaction, an inordinate amount of the $N^3$ product formed; in fact, more than was produced in the reaction with benzyl chloride. This is an unexpected result and is not consistent with the product proportions yielded by the 4-nitrobenzimidazole phenacylation. The former reaction was repeated without any real variation of the results.

The only reasonable explanation that could be devised is based on the suggestion made in the first chapter about alkylation trends. There it was considered probable that for the reaction of a benzimidazole with a graded series (in loose/tight t.s. character) of alkylating agents, localised irregularities might emerge in the overall trend of alkylation results. The reaction of the 4-carboxymethylbenzimidazole anion with phenacyl chloride may correspond to one of these anomalous regions. This effect might possibly not be apparent for the same 4-nitrobenzimidazole reaction due to the slight differences between the benzimidazoles.
It was thought that the alkylation of the 4-carboxybenzimidazole (14) dianion could provide valuable information on the work involving the anions of both 4-nitrobenzimidazole and 4-carboxymethylbenzimidazole. While the steric requirements of the carboxyl anion are similar to those of the nitro and carboxymethyl groups, it should have significantly different electronic through space and through bond effects. The oxygen atoms in the carboxyl anion will have higher negative charges resulting in a higher electrostatic potential for the N³ nitrogen and a lower electron density on that atom due to through space repulsion. However the latter result will be offset and also the electron density on N¹ increased because the carboxyl anion is only a poor electron-withdrawing group. The nett effect should therefore be an enhancement in N³ alkylation, particularly for loose reaction t.s. structures.

Alkylation Results

The usual reaction conditions were employed, except that twice the amount of base was used.

The results listed in Table 12 show quite unexpectedly that only the N¹ alkylation occurred and this remained the case.
Table 12
Alkylation of the 4-Carboxybenzimidazole Dianion

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>N^1 Alkylation (%)</th>
<th>N^3 Alkylation (%)</th>
<th>N^1:N^3 Ratio</th>
<th>δΔG° (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_6H_5CH_2OCH_2Cl</td>
<td>100±0^+ -2</td>
<td>-</td>
<td>&gt;49</td>
<td>&gt;2.36</td>
</tr>
<tr>
<td>C_6H_5CH_2Cl</td>
<td>100±0^+ -2</td>
<td>-</td>
<td>&gt;49</td>
<td>&gt;2.36</td>
</tr>
<tr>
<td>C_6H_5COCH_2Cl</td>
<td>100±0^+ -2</td>
<td>-</td>
<td>&gt;49</td>
<td>&gt;2.36</td>
</tr>
</tbody>
</table>

when the reactions were carefully repeated. It was envisaged that a water molecule could be binding between the N^3 site and a carboxyl oxygen, therefore restricting alkylation at this position. To test this hypothesis the reactants were thoroughly dried and the reaction performed again, but instead with a great excess of base to ensure removal of any water present. The results were unchanged.

The most likely explanation of the problem is that the negative environment around N^3 is so great that sodium ions (present in twice the normal concentrations) are preferentially bound there. This selective association by "counterions" has been well established in other ambident nucleophilic systems^7 and results in preferential alkylation at the alternate reaction site. This explanation is equally pertinent to the alkylations in this system. The ion association, if present, might be prevented by removal or replacement of the cation. For example, a crown ether could be used to preferentially bind the cations and thus restrict their association with the nucleophile. An attempt was made to do this but the crown ether proved insoluble in the reaction solvent, DMF.

Alternately, cationic interference could be minimised
by employing a cation with binding ability less than sodium ion, e.g. a tetramethyl ammonium ion.

D. Alkylation of 4-Methylbenzimidazole Anion

The methyl substituent in 4-methylbenzimidazole (15) is an electron-donating group but only weakly so. It has been established by infrared studies that the presence of the methyl group leads to higher electron densities on the two nitrogen atoms. However, it is unlikely that this enhancement in electron density will differ very much between these atoms. Therefore direct electrostatic and steric effects of the substituent should dictate the alkylation pattern, as has previously been the case.

Alkylation Results

Again a direct relationship was observed between the tightness of reaction t.s. corresponding to each alkylating agent and the amount of \( \text{N}^1 \) alkylation (Table 13). In the loose t.s. situation the methyl protons act as positive barriers to alkylation at \( \text{N}^3 \) and possibly reduce its electrostatic potential, leading to a preference for \( \text{N}^1 \) alkylation.
Table 13
Alkylation of the 4-Methylbenzimidazole Anion

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>P.m.r. Signal</th>
<th>N&lt;sup&gt;1&lt;/sup&gt; Alkylation (%)</th>
<th>N&lt;sup&gt;3&lt;/sup&gt; Alkylation (%)</th>
<th>N&lt;sup&gt;1&lt;/sup&gt;:N&lt;sup&gt;3&lt;/sup&gt; Ratio</th>
<th>δΔG° (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>NCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>57.5±4</td>
<td>42.5</td>
<td>1.35</td>
<td>0.18</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>77.0±4</td>
<td>23.0</td>
<td>3.30</td>
<td>0.72</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;COCH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>86.5±4</td>
<td>13.5</td>
<td>6.41</td>
<td>1.13</td>
</tr>
</tbody>
</table>

In the tighter t.s. structure of the benzyl chloride reaction, polarization effects should become superimposed upon the electrostatic effects. Again the former would not be expected to markedly change the alkylation pattern as defined by the electrostatic interactions and so the enhanced yield of N<sup>1</sup> product was probably due to the steric factors. These latter interactions should favour alkylation at N<sup>1</sup> over reaction at the sterically hindered N<sup>3</sup> site and should show an escalating influence as the reaction t.s. becomes tighter. The steric preference in the present system should always be smaller than that displayed by the 4-nitrobenzimidazole compound. However, steric preferences in 4-methylbenzimidazole are reinforced rather than opposed by the electrostatic effects resulting in N<sup>1</sup> alkylation being more favoured in the benzyl-ation reaction than is the case for 4-nitrobenzimidazole.

The reaction of the 4-methylbenzimidazole anion with phenacyl chloride showed an even more marked preference for N<sup>1</sup> alkylation. Presumably this is due to the greater influence of steric effects to which the other proximity effects should be subordinate. The results in this case are
similar to those obtained for the corresponding 4-nitrobenzimidazole reaction; the more pronounced increase of the steric preferences in the latter case would account for this fact.

In the loose t.s. structure, the electrostatic factors govern which site is given precedence, but as the t.s. structure becomes tighter steric factors also become important. If the direction of the alkylation preference for both factors coincides then the product favoured in the loose t.s. reaction will still be preferred and this preference will increase as the t.s. tightens. This effect is illustrated by the reaction of the 4-methylbenzimidazole anion. On the other hand, if the steric and electrostatic effects oppose one another then the product preferred in the loose t.s. reaction will be produced in diminishing amounts as the t.s. tightens and indeed large steric effects may cause the alternate product to predominate. This course is illustrated by the reactions of the 4-nitrobenzimidazole anion.

E. Alkylation of the 4-Methoxybenzimidazole Anion

In 4-methoxybenzimidazole (16) the substituent is a
good π-electron-donor and so this system is quite different from those previously studied. Additionally, the methoxy group is sterically smaller, for reaction purposes, than any other 4-substituents studied thus far.

At the beginning of this chapter reference was made to articles\textsuperscript{36,44} which provided information on the tautomeric behaviour of 4-methoxybenzimidazole related compounds. The tautomeric ratios were shown to be close to unity, with perhaps a slight preference for the N\textsuperscript{1} tautomer being evident. This result suggests that the substituent oxygen does not participate in hydrogen bonding and hence provides only a small contribution to the negative environment around N\textsuperscript{3}. However, it should be noted that one of the articles\textsuperscript{36} which indicated tautomeric equivalence in 4-methoxybenzimidazole did the same for 4-nitrobenzimidazole and this was shown to be highly unlikely in Section A (of this chapter).

Only one report\textsuperscript{48} was discovered describing the alkylation of a related 4-methoxybenzimidazole system. This involved the reaction of methyl iodide with the 2-chloro-4-methoxybenzimidazole anion in ethanol. No exact measurement of the product proportions was cited but the implication given was that although the N\textsuperscript{1} compound was favoured, the N\textsuperscript{3} compound was still present in substantial amounts. In summary, previous tautomeric and alkylation studies seem to indicate that N\textsuperscript{1} will be the preferred site of alkylation on the 4-methoxybenzimidazole anion.

**Alkylation Results**

The results (Table 14) show that alkylation always favoured the N\textsuperscript{3} site. This preference was most marked in the reaction with benzyl chloromethyl ether and was even greater...
than that observed in the corresponding anionic 4-nitro-
benzimidazole reaction. This is unexpected in the light of
introductory comments concerning the 4-methoxybenzimidazole
system.

Table 14
Alkylation of the 4-Methoxybenzimidazole Anion

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>P.m.r. Signal</th>
<th>N₁ Alkyl-</th>
<th>N₃ Alkyl-</th>
<th>N₁ : N₃ Ratio</th>
<th>δΔG° (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅CH₂OCH₂Cl</td>
<td>NCH₂</td>
<td>29.0±4</td>
<td>71.0</td>
<td>1:2.45</td>
<td>-0.53</td>
</tr>
<tr>
<td>C₆H₅CH₂Cl</td>
<td>CH₂</td>
<td>43.0±3</td>
<td>57.0</td>
<td>1:1.33</td>
<td>-0.17</td>
</tr>
<tr>
<td>C₆H₅COCH₂Cl</td>
<td>CH₂</td>
<td>39.0±3</td>
<td>61.0</td>
<td>1:1.56</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

Thus far, the present study of 4-substituted-
benzimidazoles has indicated that electrostatic and steric
effects dominate the alkylation pattern. Consequently, the
results of the benzyl chloromethyl ether reaction in the
present system will be explained in these terms.

The strong preference for N₃ alkylation corresponding
to a loose t.s. structure suggests that electrostatic inter-
actions favour this site. However, the preference based
solely on electrostatic grounds cannot be as great as that of
the 4-nitro compound. In the latter the nitro oxygen facing
N₃ is much closer to it and is much more negatively charged
than the substituent oxygen in 4-methoxybenzimidazole. Also
the lone electron pairs of the methoxy oxygen may be out of
plane and thus less enhance the M.E.P. minima of N₃ which is
in plane. Therefore, the large N₃ preference in the 4-methoxy
system must require a steric explanation and this should involve a consideration of reaction approach geometries.

The M.E.P. maps constructed for the 4-substituted-benzimidazoles (see Figure 17) show that the minima position is in the molecular plane and they also reveal that electrostatic interaction only diminishes gradually on moving out of this plane and thus attack is not constrained to it. Recent alkylation work\textsuperscript{11d} on related heterocycles has also been interpreted in terms of allowed non-planar attack of the alkylating agent upon the nucleophile.

It is apparent, therefore, that the preferred approach of the alkylating agent may deviate from the molecular plane, but the question of the magnitude of this effect is unresolved. The great dependence of the alkylation results on steric effects shown by the 4-nitrobenzimidazole system suggests that deviance from this plane cannot be large. The suggestion is increasingly pertinent for tight t.s. structures which upon becoming non-planar should interfere with molecular π-bond conjugation.

The calculation of H.O.M.O. (π) coefficients for each 4-substitutedbenzimidazole also provides information on attack geometries. The H.O.M.O.s are manifested at right angles to the molecular plane (Figure 18) and so they must participate in the interactions resulting from electrophilic attack with a component in that direction. In view of the fact that the H.O.M.O. predictions do not correlate at all with the experimental results the perpendicular component of attack cannot be great.

If reaction approach geometries are planar then the bulky 4-nitro substituent, also in the molecular plane,
The minimum is in the molecular plane

Perpendicular to the plane, through the nitrogens

Figure 17

Figure 18
may sterically retard $N_3$ alkylation. In the 4-methoxybenzimidazole anion the hindrance to $N_3$ alkylation should be reduced as the methyl should twist away from this site during reaction. Moreover, CPK space-filling molecular models indicate that the reaction conformation of this group will not correspond to the molecular plane.

Consequently, the strong preference for $N_3$ benzyl oxymethylation of anionic 4-nitrobenzimidazole suggested by electrostatic considerations may be largely offset by steric effects. In the 4-methoxybenzimidazole anion the $N_3$ electrostatic preference is less but so is the adverse steric one. The result is that the $N_3$ alkylation with benzyl chloromethyl ether is more favoured in the 4-methoxy compound than in the nitro compound.

It should be noted that the steric effects of the 4-substituent have a dual effect since they disfavour the $N_3$ t.s. structure through entropy considerations as well as those of potential energy. The former is manifested as a reduced accessibility of the $N_3$ site to attack in some directions (reduced approach cross section), particularly for relatively large groups such as the nitro. This effect would be accentuated for in plane alkylation and may further explain the results discussed above.

The reaction of benzyl chloride with the 4-methoxybenzimidazole anion shows that $N_1$ alkylation has increased only a little and is still disfavoured. The $N_1/N_3$ polarization differences may account for this as the steric differences should not be sizable for the t.s. structure of this reaction. The steric requirements of each nucleophilic site in the present compound should be similar and consequently a
tight t.s. structure may be necessary to produce an effect. The reaction with phenacyl chloride should form such a complex and thereby reduce the amount of N³ alkylation which is disfavoured on steric grounds. The results do not support this prediction and instead show an increase in N³ alkylation. The reactions with benzyl chloride and phenacyl chloride were both repeated but the relationship between the results was unchanged. Therefore, it seems that steric differences are very small between the N¹ and N³ sites and so other proximity effects may have a larger influence on the alkylation preference. These effects plus those of the electrostatic and polarizability factors would then determine the entire alkylation preference. The alkylation results indicate that the electrostatic effects are most important in this regard and the other effects apparently oppose the site so preferred. Such an interplay of factors was suggested earlier in this chapter to explain why P.E. values show a similar but reduced preference to that of the M.E.P. values. This correspondence is not unreasonable for the present reaction because its tight t.s. structure and small steric effects make P.E. predictions quite appropriate.

The increase in the amount of N³ product for the change from benzyl chloride to phenacyl chloride is hard to explain but may be the result of an unusual juxtaposition of preferences (see Chapter 1 concerning Interaction Curves).

F. Alkylation of the 4-Aminobenzimidazole Anion

Thus far it appears that direct interactions between the 4-substituent and N³ dictate the alkylation pattern. This suggestion may be further tested by comparing the alkylation
results of the 4-aminobenzimidazole (17) anion with those of the anion of the 4-methoxy compound. The methoxy and amino substituents should have similar through bond effects but very different through space effects for their anticipated conformations. For the amino conformation, the line between the amino hydrogens should be parallel to the plane of the ring but somewhat below or above it (see Figure 19). The preferred conformation for the methoxy group is described in the previous section and should emulate that of the amino group when the latter's imidazole directed proton is missing. Consequently, the through space interactions of these two
substituents with the N<sup>3</sup> site should differ mainly due to the effect of this proton.

In the adenine molecule (18) the proportions of the N<sup>7</sup> (equivalent to the benzimidazole N<sup>3</sup>) and N<sup>9</sup> (equivalent to N<sup>1</sup>) were found to be 15 and 85% respectively. In view of this, the N<sup>1</sup> tautomer would be expected to be favoured in 4-aminobenzimidazole. Such a tautomeric equilibrium is presumably due to adverse electrostatic interaction between the amino protons and a proton at the N<sup>3</sup> site. The fact that the N<sup>7</sup>(N<sup>3</sup>) tautomer in 6(4)-methoxypurine is favoured to more than twice the extent of the N<sup>7</sup>(N<sup>3</sup>) tautomer in 6(4)-aminopurine (adenine) adds further support to this conclusion. Thus, for an electrostatic controlled alkylation the N<sup>1</sup> product of 4-aminobenzimidazole should be preferentially formed.

No alkylation results have been reported for 4-aminobenzimidazole or its anion although such information has been extensively produced for the adenine system<sup>12,14</sup>. For the latter N<sup>9</sup>(N<sup>1</sup>) alkylation is usually preferred for steric reasons and the details of these reactions will be discussed later.

### Alkylation Results

A rough trend in alkylation results is apparent in Table 15. There appears to be a positive correlation between the tightness of the reaction t.s. structure and the amount of N<sup>1</sup> product formed. The N<sup>1</sup> alkylation preference in

* Henceforth, where deemed necessary, the equivalent benzimidazole numbering will be italicised in brackets behind the purine numbering.
the reaction with benzyl chloromethyl ether suggests that the amino protons cause the N\textsuperscript{3} site to be disfavoured on electrostatic grounds. As the t.s. structure tightens the

Table 15

<table>
<thead>
<tr>
<th>Alkylation of the 4-Aminobenzimidazole Anion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylation Agent</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}OCH\textsubscript{2}Cl</td>
</tr>
<tr>
<td>(CH\textsubscript{3})\textsubscript{3}COCOOCH\textsubscript{2}Cl</td>
</tr>
<tr>
<td>4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}Cl</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}Cl</td>
</tr>
<tr>
<td>4-O\textsubscript{2}NC\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}Cl</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}COCH\textsubscript{2}Cl</td>
</tr>
<tr>
<td>CH\textsubscript{3}I</td>
</tr>
</tbody>
</table>

A. Decomposed 4-aminobenzimidazole as well as an unknown product were present in the recovered material. See experimental section.

B. No products obtained just decomposed 4-aminobenzimidazole. Steric effects, which similarly should disfavour N\textsuperscript{3} alkylation, become superimposed on the electrostatic effects and give rise to an even greater preference for the N\textsuperscript{1} product. Therefore it appears that the different through space effects associated with the methoxy and amino substituents give rise to most dissimilar alkylation patterns. Also it should be mentioned that part of this difference could arise from hydrogen bonding
of solvent molecules to the amino group. This would tend to make \( N^3 \) attack more difficult.

In the chloromethyl pivalate reaction the preference for \( N^3 \) alkylation is a departure from the general alkylation trend and thus requires explanation. To aid in this process reference will be made to results obtained in the alkylation of the adenine anion\(^\text{12}\) (Table 16).

The alkylation studies on the adenine system\(^\text{12}\) (18) involved an identical procedure to that adopted for the present study except that a 10% excess of alkylating agent was used in the former case. Alkylation occurred at the \( N^3 \), \( N^7(N^3) \) and \( N^9(N^1) \) sites. The \( N^9(N^1) \) product usually predominated because attack at \( N^7(N^3) \) is sterically hindered while that at \( N^3 \) is strongly disfavoured on thermodynamic grounds and to a lesser extent on electrostatic grounds. The only exception to this rule was the chloromethyl pivalate reaction where the \( N^7(N^3) \) product formed in by far the greatest proportions. The explanation presented for this anomalous result should also apply to the similar result in the equivalent 4-aminobenzimidazole reaction mentioned previously. It was suggested\(^\text{12}\) that for the pivaloylmethylation of the \( N^7(N^3) \) site hydrogen bonding

\( \text{Diagram} \)

18
could occur between the amino protons and the carbonyl group of the attacking reagent. The presence of any such bonding in the t.s. complex would lower the activation energy to the extent that $N^7(N^3)$ alkylation was favoured. Although likely t.s. geometries were not estimated to be ideal for hydrogen bonding, it was nevertheless considered that this could occur. Further evidence for such an effect are the results for phenacyl chloride and tert-butyl chloroacetate reactions with

\[
\begin{array}{|c|c|c|}
\hline
\text{Alkylating Agent} & N^7(N^1) \text{ Alkylation} & N^7(N^3) \text{ Alkylation} \\
\text{(%)} & \text{(%)} & \text{(%)} \\
\hline
C_6H_5CH_2OCH_2Cl & 79 & - \quad 21 \\
(CH_3)_3CCOOC_2Cl & 12(72) \text{B} & 88(28) & -(-) \\
4-CH_3OC_6H_5CH_2Cl & 69 & 6 \quad 25 \\
C_6H_5CH_2Cl & 74(61) & 3(29) \quad 22(-) \\
4-O_2NC_6H_5CH_2Cl & 81 & - \quad 19 \\
C_6H_5COCH_2Cl & 88(89) & 7(11) \quad 5(-) \\
(CH_3)_3COCOCH_2Cl & 78(82) & 14(18) \quad 8(-) \\
CH_3I & 77 & 6 \quad 17 \\
CH_3CH_2I & 84 & - \quad C \quad 16 \\
CH_3CH_2CH_2Br & 78 & - \quad C \quad 22 \\
(CH_3)_2CHBr & 70 & 8 \quad 22 \\
(CH_3)_3CBr & - & - & - \\
\hline
\end{array}
\]

A. Rasmussen, M., and Hope, J.M., unpublished data.
B. Figures quoted in brackets are the results from the corresponding alkylation of 6-chloropurine anion.
C. Analysis of p.m.r. spectrum difficult, there may be some $N^7(N^3)$ isomer.
the adenide ion. These also showed an unexpected high amount of \( N^7(N^3) \) product but not nearly to the same degree as did the pivalate reaction. It was assumed that the presence of the carbonyl group again caused this enhancement but its different structural position diminished the effect.

More convincing proof that the previous interaction was hydrogen bonding is the absence of such an effect on the alkylation results of 6(4)-chloropurine\(^{12} \) (Table 16). On substituting the chloro for the amino group the \( N^7(N^3) \) preference markedly increased for benzyl chloride, marginally increased for both phenacyl chloride and tert-butyl chloroacetate but dramatically decreased for chloromethyl pivalate. The loss of ability for hydrogen bonding correlates with either a diminished increase or a decrease in \( N^7(N^3) \) alkylation only for alkylation agents containing carbonyl groups. Hydrogen bonding also occurs with \( N^6\)-acyladenines\(^{13} \) as will be discussed in the following section.

In the case of the 4-aminobenzimidazole anion, the enhancement of \( N^3 \) reaction with chloromethyl pivalate is less than that for the adenide ion but presumably can be explained in a similar manner.

The adenine results\(^{12} \) were thought to show a rough negative correlation between the amount of alkylation at \( N^7(N^3) \) and the degree of t.s. tightness imposed by the alkylation agent. This relationship however is distorted somewhat by the results of the carbonyl containing agents which showed hydrogen bonding and also by the unexpected absence of \( N^7(N^3) \) product in the reaction with benzyl chloromethyl ether. The relation is best illustrated by the gradual decrease of the \( N^7(N^3) \) product for the series 4-methoxybenzyl
chloride, benzyl chloride and 4-nitrobenzyl chloride. A similar gradation would be expected in the 4-aminobenzimidazole system but was not found. This could be partly due to the insensitivity of the p.m.r. analytical tool which was obstructed, in this system, by decomposed starting material.

The results obtained for the adenine anion\textsuperscript{12} are generally comparable with those found in the present work.

Theoretical Calculations

The M.E.P. calculations (Table 17) support the suggestion that the negative environment around $N^3$ is not as great as that around $N^1$. Further, since $q_{\text{tot.}}$ is slightly greater for $N^3$, the smaller negative field must be due to the adjacent amino protons. These not only reduce the electrostatic potential for the $N^3$ site but act as a positive barrier to attack there (Figure 20). Consequently, for

<table>
<thead>
<tr>
<th>Nucleophilic Atom</th>
<th>M.E.P. Minima (kcal/mole)</th>
<th>$q_{\text{tot.}}$</th>
<th>P.E. (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N^3$</td>
<td>-217.1</td>
<td>-7.396</td>
<td>-427.7</td>
</tr>
<tr>
<td>$N^1$</td>
<td>-223.6</td>
<td>-7.395</td>
<td>-432.9</td>
</tr>
</tbody>
</table>

reactions subject to electrostatic control, the $N^1$ site is preferentially alkylated.

The $q_{\text{tot.}}$ values show that the $N^3$ atom is very slightly favoured. However this bias is probably mainly due
Figure 20

The carbonyl group in the acetamide group is able to conjugate to the constituent nitrogen, thereby reducing the conjugation of the latter with the benzimidazole ring system. Consequently, the substituent would be expected to
to electrostatic attraction of negative charge by the nearby amino protons. Again the $q_{\text{tot.}}$ values have no bearing on the alkylation preferences in any of the anionic 4-amino-benzimidazole reactions.

As in previous systems, the alkylation preference indicated by the present P.E. calculations have a similar direction to but smaller magnitude than that of the M.E.P. calculations.

G. Alkylation of the 4-Acetamidobenzimidazole

Anion

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} \quad \text{N} \quad \text{H} \\
\text{C} \quad & \quad \text{N} \quad \text{H} \\
\text{O} & \quad \text{N} \quad \text{N}
\end{align*}
\]

4-Acetamidobenzimidazole (19) represents a perturbation of the previous compound in that the electron-donating ability of the substituent has been reduced and the steric hindrance to $N^3$ alkylation increased. To be able to ascertain the effect of these changes, it is necessary to determine the conformational structure of the reacting benzimidazole.

The carbonyl group in the acetamido group is able to conjugate to the constituent nitrogen, thereby reducing the conjugation of the latter with the benzimidazole ring system. Consequently, the substituent would be expected to
be roughly co-planar with the ring while also having the ability to rotate fairly readily. Even within these limits a number of conformations are still possible as shown in Figure 21. Conformers 21a and 21b would be expected to have the greatest stability because the positive amino proton is positioned adjacent to a negatively charged nitrogen, unlike the other conformers. This conclusion is supported by studies on the anion of N\textsuperscript{6}-acetyl adenine, where the corresponding conformers were also considered to be favoured. The investigation further suggested that conformer equivalent to 21a was the least preferred of the two since it contained an adverse electrostatic interaction between the carbonyl oxygen and the pyrimidine nitrogen in the adjacent position. It was considered that if a larger acyl group than the acetyl...
was used (e.g. pivaloyl), the latter preference would be reversed. In the present system there is no pyrimidine nitrogen and the acyl group is acetyl but structure 21a can be predicted to be the more stable from conformational studies on \(N^1\)-acetylbenzimidazole.\(^{22}\)

For nucleophilic attack on the imidazole nitrogens, the attachment of the acetyl group should not significantly change the steric requirements because the contribution of conformers 21c and 21d to the general molecular structure should be small. Also the acetyl carbonyl may induce a greater positive charge on the amino hydrogen and thereby diminish the negative environment around \(N^3\). Discrimination between the nucleophilic sites by through bond effects would be expected to be minimal as has been the case in previous systems.

While no alkylation studies were found on the precise compound of interest, some pertinent work was discovered on related systems. For instance the anion of 2,6-dimethyl-4-propionamidobenzimidazole has been alkylated\(^{21}\) with \(n\)-propyl bromide in dry tetrahydrofuran. No \(N^3\) compound was produced which is in keeping with the prediction made earlier. Extensive work\(^{13}\) has also been performed on the alkylation of the \(N^6\)-pivaloyladenine anion. The \(N^9(N^1)\) product was generally favoured and the details of these reactions will be considered in the following section in conjunction with the present results.

Alkylation Results

In this study it has become apparent that through space rather than through bond effects are the chief determinant
of alkylation preferences. Consequently, it would be expected that adenine compounds would react in a similar fashion to 4-aminobenzimidazole compounds. In the section on the 4-aminobenzimidazole anion this was generally found to be the case. The reaction results of the present compound (Table 18) should then be consistent with those produced for analogous reactions with the N^6-pivaloyladenine anion (Table 19).

The alkylation of the 4-acetamidobenzimidazole anion showed an expected strong preference for the N^1 product which exceeded that shown by the amino compound for comparable alkylating agents. However, the anticipated relationship between the present results and those of the N^6-pivaloyladenine anion only partly eventuated. One of the dissenting reactions was that with benzyl chloromethyl ether which showed that attack was equally preferred at both imidazole sites in the adenine derivative but strongly favoured N^1 alkylation in the 4-acetamidobenzimidazole. The former result is unexpected because in this electrostatic controlled reaction the weaker negative environment around N^7(N^3) should produce an alkylation preference at N^3(N^1). The incompatability of these reaction results in the two systems has led to a conformational explanation.

It was mentioned earlier that conformer 21a was considered to be the most stable structure for the anions of 4-acetamidobenzimidazole and N^6-pivaloyladenine. It was also considered that the amido group could fairly readily rotate out of plane with the fused ring system. Such an occurrence should be more likely for the adenine compound because in the favoured conformer, there is an adverse interaction between carbonyl oxygen and pyrimidine nitrogen.
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### Table 18

**Alkylation of the 4-Acetamidobenzimidazole Anion**

<table>
<thead>
<tr>
<th>Alkylation Agent</th>
<th>( N^1 ) Alkylation (%)</th>
<th>( N^3 ) Alkylation (%)</th>
<th>( N^4 ) Alkylation (%)</th>
<th>( N^1 : N^3 ) Ratio</th>
<th>( \delta \Delta G^\ddagger ) (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_6H_5CH_2OCH_2Cl )</td>
<td>89.5±3</td>
<td>10.5</td>
<td>-</td>
<td>8.52</td>
<td>1.30</td>
</tr>
<tr>
<td>( (CH_3)_3CCOCH_2Cl )</td>
<td>88.0±3</td>
<td>-</td>
<td>12.0</td>
<td>&gt;49</td>
<td>&gt;2.56</td>
</tr>
<tr>
<td></td>
<td>9.0±3</td>
<td>91.0</td>
<td>-</td>
<td>1:10.1</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>80.0±5</td>
<td>-</td>
<td>20.0</td>
<td>&gt;49</td>
<td>&gt;2.56</td>
</tr>
<tr>
<td>( C_6H_5CH_2Cl )</td>
<td>96.0±2</td>
<td>4.0</td>
<td>-</td>
<td>24</td>
<td>1.89</td>
</tr>
<tr>
<td>( C_6H_5COCH_2Cl )</td>
<td>90.0±3</td>
<td>10.0</td>
<td>-</td>
<td>9.0</td>
<td>1.31</td>
</tr>
</tbody>
</table>

A. The CH\(_2\) p.m.r. signal was used in all cases except for \( C_6H_5CH_2OCH_2Cl \) where CH\(_3\) was used.
B. Possibly alkylation of the acetamido nitrogen.
C. Reaction performed three times.

### Table 19

**Alkylation of the N\(^6\)-Pivaloyladenine Anion**

<table>
<thead>
<tr>
<th>Alkylation Agent</th>
<th>( N^9(H^1) ) Alkylation (%)</th>
<th>( N^7(H^3) ) Alkylation (%)</th>
<th>( N^9 : N^1 ) Ratio</th>
<th>( \delta \Delta G^\ddagger ) (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_6H_5CH_2OCH_2Cl )</td>
<td>52</td>
<td>48</td>
<td>1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>( (CH_3)_3CCOCH_2Cl )</td>
<td>&lt;2.5</td>
<td>&gt;97.5</td>
<td>1:40</td>
<td>-2.2</td>
</tr>
<tr>
<td>( C_6H_5CH_2Cl )</td>
<td>89.5</td>
<td>10.5</td>
<td>8.4</td>
<td>1.30</td>
</tr>
<tr>
<td>( C_6H_5CH_2Br )</td>
<td>90.5</td>
<td>9.5</td>
<td>9.2</td>
<td>1.35</td>
</tr>
<tr>
<td>( (CH_3)_3CCOCH_2Cl )</td>
<td>85</td>
<td>15</td>
<td>5.7</td>
<td>1.05</td>
</tr>
<tr>
<td>CH(_3)I</td>
<td>66</td>
<td>34</td>
<td>1.9</td>
<td>0.40</td>
</tr>
<tr>
<td>CH(_3)SO(_2)C_6H_4CH(_3)(4-)</td>
<td>67</td>
<td>33</td>
<td>2.0</td>
<td>0.43</td>
</tr>
<tr>
<td>( (CH_3)_3CCH_2CH_2Cl )</td>
<td>ca 93</td>
<td>ca 7</td>
<td>13</td>
<td>1.55</td>
</tr>
</tbody>
</table>

B. The sodium salt of the compound was dissolved in DMF and 10% excess of alkylation agent used. Mixture stirred at room temperature overnight.
It is thus possible that during the approach to $N^3$ of the benzyl chloromethyl ether molecule, the positive $C_\alpha$ therein may cause a rotation of the pivaloyl amido group out of plane. This would remove the positive hydrogen from the incoming alkylating agent and expose more of the electron lone pair to it, thereby enhancing the electrostatic preference for the $N^7(N^3)$ site. In this manner the $N^7(N^3)$ site may compete equally with that of $N^3(N^1)$ for alkylation. Infra-red studies\(^{13a}\) on $N^6$-pivaloyladenine have, importantly, shown that even the small methyl group, when acting as the $N-R$ substituent, is sufficient to move the amido group out of co-planarity with the ring.

In the reaction with chloromethyl pivalate another complication is introduced. This was also evident for the pivaloylmethylations of anionic 4-aminobenzimidazole and adenine\(^{12}\) where inordinate amounts of the $N^3/N^7$ products were formed. The effect was even more pronounced in the reaction with the $N^6$-pivaloyladenine anion (possibly because of the pivaloylamido rotation) and the cause in all three systems was suggested to be selective hydrogen bonding. The same reaction was performed three times on the 4-acetamido-benzimidazole anion and gave conflicting results. In two of the reactions a large amount of the $N^1$ product was obtained together with a portion of unidentified alkyl product presumed to result from attack on the acetamido nitrogen. In the remaining reaction the expected $N^3$ preference was realised. The unknown compound produced in this reaction was evident only by thin layer chromatography, as was the $N^3$ product in the other reactions. In each pivaloylmethylation reaction the yields indicated that the predominance of the main product
resulted from preferential formation rather than decomposition of alternate products. Consequently, selective product hydrolysis, which has been demonstrated in equivalent \( N^6 \)-pivaloyladenine products, must be eliminated as a possible explanation for the inconsistent results. Redistribution of the products via a dialkylation reaction is also unlikely because less than the required stoichiometric amount (by 5%) of alkylating agent was used in the reactions.

At present the diverse results obtained in the reactions with chloromethyl pivalate have not been adequately explained. The corresponding alkylation preference for this set of reactants is, therefore, uncertain. Although two of the three reactions predominantly yield the \( N^1 \) product, some credence should be given to the third which favours \( N^3 \) alkylation. This is because the results of the first two reactions not only disagree with those predicted but do not even follow the observed general trend in alkylation results.

It should be noted that in the reaction of chloromethyl pivalate with anionic 4-nitrobenzimidazole, inexplicably no \( N^3 \) product was formed.

The reaction with benzyl chloride should proceed by a t.s. intermediate in loose/tight character and, as expected, the results indicated a very strong preference for \( N^1 \) alkylation. An analogous result was obtained for the reaction of the \( N^6 \)-pivaloyladenine anion with the same alkylating agent which suggests that, in this case, rotation of the amido group no longer accommodates the reaction t.s. complex. This could be due, in part, to the lesser role played by electrostatic effects in the t.s. stabilisation. Also for such a t.s. structure the electron excess for the
adenine nucleus has been reduced and so the amido group will be more π-donating and less likely to be displaced from coplanarity with the ring.

In the phenacylation reaction, both systems again produce similar results, presumably for the reasons outlined above. The only irregularity associated with these results was the increased yield of the N³ compound compared to the benzylolation reaction. As steric effects should be greater in the relatively tight phenacylation t.s. structure, less N³ product would be expected to form. In the case of the N⁶-pivaloyladenine anion this result was explained in terms of a t.s. energy lowering, for N⁷(N³) alkylation, through hydrogen bonding between the amido hydrogen and the carbonyl group of the approaching alkylating agent. This explanation should be equally applicable to the 4-acetimidobenzimidazole system. It is noteworthy that the enhancement in N³ alkylation is less for the phenacylation than for the reaction with chloromethyl pivalate probably because of the differing placement of the carbonyl group in the alkylating agents.

Therefore the alkylation results in the 4-acetamido-benzimidazole system are generally in keeping with the present work performed on the amino compound and also with that reported on the N⁶-acyladenines.

H. Summary

In the 4-substitutedbenzimidazole system, a large number of alkylations have been performed. The results obtained have ranged from a marked preference for the N³ site to an even stronger specificity in favour of the N¹. The free energy variation for this range of results was ca 3 kcal/
mole with ca 2.5 kcal/mole corresponding to the greatest spread for any particular substituent. These free energy values are far larger than the comparable ones calculated for the 5-substitutedbenzimidazole system, ca 0.5 and 0.2 kcal/mole respectively. In the latter system, the substituent is remote from the nucleophilic sites and so their differentiation by through bond interaction is small. The same interaction operates in the 4-substitutedbenzimidazoles and may even be enhanced by the closer proximity of the substituent. However, this influence is obscured by the direct substituent interactions with the N³ site which dominate the alkylation preference. The substituent directly influences alkylation at N³ by electrostatic and steric means. Depending on its electronic nature the substituent may enhance or diminish the negative environment around N³ and thereby promote or deter alkylation at this site. The effect is most marked in reactions with loose t.s. structures where the electrostatic factor is dominant. M.E.P. calculations have been found successful in estimating the extent of substituent interaction with the N³ site and therefore, for the above reactions, in predicting the alkylation preference. In the 5-substitutedbenzimidazoles qtot. values were a little better than those of M.E.P. in making such predictions. However, in the 4-substitutedbenzimidazoles qtot. values appeared to be totally unrelated to the experimental results.

In reactions with tighter t.s. structures, non-bonded steric interactions may occur between a 4-substituent and an alkylation agent attacking the N³ position. This effect will always hinder the N³ site and together with the electrostatic preference will determine the alkylation ratio for the reaction. For the experiments described herein, the
electrostatic and steric alkylation preferences have often differed greatly in both direction and magnitude. In combination they have produced quite variable alkylation patterns.

Polarizability and charge transfer are the other effects which may influence alkylation preferences. The polarizability effect is thought to be inconsequential in both 5- and 4-substituted benzimidazoles. However, the charge transfer effect (believed to correlate positively with $q_{\text{tot}}$) is important in the 5-substituted compounds and is significant but usually masked by steric effects in the 4-substituted benzimidazoles.

Recently extensive investigation has been made into the use of H.O.M.O.($\pi$) coefficients as a predictive tool for reaction sites. In the benzimidazole system these calculations have proven to be completely unsatisfactory in predicting the direction of alkylation. Possibly this is because electrophilic attack is predominantly in the molecular plane rather than at an angle to it. If the direction of approach had a greater perpendicular component then the H.O.M.O.($\pi$) calculations should have been more applicable as they describe an effect on alkylation which is manifested in the perpendicular direction.

In this chapter a general correspondence has been shown to exist between the alkylation behaviour of the anionic 4-amino- and 4-acetamidobenzimidazoles and those of the alkylation patterns exhibited by anions of adenine and its $N^6$-pivaloyl derivative. As through space rather than through bond effects dictate alkylation patterns, this correlation is not unexpected. These systems also demonstrate
that substituent through space effects on $N^3/N^7$ alkylation are not confined to simple electrostatic and steric interactions. The substituent may hydrogen bond to the approaching alkylating agent or rotate to accommodate the agent's electrostatic or steric requirements.
Chapter 4. Conclusions

In this project, it was undertaken to explore and explain the alkylation processes in 4- and 5-substituted-benzimidazoles. The exploration has been systematic and the results obtained have generally been explained with the aid of various conceptual representations and theoretical methods.

As was suggested in the introduction the reactivity differences of the nucleophilic sites in 5-substituted-benzimidazoles are small since they arise from the through bond effects of a remote substituent. It was also found that the most electron rich site, as indicated by calculated $q_{\text{tot.}}$ values, was preferentially alkylated under most circumstances. This result contradicts the general theory for ambident nucleophiles$^{4,7}$ in which such an atom is considered to be the prime alkylation site in $S_{N1}$ like reactions but not so when the $S_{N2}$ character increases. The inconsistency is resolved on realising that the general theory is based on systems containing different types of atoms as nucleophilic sites whereas in benzimidazoles these atoms are of the same type. In fact, examples of both nucleophilic systems are combined in anionic 2-substituted-4-hydroxy-pyrimidine in which one oxygen atom and two distinctive nitrogen atoms may react. Moreover, the $S_{N2}$ alkylation pattern$^{9c}$ for this compound satisfies the requirements for both systems. The oxygen atom, which has the highest electron density, is least favoured for alkylation while the more electron rich of the two nitrogen atoms is most favoured.

In the 4-substituted-benzimidazoles direct effects of the substituent become superimposed on and dominate its
through bond effects. Previous alkylation studies\textsuperscript{11a,11d,12,13,14,21,22,48} on these and related compounds have indicated that the N\textsuperscript{3} site is always disfavoured because of direct steric interference by the 4-substituent. In the present study, this was frequently found not to be the situation, particularly for S\textsubscript{N}\textsuperscript{1} like reactions where electrostatic considerations are important.

In Chapter 1 the main factors predicted to dominate the alkylation preferences were electrostatic, polarizability and proximity interactions. These considerations are more diverse and their interrelationships better explored than is usually the case in studies\textsuperscript{4,7,8} of ambident nucleophilic alkylation patterns. In this system only the electrostatic factor and the steric aspect of the proximity effects were really evident and the results were explained mainly in these terms. The polarizability factor which is very prominent in general ambident nucleophile theory\textsuperscript{4,7} was not manifested at all. Presumably the difference is again related to the chemical identities of the nucleophilic atoms used in this system and those upon which the theory is based.

The importance of each selectivity factor was envisaged to depend on the reaction t.s. structure and, accordingly, attempts were made to vary this to test and exploit the relationship. The approach taken to this variation was to change the benzimidazole substituent and the alkylating agent used which were thought to alter the early/late and loose/tight character of the t.s. structure respectively. It was found that the early/late character was either not easily varied or had a minimal effect on alkylation patterns. The t.s. structure appeared, moreover, to be intermediate between the two extremes in this variable.
In contrast, the loose/tight composition of the t.s. structure proved to have a marked influence on alkylation results and the importance of various selectivity factors.

A number of theoretical calculations have been employed in this investigation to establish alkylation preferences under various circumstances. The M.E.P. calculations have been the most successful of these and, for reactions controlled by electrostatic effects, have consistently predicted the preferred alkylation sites. This device was particularly useful for the 4-substituted benzimidazoles and to a lesser extent for the 5-substituted compounds. Conventionally, \( q_{\text{tot}} \), or electron density values are used to predict the alkylation preferences in such reactions. Although the \( q_{\text{tot}} \) calculations were slightly better than M.E.P. at indicating preferences in the 5-substituted benzimidazoles, they were totally unsuitable in the 4-substituted case.

In reactions dominated by thermodynamic considerations calculated P.E. values were expected to describe reaction preferences. This expectation was realised in the 5-substituted benzimidazoles but substituent through space interactions made it inapplicable in the 4-substituted compounds.

The above concepts and calculations have greatly facilitated the interpretation of results in the present study, indicating that they are a good representation of the processes operating in alkylation reactions. As such, these techniques may be appropriate to similar ambident nucleophilic systems particularly since the general theory has been shown to be not universally applicable. Already some of the
concepts have been successfully applied to the adenine system\textsuperscript{12,13,14}. The approach is particularly useful in having the potential to predict alkylation preferences without prior experimental work. In this regard it has an advantage over the recently developed allopolarization system\textsuperscript{8} which requires some experimental data and is restricted with respect to reactant modifications. Thus it is possible that the present approach may be usefully employed in the study of ambident nucleophilic systems in general.
Chapter 5. Spectral Correlations

In this investigation proton magnetic resonance (p.m.r.) spectroscopy was used to determine the proportions of each product resulting from an alkylation reaction. However, for these values to be meaningful, the products must also be identified by this technique. The identification may be achieved by direct p.m.r. analysis or, after separation, by some other method of product characterisation, the results of which may subsequently be correlated with the p.m.r. spectrum. As p.m.r. was already an integral part of the study, this was preferred and was considered adequate to distinguish between isomers. If p.m.r. spectra of previously identified compounds are available, the process is of course facilitated. This is usually not the case and so the product spectrum itself must be analysed to obtain identification.

Note that the p.m.r. signals used for identification and those used for quantitative evaluation need not coincide. However, for a particular compound, the two may readily be related by their dependence on the proportion of that compound in the product mixture.

In this study the direction of the reaction was certain. Thus only the isomeric identity and not the exact identity of the reaction product needed to be determined.

A. 5-Substituted benzimidazoles

Approach to Identification

To assist in the identification process, some N alkylated products of interest were synthesised by unambiguous
methods. For such a compound to be of use, it is necessary that the products of the corresponding benzimidazole alkyl-
ination have distinguishable p.m.r. spectra. The possibility of this differentiation may be assessed by considering the features of a typical N-alkyl-5-substituted benzimidazole p.m.r. spectrum (Spectrum 1), together with the general structures of the two isomeric forms (Figure 22).

Ostensibly, the N-CH$_2$ signal has the greatest potential for identification since it appears as a singlet which is upfield from, and larger than, most of the other signals. However, despite this suitability of form, the chemical shift of the signal should not differ much between the two isomers. This is, in part, due to the weakness of the inductive effects reaching the two N-CH$_2$ groups from the substituent (X). Also, conjugative differences between the N-CH$_2$ groups are diminished by bridging through the C$^2$.

The C$^2$H signal also appears as a singlet but is smaller than that of the NCH$_2$ and is more likely to overlap with the benzene aromatic signals appearing just upfield from it. In either isomer, the location of the C$^2$H, relative to
P.m.r. Spectrum (DMSO-d$_6$) of
N'-Benzyl-5-Nitrobenzimidazole

$R = \text{Cl}_3\text{C}_6\text{H}_5$

Figure 22
the substituent is the same and, therefore, inductive effects should not change between isomers. However, conjugation between the substituent and C²H differs markedly between the two isomers (in N³ the conjugation is direct) and should be reflected in a significant C²H signal separation.

The C⁴H, C⁶H and C⁷H signals appear together in the benzene aromatic region of the p.m.r. spectrum. The C⁴H signal is a finely split doublet and thus will be more obvious than the C⁶H and C⁷H signals which appear as a doublet of doublets and a doublet respectively. Also, the C⁶H and C⁷H signals may be easily confused since one of the C⁶H doublets is only finely split.

The isomeric identity of the molecule should affect the p.m.r. chemical shifts of C⁴H and C⁷H mainly through the presence or absence of a pyridine-like nitrogen (N=) in the adjacent position. The influence of N= stems from the associated sp² hybridised lone pair of electrons which may cause deshielding⁴⁸,⁴⁹,⁵⁰ in the plane of the molecule. For example, since the C⁴ and C⁷ protons are in the molecular plane, their p.m.r. signals may be moved downfield by up to 0.3-0.4 ppm if the neighbouring nitrogen is pyridine-like. Other influences are not expected to change much between isomers.

The C⁶H should be most subject to inductive and conjugative differences from one isomer to the other. Hence, as for the N-CH₂ signals, the position of the C⁶H signal should not be significantly dependent on alkylation site.

Other structural variables in these compounds, apart from isomeric form, are the nature of the substituent and R groups. A change in one of these will result in a change in
the overall p.m.r. pattern of the compound. If the substituent is varied the effect will probably be different for each isomer. Thus, without reassessment of the system, the identification signals used for one substituent may not be applicable for another. In contrast, a change in the remote R group should affect the chemical shifts of equivalent protons in each isomer equally. Thus, if any alkylation products of a particular benzimidazole can be identified, the identification procedure may be extended to the products of that benzimidazole with other alkylation agents.

Hence, the usefulness of the p.m.r. spectrum of an identified compound may extend beyond the reaction with which it is associated. Not only could such a spectrum be employed as above, but it could also reliably indicate which factors cause signal chemical shift differences between isomers. Such information, may then be applied to related systems in which these factors are considered to be active. This principle has been extensively employed in the present study.

Identification

In this investigation N^1-benzyl-5-nitrobenzimidazole and N^1-benzyl-5-methoxybenzimidazole were synthesised and used to identify the products of the benzylations of 5-nitrobenzimidazole (Spectrum 2) and 5-methoxybenzimidazole. The p.m.r. signals discussed above were then used to identify the reaction products of the parent benzimidazoles with other alkylation agents. The N-CH_2 and C^2H signals were the most useful for this purpose.

The N-CH_2 signal for the isomeric products of 5-nitrobenzimidazole varied as predicted but was found to be
P.M.R. Spectrum (DMSO-d$_6$) of

$N^1$- and $N^3$-Benzyl-5-Nitrobenzimidazole

Spectrum 2
invariant for the products of 5-methoxybenzimidazole. The signal difference was suppressed in the 5-nitrobenzimidazole system when the p.m.r. solvent was changed from DMSO- $d^6$ to CDCl$_3$. Similar results were found by Vivarelli$^4$ in a CDCl$_3$ p.m.r. study involving the N-methyl products of 2-chloro-5(Cl-,NO$_2$-,CH$_3$-,OCH$_3$-)benzimidazoles.

The C$^2$H signal displayed the expected trends in all 5-substitutedbenzimidazoles investigated and, therefore, was principally employed for identifying isomeric products.

In an extension of his previous work, Vivarelli$^5$ found that the 5-substituent in benzimidazoles affected the C$^2$ position in the predicted manner. In this case, however, the effect was manifested in the rate of chlorine substitution in the 2 position rather than in the p.m.r. chemical shift of the C$^2$H signal. In other work$^2$ these signals showed the expected variation for the N-methyl products of 5-nitrobenzimidazole. Thus, the C$^2$H proton is more useful for p.m.r. identification than those of N-CH$_2$ and where the two methods overlapped their indication of product structures was in agreement.

In the present study of 5-substitutedbenzimidazoles, the C$^4$H and C$^7$H signals did not prove useful. This is because the p.m.r. effects of N= and N-alkyl, on the adjacent protons, do not markedly differ in the principal p.m.r. solvent, DMSO- $d^6$. However, the expected differentiation was displayed in CDCl$_3$, a solvent that was only used in a limited way. More extensive use of CDCl$_3$ was not made because many benzimidazole compounds are insoluble in this solvent. Furthermore, sufficient identification procedures had already been developed.

Despite the limited application of the C$^4$H and C$^7$H
signals in this part of the investigation their potential is still evident. For example, in CDCl$_3$ the position of these signals differed by approximately 0.4 ppm from one isomer to the other. The magnitude of this difference simplifies identification and enables much wider application of the method. Single alkylation products could also be identified by this means. Other signals, which rely solely on chemical shift data comparison between isomers for identification, are unlikely to identify a lone product.

The utility of these signals can be demonstrated by the successful identification of the isomeric N-alkyl-5-substitutedbenzimidazoles in the articles by Vivarelli$^{48}$ and Pappalardo$^{22}$ using p.m.r. data provided therein.

Thus the characteristic p.m.r. signals of the synthesised materials were also used to identify the other 5-substitutedbenzimidazole alkyl products formed in this investigation. The C$_2^H$ signal, and to a lesser extent the N-CH$_2$, were found to be the most useful in this regard.

B. 4-Substitutedbenzimidazoles

Approach to Identification

In the field of 4-substitutedbenzimidazoles some p.m.r. data was available on compounds of interest.

The work of Pappalardo$^{22}$ listed the p.m.r. values of the N$_1$-methyl- and N$_3$-(methyl-,ethyl-)-4-nitrobenzimidazoles.

Also of use were the chemical shift tabulations of N-methyl-2-chloro-4-(Cl-,NO$_2$-,CH$_3$-,OCH$_3$-)benzimidazoles and N-propyl-4-amino-2,6-dimethylbenzimidazoles by Vivarelli$^{48}$ and Lyle$^{21}$ respectively.

The most useful p.m.r. signals for identification
purposes in the present series of alkyl compounds are those of \( N-\text{CH}_2 \), \( C^2\text{H} \) and \( C^7\text{H} \). The nature of these and the other p.m.r. signals is shown in Spectrum 3, which is typical for an \( N \)-alkyl-4-substitutedbenzimidazole. Also, the dependency of the corresponding chemical shifts on isomeric identity may be assessed by considering the two isomeric structures (Figure 23).

![Figure 23](image)

In nearly all alkyl products the \( N-\text{CH}_2^* \) signal appears as a large singlet which is generally furthest upfield in this form, provided that its chemical shift varies sufficiently between isomers, it is the most convenient of the signals for identification. In this case, the differentiation should occur for the same reasons as for the \( N \)-alkyl-5-substitutedbenzimidazoles. It may, however, be accentuated due to the closer placement of the substituent. The steric, electrostatic and anisotropic influence of the substituent on the peri \( \text{CH}_2 \) (i.e. \( N^3-\text{CH}_2 \)) should also have a marked effect.

* This is true also for the \( N-\text{CH}_3 \) signal.
P.I.r. Spectrum (DCl) of N'-Pivaloyl-4-Nitrobenzimidazole

R = Cl₃CCl₃

Figure 23

Spectrum 3
The C₂H signal again appears as a smaller singlet downfield from most of the other signals. Its chemical shift differences between the two isomers should still depend on the directness of conjugation to the substituent.

The C⁵H, C⁶H and C⁷H signals resonate in the benzene aromatic region of the p.m.r. spectrum. They appear as doublet, doublet and triplet respectively. Only the C⁷H signal should be useful as it is subject to the full effects of changing the position of the saturated nitrogen.

The above information was used in conjunction with data from the literature to develop effective techniques for isomer identification.

**Identification**

The spectra of N¹ and N³-methyl-4-nitrobenzimidazole, reported in the literature, indicate that the N³-CH₂ signal is downfield of the N¹-CH₂. This result is expected due to the greater inductive and anisotropic effects of the nitro group on a peri CH₂. It has been used for identification in all the 4-nitrobenzimidazole alkylations where two products have formed (Spectrum 4). The same pattern of N-CH₂ signals is repeated with the alkylated 4-substitutedbenzimidazoles described in the articles of Vivarelli⁴⁸ and Lyle²¹. However, in some of these cases, inductive and anisotropic effects alone cannot explain the trend and, in fact, would sometimes indicate an opposite trend to that observed. Hence, some sort of interaction must occur between X and CH₂ which outweighs all other effects.

Jackman⁴⁹ reported that all types of substituents are capable of producing a p.m.r. deshielding effect on the
In addition, a study of the p.m.r. of diethylaminophenol explained the actual vibration of proteins in a given environment.

Methods usually had to be employed.

In the literature p.m.r. spectra of N'- and N-methyl-N'-terphenylazetidone the C'H signals were also
peri position. In addition, a study of the p.m.r. of dimethyl-naphthalenes explained the mutual deshielding of protons in perimethyls in terms of steric strain\textsuperscript{52}. The fact that steric strain is considerable is evident in the work of Vivarelli\textsuperscript{48} where it appeared that a methyl group has forced the peri NO\textsubscript{2} substituent out of the benzimidazole ring plane.

P.m.r. studies on the N\textsuperscript{7}- and N\textsuperscript{9}-alkyl products of adenine\textsuperscript{12} and its N\textsuperscript{6}-acyl derivatives\textsuperscript{13} also showed that the CH\textsubscript{2} group peri to the amino (or amido) substituent always had the downfield signal.

The appearance of this pattern in systems which are the same as or similar to the 4-substitutedbenzimidazoles has led to its adoption as the main identification method for the present compounds.

It was found that the N-CH\textsubscript{2} signals are usually well separated in DMSO-d\textsuperscript{6}. However, addition of CDCl\textsubscript{3}, or its use as the primary solvent, invariably increased separation. Thus the few reaction products where the N-CH\textsubscript{2} signals were inseparable or slightly reversed in DMSO-d\textsuperscript{6} displayed the conventional pattern in CDCl\textsubscript{3}. The exceptions to the rule in DMSO-d\textsuperscript{6} were the phenacil and 4-methoxybenzyl products of 4-nitrobenzimidazole, the phenacil products of 4-methoxy-benzimidazole and the phenacil, benzyloxymethyl and pivaloyl-methyl products of 4-acetamidobenzimidazole.

The great majority of reaction products were identified in this manner and, where possible, the results were verified. However, if only one product was formed the N-CH\textsubscript{2} method was unsatisfactory and other identification methods usually had to be employed.

In the literature p.m.r. spectra of N\textsuperscript{1}- and N\textsuperscript{3}-methyl-4-nitrobenzimidazole\textsuperscript{22} the C\textsuperscript{2}H signals were also
differentiated in the predicted direction. Consequently, the signal was used to identify other alkylation products of 4-nitrobenzimidazole, the results agreeing with those of the N-CH₃ approach. In addition, the C²H signal was used for identification in the 4-carboxybenzimidazole and 4-carboxymethylbenzimidazole systems which are structurally similar to 4-nitrobenzimidazole.

In DMSO-d⁶ the C²H signals of the other N-alkyl-4-substitutedbenzimidazoles were found to be invariant between the two isomers. Use of CDCl₃, however, produced the predicted separation in the alkyl products of 4-methoxybenzimidazole and enhanced the separation in those of 4-nitro-, 4-carboxy-, and 4-carboxymethylbenzimidazole. For the 4-methyl-, 4-amino- and 4-acetamidobenzimidazoles the isomeric C²H signals either did not differ or varied slightly and randomly in both solvents. Also, for these compounds, the product ratios were often disproportionate and hence it was difficult to find the minor product for assessment.

Comparing the differentiation of the C²H signal position in 4-substituted and 5-substitutedbenzimidazole compounds, it becomes apparent that the differences have been suppressed in the former. Although the effects were noticed the cause has not been ascertained. The effect of a 4-substituent on the C² position was discussed by Vivarelli with respect to the rate of 2-chloro substitution in the N-methyl isomers of 2-chloro-4-(NO₂-,CH₃-)benzimidazole. The electronic differentiation of the isomeric C² atoms was consistent with the p.m.r. results for the corresponding compounds in this investigation.

The C⁷H signal was not used extensively for
identification in this study due to difficulty encountered in observing it in the p.m.r. spectrum. The problem lies in the frequent obstruction of this signal by others and its small size in the case of the minor isomer.

In this section the $C^7H$ signal was used to verify some identifications made by other means and to identify the lone products of reactions.

The reaction products of the 4-nitrobenzimidazole system have received greatest attention regarding the $C^7H$ signal. Although the signal's chemical shift did not differ between isomers in DMSO-$d^6$, it did vary in the case of CDCl$_3$. In this solvent, the separation approached predicted levels because the $C^7H$ signal of the $N^1$ product moved dramatically upfield (by 0.19-0.45 ppm). The expected difference was also exhibited in the compounds studied by Lyle$^{21}$, Pappalardo$^{22}$ and Vivarelli$^{48}$. Thus a great range of 4(and 5)-substituted benzimidazoles are subject to this effect. However, for the movements of the $C^7H$ signal to act as a primary method of identification, the nature of the system to which it is applied must be considered.

Pappalardo$^{22}$ showed that the differentiation diminished in acetone-$d^6$, and, as corroborated by Vivarelli$^{48}$, very little differentiation occurred in trifluoroacetic acid.

A useful way of employing the $C^7H$ signal for identification purposes is to subtract its chemical shift from that of the $C^5H$. Since, in CDCl$_3$, the $C^5H$ signal remains fairly constant between isomers and the $C^7H$ signal varies markedly, the difference of the two should yield a useful quantitative parameter for isomeric characterisation. In addition this procedure reduces the requirement that two products be formed.
For the alkyl isomers of 4-nitrobenzimidazole, the chemical shift difference should be greater in the N1 compound than in the N3. This was found to be the case in CDC13 (Table 20) where the isomers are readily distinguishable. Also this approach allowed the lone product of 4-nitrobenzimidazole isopropylolation to be identified as the N1 isomer. The nature of the product from the pivaloylmethylation was still in doubt, however.

A related procedure was followed by Schulze and Letsch38 in identifying the N-alkyl isomers of 5-nitrobenzimidazole by p.m.r.

A refinement of the subtraction method, which allows more precise identification, involves subtracting the C5H/C7H signal separation in DMSO-d6 from that in CDC13 (Table 20). The values so obtained suggest that the product of pivaloylmethylation has a N1-alkyl structure. This is supported by N1-pivaloylmethyl-4-nitrobenzimidazole and N1-benzyloxymethyl-4-nitrobenzimidazole, compounds expected to be similar in this respect, having similar shift differences.

The procedure also identified the alkylation products of 4-carboxymethylbenzimidazole in the single case where the C5H and C7H signals were observable.

Another way of utilizing the C7H effect has been described by Pappalardo22. He identified the N1- and N3-methyl products of 4-nitrobenzimidazole by comparing the chemical shifts of their C7H signals with that of the parent benzimidazole. For the N1 product the C7H signal was found to move greatly upfield (by 0.38 ppm), while that of N3 showed no movement. The direction and magnitude of this shift relies on the tautomeric ratio in the parent material. The greatest
Table 20

Identification of 4-Nitrobenzimidazole Alkyl Products

| Isomer-Alkyl Group | \( |\delta \text{C}^5\text{H} - \delta \text{C}^7\text{H}| \) \( \text{A} \) (ppm) | (1) DMSO | (2) CDC\(_1\text{3}\) | (2)-(1) (ppm) |
|--------------------|---------------------------------|--------|---------|---------|
| \( \text{N}_1\)-CH\(_2\)OCH\(_2\)C\(_6\)H\(_5\) | 0.03 | 0.28 | 0.25 |
| \( \text{N}_1\)-CH\(_2\)4(CH\(_3\)O)C\(_6\)H\(_5\) | 0.00 | 0.38 | 0.38 |
| \( \text{N}_1\)-CH\(_2\)C\(_6\)H\(_5\) | 0.00 | 0.48 | 0.48 |
| \( \text{N}_1\)-CH\(_3\) | 0.10 | 0.41 | 0.31 |
| \( \text{N}_1\)-CH\(_2\)CH\(_3\) | 0.04 | - | - |
| \( \text{N}_3\)-CH\(_2\)OCH\(_2\)C\(_6\)H\(_5\) | 0.12 | 0.16 | 0.04 |
| \( \text{N}_3\)-CH\(_2\)4(CH\(_3\)O)C\(_6\)H\(_5\) | 0.24 | 0.23 | -0.01 |
| \( \text{N}_3\)-CH\(_2\)C\(_6\)H\(_5\) | 0.22 | 0.22 | 0.00 |
| \( \text{N}_3\)-CH\(_3\) | 0.09 | 0.03 | -0.06 |
| \( \text{N}_3\)-CH\(_2\)CH\(_3\) \( \text{B} \) | 0.13 | 0.07 | -0.06 |
| N-CH(CH\(_3\))\(_2\) | 0.10 | 0.39 | 0.29 |
| N-CH\(_2\)OCOC(CH\(_3\))\(_3\) | 0.07 | 0.26 | 0.19 |

A. The absolute difference is given since the identities of the \( \text{C}^5\text{H} \) and \( \text{C}^7\text{H} \) signals are not distinguishable at this stage.

B. Both literature\(^22\) (CDC\(_3\)) and experimental (DMSO-\(d^6\)) values.

shift should occur when the isomeric structure of the alkyl product was not the favoured tautomeric form.

The same paper showed that the method worked best in CDC\(_3\). Using this solvent, the 4-nitrobenzimidazole products in this investigation were similarly identifiable. This did not, however, include the products of the isopropyl-
ation and pivaloylmethylation reactions which require some modification to the procedure before they can be identified.

A major problem associated with Pappalardo's method (of identification) is that many parent benzimidazoles are not soluble in the preferred solvent, CDCl₃. In fact, 4-nitrobenzimidazole is not sufficiently soluble in CDCl₃, and Pappalardo²² found it necessary to estimate the chemical shift values using a computer procedure.

Another system in which the C⁷H signals were readily apparent was in the alkyl products of 4-aminobenzimidazole. In contrast to the alkylated 4-nitrobenzimidazoles, the C⁷H signals here were not properly differentiated in CDCl₃. However, in DMSO-d⁶ the difference in the C⁷H signals was both more pronounced and in the predicted direction. In this solvent, the values obtained by subtracting the chemical shifts for C⁷H from those for C⁵H readily identified the isomeric products. In reactions where two products were formed, identification by this method agreed with the assessment made using the N-CH₂ signals. Also, the lone products produced by reaction with the 4-methoxybenzyl and 4-nitrobenzyl chlorides were both found to be the result of attack on N¹.

In summary, nearly all of the N-alkyl-4-substituted-benzimidazoles studied here were identified using the N-CH₂ signal. Most remaining compounds were identified using the C²H and C⁷H signals and where the methods overlapped, the N-CH₂ results were verified. However, in the 4-carboxybenzimidazole and 4-acetamidobenzimidazole systems, alternate means of identification and/or verification were necessary.

In this investigation, 4-carboxybenzimidazole
yielded only one product when benzylated or benzyloxymethylated. The phenacylation reaction was unsuccessful. The lone products were both initially identified as the N\textsuperscript{1} isomer by p.m.r. comparison with the products of the corresponding 4-carboxymethylbenzimidazole alkylations. Verification was then obtained by hydrolysing the product mixture of the 4-carboxymethylbenzimidazole benzylaion to the equivalent 4-carboxy compounds. Before hydrolysis the ester products had been identified by various means. This identification could also be applied to the hydrolysis products due to the constant quantitative ratio maintained between the two isomers. In addition, the benzylated 4-carboxybenzimidazole compounds produced were, themselves, identifiable using the relative positions of the N-CH\textsubscript{2} signals.

In the alkylation of 4-acetamidobenzimidazole the product ratios, in each case, were greatly disproportionate. The existence of the minor isomer was consequently doubtful. In the pivaloylmethylation the nature of the products varied between reactions. In order to clarify both situations, an attempt was made to separate the reaction products by thin layer chromatography (t.l.c.). In every reaction two species were present and ultraviolet spectra were obtained on each. With the exception of one of the pivaloylmethyl products, the compounds were readily separable into two groups based on ultraviolet and t.l.c. character. A p.m.r. spectrum was obtained on each compound and, using the N-CH\textsubscript{2} signals, it was clear that the groups corresponded to the N\textsuperscript{1} and N\textsuperscript{3} products. In this way, excluding two of the three pivaloylmethylations, every reaction was proven to yield both the N\textsuperscript{1} and N\textsuperscript{3} compounds. In the exceptions, the N\textsuperscript{3} product was
replaced by another, possibly resulting from alkylation on the acetamido nitrogen.

Some ultraviolet spectra for members of the above isomeric groupings are shown in Spectra 5, 6, 7 and 8. Characteristic features of each isomer are displayed under both neutral and acidic conditions. These readily allow differentiation between the N¹ and N³ products.

The alkyl products from other benzimidazole systems (4-nitro- and 4-amino-) were also separated and their ultraviolet spectra obtained. However, in these cases no feature was found to be characteristic of each isomer.

Therefore, all of the products were identified either by direct or indirect means and often the results of one procedure were verified by another. These identifications were considered reliable. As such, they may be confidently used to aid the interpretation of benzimidazole alkylation patterns.
UV. Spectrum of
N\textsuperscript{1}-Pivaloyl-1,4-Acetanilidobenzimidazole

1. Neutral
2. Acid
Standard 279.4

Spectrum 5

UV. Spectrum of
N\textsuperscript{3}-Pivaloyl-4-Acetanilidobenzimidazole

1. Neutral
2. Acid
Standard 279.4

Spectrum 6
## Experimental

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1. Instruments, Services and Techniques

Ultraviolet spectra were recorded on a Unicam SP800 ultraviolet spectrophotometer using 95% aqueous ethanol as solvent. For spectra of protonated species 2 drops of 1M HCl were added to the solution (yielding pH ca 1).

Proton magnetic resonance spectra were recorded at 60 MHz on a JEOLCO-MH 100 MINIMAR spectrophotometer and chemical shifts were measured on the δ scale relative to tetramethylsilane as an internal standard.

Mass spectra were determined on a Varian-Mat CH7 spectrometer.

Qualitative and preparative thin layer chromatography was carried out on plates using aluminium oxide 60F254 (Type E) and silica gel 60F254 as adsorbents.

Microanalysis was performed by the Australian National University Microanalytical Service.

Melting points were obtained on an Electrothermal melting point apparatus and are corrected.

For convenience the following abbreviations are used throughout the experimental section: - b.p., boiling point; bs, broad singlet; CDCl₃, deuterochloroform; cm, complex multiplet; d, doublet; d of d, doublet of doublets; DMSO-d₆, deuterated dimethyl sulphoxide; DMF, N,N-dimethylformamide; J, coupling constant (in Hz); lit., literature; m, multiplet; M⁺, molecular ion; m.p., melting point; p.m.r., proton magnetic resonance; q, quartet; s, singlet; sh, shoulder; t, triplet; t.l.c., thin layer chromatography; u.v., ultraviolet; and vbs, very broad singlet.

Note that for the p.m.r. data of alkylation products only the signals used for quantitative analysis are given
integration values. Although not measured, the expected proportions were visually evident for the remaining signals.

With regard to u.v. spectra a qualitative method has been adopted to demonstrate changes in peak size on addition of acid. Following the specified peak wavelength any one of the following can appear; (+), (++), (-) or (---). These indicate whether the peak has increased, greatly increased, decreased or greatly decreased, respectively, on addition of acid.

2. Preparation and Purification of Reaction Materials

A. Alkylating agents

Benzyl chloride - obtained commercially and distilled before use (b.p. 75°/19 mm Hg).

Phenacyl chloride - obtained commercially and recrystallized from ethanol prior to use.

Chloromethyl methyl ether - obtained commercially and used without further purification.

Benzyl chloromethyl ether - prepared from benzyl alcohol, formamide and HCl gas using a literature procedure. It was found impossible to exclude the contaminant, benzyl chloride. Consequently, the final working material contained an 8% impurity. The agent was stored at 0°C and checked by p.m.r. regularly.

4-Methoxybenzyl chloride - prepared by Allen Beasley by the following method:

"11M hydrochloric acid (17 ml) was added dropwise to a stirred suspension of powdered paraformaldehyde (6.25 gm,
0.20 mol.) in anisole (20 ml, 0.18 mol.). The temperature of this mixture was maintained below 0° (ice-salt bath) during the addition of hydrochloric acid. To this solution hydrogen chloride gas was slowly bubbled in at a rate which maintained the temperature of the mixture below 2°. After 6.5 hours the translucent mixture was filtered. The upper organic phase was collected and dried over CaCl₂ for ca 1 hour. The solution was filtered and the filtrate was stirred under high vacuum to remove last traces of hydrochloric acid. Distillation under reduced pressure gave a fraction with b.p. 72°/2 mm Hg; p.m.r. (CDCl₃): δ 6.72, 6.82, 7.15, 7.24 (4H, s, Ph); 4.58, 4.46 (2H, s, CH₂, ortho and para isomers; 80% para and 20% ortho), 3.75, 3.69 (2H, s, ortho and para). Fractional distillation failed to separate these two isomers." This material was used for alkylation as was another batch (ortho free), prepared later by Allen Beasley using the same procedure.

4-Nitrobenzyl chloride - obtained commercially and recrystallised from ethanol prior to use.

Chloromethyl pivalate - provided by Malcolm Rasmussen from a stock made using a literature procedure and distilled before use. P.m.r. (CDCl₃): δ 1.26 (9H, s, C(CH₃)₃) and 5.71 (2H, s, CH₂).

Methyl iodide - obtained commercially and distilled before use (39° at room pressure).

Ethyl bromide - the commercial product was washed, initially, with conc. sulphuric acid and subsequently with a 10% Na₂CO₃ solution followed by water. The resultant material was dried (MgSO₄) and distilled at 35°.

Isopropyl bromide - the commercial product was
purified by washing with conc. sulphuric acid followed by washing with conc. sulphuric acid followed by washings with 10% NaHSO₄, 10% Na₂CO₃ and finally with water. The agent was dried (Na₂SO₄) and then distilled at 58°.

tert-Butyl bromide - obtained commercially. Purified as for isopropyl bromide and distilled at 71°.

B. Solvents

N,N-Dimethylformamide - dried by stirring over P₂O₅ for 2 hours. The solution was decanted off and then distilled (52°/22 mm Hg). DMF was stored in the dark over molecular sieve (4 Å).

Methanol - refluxed over CaH₂ and then distilled (62°).

Ethanol - refluxed over CaH₂ and then distilled (75°).

1,4-Dioxane - distilled (98°) over NaH and stored in the dark.

Acetonitrile - refluxed over P₂O₅ and then distilled (79°).

Hexamethylphosphoramide - refluxed over CaH₂ and then distilled (80°/0.35 mm Hg).

Formamide - purified by passing ammonia through the solution until a slight alkaline reaction was obtained. The ammonium formate formed was then precipitated by addition of acetone and filtered off. The filtrate was dried (MgSO₄) and distilled (105°/11 mm Hg).

Tetrahydrofurane - refluxed over NaH and then distilled (65°).
C. Base

Sodium hydride was used to generate the benzimidazole anion. A commercial preparation of NaH dispersion in oil was used. The actual % of NaH was determined by dissolution of a given amount in a hexane/water two phase solution. Phenolphthalein was added and the solution titrated against standard 0.1M HCl until end point was reached. The content of NaH proved to be 57.5% by weight.

3. General Alkylation and Analysis Procedure

A. Alkylation

The relevant benzimidazole was dissolved in DMF (unless another solvent is specified) resulting in a 0.05 molar solution (0.5-1 mM of compound was used in 10-20 ml DMF). The solution was stirred in a stoppered and jacketed conical flask kept at 30±0.1° by the use of a constant temperature pump. Following dissolution of the benzimidazole, 1.05 equivalents of NaH in oil dispersion were added and the ensuing reaction allowed to go to completion.

After completion 1.05 equivalents of alkylating agent were added (from a microsyringe in the case of a liquid). Part way through the project the reaction amount of the agent was altered to 0.95 equivalents to ensure that dialkylation did not occur.

The resulting solution was stirred overnight and the product recovered the following day.

B. Isolation of Products

The reaction solution was mixed with toluene and the resulting combination of solvents removed by vacuum rotary
evaporation on a waterbath. Further additions of toluene were sometimes used to ensure that there was no residual DMF. The resulting oily solid was dissolved in CH$_2$Cl$_2$ (later changed to CHCl$_3$, the p.m.r. of which is less obstructive) and extracted 4 times with sat. Na$_2$CO$_3$ solution (pH ca 11) to remove starting material. The CH$_2$Cl$_2$ solution was then dried overnight using Na$_2$SO$_4$, which was removed by filtration the following morning. The solid residue was washed with CH$_2$Cl$_2$ and the washings added to the filtrate. The resulting liquid was then reduced to a more convenient volume and divided into 2 or 3 portions. One fraction was stored at 0° and the others used for p.m.r. analysis after solvent removal. The aqueous washings were also checked by p.m.r. for the presence of products.

C. Analysis of Results

P.m.r. spectra were obtained with the product dissolved in DMSO-d$_6$ and/or CDCl$_3$ (ca 0.5 ml). The most suitable resonance signal for ascertaining the relative isomeric proportions was then sought. This was usually found to be the methylene (or methyl), of the attached alkyl group, immediately adjacent to the alkylated nitrogen.

If the resonance signals of the two isomers were sufficiently separated the spectrum was expanded 10 fold and 4 sweeps of this region were recorded, care being taken that no saturation occurred. The expanded spectrum traces were then photocopied and individual resonances cut out and weighed with all handling being done with gloves. The weights allowed the relative proportion of isomers present to be determined and these were then converted into percentages of the total...
N alkylated material obtained. At this stage the percentages obtained for the 4 runs were averaged for each isomer and have been presented in this form after rounding off to the nearest 0.5%.

When the resonance signals of interest were not sufficiently separated another convenient signal was used, e.g. that of $\text{C}_2\text{H}_4$, or improved separation was attempted either by using a different p.m.r. solvent (CDC$_1$$_3$, or D$_6$DMSO) or by solvent mixing. For the latter, portions of CDC$_1$$_3$ were added if the solvent was D$_6$DMSO (or vice versa) until sufficient separation was achieved (if at all).

When the analytical signals overlapped, an estimate of the midpoint was made and this was used to define a cutting line.

Errors were gauged for all of the final calculated values quoted. These were attributable to the following 3 sources:

(a) possible error introduced when defining the boundary line between overlapping resonance signals;
(b) error arising from the lack of reproducibility of alkylations as seen by the final answer in each case;
(c) error due to inability to reproduce the same values from the 4 cuttings.

In the first case an upper and lower limit for the position of the boundary line were defined and differences between these and that chosen were assessed.

The magnitude of the second error was estimated by repeating a number of reactions and noting the differences between final determined answers. The maximum difference was then applied to all alkylations as the error for reaction reproducibility.
Finally the errors in cutting reproducibility were taken as the difference between the average percentage and the upper and lower extremes of the 4 runs.

The 3 errors were incorporated by simple addition and appear as a % of the total N alkylation product. Values vary from ±2% to ±6% and are quoted for each isomer. Where fractions were involved the errors were usually rounded up to the nearest 1%. Work in a related field\textsuperscript{13a} suggests that ±5% is a good estimate of errors involved.

As well as the alkylation of the substituted benzimidazole anion there are two other types of alkylations which can be mentioned.

The first is the alkylation of the substituted benzimidazole itself. The reaction and isolation procedures are identical with that for the anion except that no NaH is added.

The second involves the realkylation of the alkylated products. This is undertaken at high temperatures in order to create a pathway for the interconversion of the 2 isomers. For consistency only benzylated products and benzyl chloride were involved.

The general procedure was to first dissolve the benzyl isomers in a small quantity of DMF (producing 0.15-0.20 molar concentrations) and then to add ca 0.3 equivalents of benzyl chloride. The mixture was heated to ca 120\textdegree and at certain times aliquots of the mixture were removed. The DMF was co-distilled off with toluene and the pmr spectra of these samples were obtained without further purification. The proportions of the alkylated isomers were assessed by the methods described above.

In the following sections when p.m.r. assignments
are made for the signals of the unreacted 4-substituted-benzimidazoles there is a degree of uncertainty involved. The doublets representing the C^5 and C^7 protons are positively assignable only if the predominant tautomer is known. Hence it was estimated which of N^1 and N^3 tautomers was favoured for each 4-substituted benzimidazole and the doublets assigned accordingly. The estimation was based on both the characteristics of the unalkylated compound and the pattern arising from alkylation.

4. Alkylation of 5-Substituted Benzimidazoles

A. 5-Nitrobenzimidazole

Preparation

Originally synthesised by a student preparation following a literature procedure^55. The material was found to consist of the 4- and 5-nitrobenzimidazole which were separated by column chromatography on alumina (1000 g) with CHCl_3 as elutant. The first fraction obtained was 4-nitrobenzimidazole (1.23 g) followed by 5-nitrobenzimidazole (8.4 g). The 5-nitrobenzimidazole was recrystallised from water to give 7.7 g of fine yellow needles, m.p. 207-8° (lit. 204-5°)

(Found: C, 51.57; H, 3.57; N, 26.33. C_7H_5N_3O_2 requires C, 51.53; H, 3.09; N, 25.76%). P.m.r. (DMSO-d_6): δ 7.82 (1H, d, J 9 Hz, C_7H), 8.18 (1H, d of d, J 9 & 2 Hz, C_6H), 8.58 (1H, d, J 2 Hz), 8.64 (1H, s, C_2H) and 13.02 (1H, vbs, NH). Mass spectrum: m/e 163(M^+ , 100%), 133(13), 117(53), 105(11), 90(40) and 63(24).
Alkylation of 5-Nitrobenzimidazole Anion with Chloromethyl Methyl Ether

Sodium hydride (0.0439 g, 1.05 mM) was added to a stirred solution of 5-nitrobenzimidazole (0.163 g, 1.00 mM) in DMF (20 ml). Upon completion of H₂ evolution the solution was stirred for a further 0.5 hr before chloromethyl methyl ether (0.080 ml, 1.05 mM) was added. After stirring overnight at 30° the solid product was isolated and p.m.r. (DMSO-d⁶) analysis showed broadened signals but those of the methylene indicated 2 isomeric products to be present. The same signals determined the product proportions to be 54.0±3% N¹ and 46.0% N³.

P.m.r. (DMSO-d⁶): δ 3.29 (s, CH₃[N¹ & N³]), 5.79 (2.16H, s, CH₂[N¹]) and 5.85 (1.84H, s, CH₂[N³]).

Alkylation of 5-Nitrobenzimidazole Anion with Benzyl Chloride

The standard alkylation and isolation procedure was followed. P.m.r. (DMSO-d⁶) analysis showed two products to be present and the methylene signal indicated their proportions to be 54.0±2% N¹ and 46.0% N³. The C²H signal showed 56.0±4% N¹ and 44.0% N³.

P.m.r. (DMSO-d⁶): δ 5.67 (2.16H, s, CH₂[N¹]), 5.74 (1.84H, s, CH₂[N³]), 7.24 (s, C₆H₅[N¹]), 7.42 (s, C₆H₅[N³]), 7.85 (d, J 9 Hz, C⁷H[N¹]), 7.94 (d, J 9 Hz, C⁷H[N³]), 8.18 (d of d, J 9 & 2 Hz, C⁶H[N¹]), 8.22 (d of d, J 9 & 2 Hz, C⁶H[N³]), 8.65 (s, C⁴H[N¹ & N³]), 8.83 (2.24H, s, C²H[N¹]) and 8.88 (1.76H, s, C²H[N³]).

P.m.r. (CDCl₃): δ 5.47 (s, CH₂[N³]), 5.49 (s, CH₂[N¹]), 7.21-42 (cm, [C₆H₅ & C⁶H][N¹ & N³]), 7.42 (d, J 9 Hz, C⁷H[N¹]), 7.92 (d, J 9 Hz, C⁷H[N³]), 8.21 (s, C²H[N¹]), 8.26
(s, C²H[N³]), 8.34 (d, J 2 Hz, C⁴H[N³]) and 8.77 (d, J 2 Hz, C⁴H[N¹]).

The reaction was repeated and gave 56.0±2% N¹ and 44.0% N³. The two sets of results were averaged to give 55.0±3% N¹ and 45.0% N³.

Preparation of N¹-Benzyl-5-Nitrobenzimidazole

The conversion of 2,4-dinitrochlorobenzene (39.3 g) to 2-amino-1-benzylamino-4-nitrobenzene (13.0 g, 28%) was performed using a literature method⁵⁶. Cyclization with formic acid⁵⁷ then gave N¹-benzyl-5-nitrobenzimidazole (4.3 g, 32%). Recrystallisation from methanol gave yellow needles, m.p. 155° (lit. ¹⁵³°) (Found: C, 64.12; H, 4.42; N, 16.25. C₁₄H₁₁N₃O₂ requires C, 66.39; H, 4.38; N, 16.60%). P.m.r. (DMSO-d⁶): δ 5.68 (2H, s, CH₂), 7.42 (5H, s, C₆H₅), 7.84 (1H, d, J 9 Hz, C⁷H), 8.21 (1H, d of d, J 9 & 2 Hz, C⁶H), 8.63 (1H, d, J 2 Hz, C⁴H) and 8.83 (1H, s, C²H); P.m.r. (CDCl₃): δ 5.50 (2H, s, CH₂), 8.23 (1H, s, C²H), 8.25 (1H, d of d, J 9 & 2 Hz, C⁶H) and 8.80 (1H, d, J 9 Hz, C⁴H). Mass spectrum: m/e 253 (M⁺, 44%) and 91(100).

Alkylation of 5-Nitrobenzimidazole Anion with Phenacyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d⁶) of the isolated material showed the presence of 2 isomeric products. The proportion of each was determined to be 55.0±3% N¹ and 45.0% N³ using the methylene signals.

P.m.r. (DMSO-d⁶): δ 6.24 (2.20H, s, CH₂[N¹]), 6.29 (1.80H, s, CH₂[N³]), 7.68-80 (cm, [C₆H₅ & C⁶H][N¹ & N³]), 7.90 (d, J 9 Hz, C⁷H[N¹]), 7.96 (d, J 9 Hz, C⁷H[N³]), 8.58 (s, C²H[N¹]), 8.63 (s, C²H[N³]), 8.68 (d, J 2 Hz, C⁴H[N¹]) and
8.87 (d, $J$ 2 Hz, $C^4H[N^3]$).

Relative Thermodynamic Stabilities of $N^1$- and $N^3$-Benzyl-5-Nitrobenzimidazoles

To determine the relative thermodynamic stabilities of the 2 benzylated products of 5-nitrobenzimidazole an attempt was made to establish equilibrium between them. This was done by separately realkylation of both isomers at high temperatures.

Separation of the $N^1$ and $N^3$ isomers was achieved by silica gel/benzene t.l.c. using continuous development over 6-7 hrs.

To solutions of each isomer (0.220 g, 0.87 mM) in DMF (6 ml) was added benzyl chloride (0.110 ml, 0.96 mM) and each solution was heated at 120°. At intervals four aliquots (1.5 ml) were removed from each and p.m.r. spectra were obtained after solvent removal. The results appear in Table 21.

| Table 21 |
| Reversible Dibenzylation of $N^1$- and $N^3$-Benzyl-5-Nitrobenzimidazoles |

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (hrs)</th>
<th>$N^1$ Starting Material</th>
<th>$N^3$ Starting Material</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$N^1$ (%)</td>
<td>$N^3$ (%)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>56.5</td>
<td>$80.0\pm4$</td>
<td>$20.0$</td>
</tr>
<tr>
<td>2</td>
<td>168</td>
<td>$64.5\pm4$</td>
<td>$35.5$</td>
</tr>
<tr>
<td>3</td>
<td>336</td>
<td>$63.0\pm4$</td>
<td>$37.0$</td>
</tr>
<tr>
<td>4</td>
<td>504</td>
<td>$61.5\pm4$</td>
<td>$38.5$</td>
</tr>
</tbody>
</table>

A. Figures calculated for 30° using the equation $N^1/N^3 = e^{-\frac{\Delta G}{RT}}$
The p.m.r. spectra became increasingly broadened with time and in the 4th sample taken from the N³ starting material product analysis was not possible. The monobenzyl compounds were found to constitute ca 80% of the material present, the remainder being the dibenzyl species.

From the above results the equilibrium proportions of the alkyl isomers were estimated to be 62.0±4% N¹ and 38.0% N³ for results extrapolated to 30°.

Alkylation of 5-Nitrobenzimidazole with Benzyl Chloride

The alkylation and isolation procedure was standard except for the omission of sodium hydride and the adoption of a 7 day reaction period. The p.m.r. spectrum (DMSO-d⁶) of the isolated material showed only the two isomeric products to be present in small amounts. Evidently little reaction had occurred but the starting material had been removed in the isolation procedure. The isomeric products were determined to be 42.5±4% N¹ and 57.5% N³ using the methylene signals.

Alkylation of 5-Nitrobenzimidazole Anion with Benzyl Chloride in Hexamethylphosphoramide

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d⁶) of the isolated material showed the 2 isomeric products to be present. The proportions of these were found to be 56.0±3% N¹ and 44.0% N³ based on the methylene signals. The C²H signals suggested a composition of 55.5±5% N¹ and 44.5% N³.

Alkylation of 5-Nitrobenzimidazole Anion with Benzyl Chloride in Acetonitrile

The standard alkylation and isolation procedure was followed, although the sodium salt was not completely
soluble in acetonitrile. The p.m.r. spectrum (DMSO-d<sub>6</sub>) of
the isolated material showed it to consist of ca 50% starting
compound and ca 50% alkylated product. The latter was
determined to be 56.0±3% N<sup>1</sup> and 44.0% N<sup>3</sup> using the methylene
signals.

**Alkylation of 5-Nitrobenzimidazole Anion with Benzyl Chloride in Ethanol**

The standard alkylation and isolation procedure was
followed. The p.m.r. spectrum (DMSO-d<sub>6</sub>) of the isolated
material showed it to consist of ca 80% starting compound and
ca 20% alkylated products. The latter consisted of 59.0±3% N<sup>1</sup>
and 41.0% N<sup>3</sup> based on the methylene signals.

**Alkylation of 5-Nitrobenzimidazole Anion with Benzyl Chloride in Methanol**

The standard alkylation and isolation procedure was
followed using methanol as solvent. The p.m.r. spectrum
(DMSO-d<sub>6</sub>) showed that little reaction had occurred and that
the isolated material consisted of ca 90% 5-nitrobenzimidazole
and only ca 10% alkylated products. The latter were found to
consist of 55.5±3% N<sup>1</sup> and 44.5% N<sup>3</sup> using the methylene signals.

**Alkylation of 5-Nitrobenzimidazole Anion with Benzyl Chloride in Formamide**

The standard alkylation and isolation procedure was
followed. The p.m.r. spectrum (DMSO-d<sub>6</sub>) of the isolated
product showed it to consist of ca 50% 5-nitrobenzimidazole
and ca 50% alkylated products. The latter were determined to be
43.5±3% N<sup>1</sup> and 56.5±3% N<sup>3</sup> using the methylene signals. The C<sup>2</sup>H
signals showed 44.5±4% N<sup>1</sup> and 55.5% N<sup>3</sup>.
B. 5-Methoxybenzimidazole

Preparation

A literature procedure\(^{59}\) gave 3,4-diaminoanisole in 67% yield from 3-nitro-4-aminoanisole. This intermediate was cyclised using formic acid\(^{57}\) to give the desired product (93%) which was recrystallised from water as white crystals, m.p. 124° (lit.\(^{17}\) 123°) (Found: C, 65.03; H, 5.52; N, 18.99. \(\text{C}_9\text{H}_8\text{N}_2\text{O}\) requires C, 64.87; H, 5.44; N, 18.91%). P.m.r. (DMSO-d\(^6\)): \(\delta 3.84\) (3H, s, \(\text{CH}_3\)), \(6.92\) (1H, d of d, \(J 9 \& 2\) Hz, \(\text{C}^6\text{H}\)), \(7.19\) (1H, d, \(J 2\) Hz, \(\text{C}^4\text{H}\)), \(7.58\) (1H, d, \(J 9\) Hz, \(\text{C}^7\text{H}\)), \(8.23\) (1H, s, \(\text{C}^2\text{H}\)) and \(12.42\) (1H, vbs, \(\text{N}^3\text{H}\)); P.m.r. (CDCl\(_3\)): \(\delta 3.87\) (1H, s, \(\text{CH}_3\)), \(7.02\) (1H, d of d, \(J 9 \& 2\) Hz, \(\text{C}^6\text{H}\)), \(7.18\) (1H, d, \(J 2\) Hz, \(\text{C}^4\text{H}\)), \(7.63\) (1H, d, \(J 9\) Hz, \(\text{C}^7\text{H}\)), \(8.18\) (1H, s, \(\text{C}^2\text{H}\)) and \(11.27\) (1H, bs, \(\text{N}^3\text{H}\)). Mass spectrum: \(m/e 148(M^+\cdot, 100\%), 133(79)\) and \(104(43)\).

Alkylation of 5-Methoxybenzimidazole Anion with Chloromethyl Methyl Ether

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d\(^6\)) of the isolated material showed the 2 isomeric products to be present. The latter were resolved into 48.0±3% \(\text{N}^1\) and 52.0% \(\text{N}^3\) using the signals of the benzimidazole methoxy methyl since those of the methylene were inseparable. The \(\text{C}^2\text{H}\) signals showed 49.0±4% \(\text{N}^1\) and 51.0% \(\text{N}^3\).

P.m.r. (DMSO-d\(^6\)): \(\delta 3.24\) (s, \(\text{CH}_2\text{OCH}_3[\text{N}^1]\)), \(3.26\) (s, \(\text{CH}_2\text{OCH}_3[\text{N}^3]\)), \(3.84\) (2.88H, s, \(\text{CH}_3[\text{N}^1]\)), \(3.86\) (3.12H, s, \(\text{CH}_3[\text{N}^3]\)), \(5.65\) (s, \(\text{CH}_2[\text{N}^1 \& \text{N}^3]\)), \(6.96\) (d of d, \(J 9 \& 2\) Hz, \(\text{C}^6\text{H}[\text{N}^1]\)), \(7.02\) (d of d, \(J 9 \& 2\) Hz, \(\text{C}^6\text{H}[\text{N}^3]\)), \(ca 7.29\) (d, \(J 2\) Hz, \(\text{C}^4\text{H}[\text{N}^1 \& \text{N}^3]\)), \(7.61\) (d, \(J 9\) Hz, \(\text{C}^7\text{H}[\text{N}^1]\)), \(7.65\) (d,
\( J \) 9 Hz, \( C^7 H[N^3] \), 8.32 (1.02H, s, \( C^2 H[N^3] \)) and 8.39 (0.98H, s, \( C^2 H[N^1] \)).

Alkylation of 5-Methoxybenzimidazole Anion with Benzyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-\( d^6 \)) of the isolated material showed the 2 isomeric products to be present. The latter were resolved into 46.0±3% \( N^1 \) and 54.0% \( N^3 \) using the \( C^2 H \) signals since those of the methylene were inseparable.

P.m.r. (DMSO-\( d^6 \)): \( \delta \) 3.81 (s, \( CH_3[N^1 \& N^3] \)), 5.54 (s, \( CH_2[N^1 \& N^3] \)), 6.91 (d of d, \( J \) 9 & 2 Hz, \( C^6 H[N^3] \)), 6.93 (d of d, \( J \) 9 & 2 Hz, \( C^6 H[N^1] \)), 7.17 (d, \( J \) 2 Hz, \( C^b H[N^3] \)), 7.28 (d, \( J \) 2 Hz, \( C^b H[N^1] \)), 7.40 (s, \( C^b H_5[N^1 \& N^3] \)), 7.46 (d, \( J \) 9 Hz, \( C^7 H[N^1] \)), 7.63 (d, \( J \) 9 Hz, \( C^7 H[N^3] \)), 8.36 (1.08H, s, \( C^2 H[N^3] \)) and 8.44 (0.92H, s, \( C^2 H[N^1] \)).

Preparation of \( N^1 \)-Benzyl-5-Methoxybenzimidazole

2-Amino-1-benzylamino-4-methoxybenzene was prepared in 60% yield from 3-nitro-4-aminoanisole using the method of Lott. This was cyclised with formic acid to \( N^1 \)-benzyl-5-methoxybenzimidazole (53%) which upon recrystallisation from aqueous methanol gave pale yellow crystals, m.p. 110° (Found: C, 75.55; H, 5.84; N, 11.59. \( C_{15}H_{14}N_2O \) requires C, 75.60; H, 5.92; N, 11.76%). P.m.r. (DMSO-\( d^6 \)): \( \delta \) 3.82 (3H, s, \( CH_3 \)), 5.53 (2H, s, \( CH_2 \)), 6.92 (1H, d of d, \( J \) 9 & 2 Hz, \( C^6 H \)), 7.28 (1H, d, \( J \) 2 Hz, \( C^b H \)), 7.46 (1H, d, \( J \) 9 Hz, \( C^7 H \)) and 8.42 (1H, s, \( C^2 H \)). Mass spectrum: m/e 238(\( M^+ \), 75%), 223(7), 91(100) and 65(12).
Alkylation of 5-Methoxybenzimidazole Anion with Phenacyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material was too broadened for analysis. The reaction was repeated and another p.m.r. spectrum (DMSO-d$_6$) revealed ca 70% of the isolated material to be 5-methoxybenzimidazole with the remainder being its alkylated products. 5-Methoxybenzimidazole was removed by preparative t.l.c., on silica gel using CHCl$_3$ as eluant, since its methyl signal obstructed those of the alkylated products. The p.m.r. spectrum (DMSO-d$_6$) of this purified material indicated the alkyl products to consist of 46.5±3% N$_1$ and 53.5% N$_3$ based on the methoxy methyl signals.

P.m.r. (DMSO-d$_6$): δ 3.79 (2.79H, s, CH$_3$[N$_1$]), 3.84 (3.21H, s, CH$_3$[N$_3$]), 6.08 (s, CH$_2$[N$_1$ & N$_3$]), 6.94(d of d, J 9 & 2 Hz, C$_6$H[N$_1$ & N$_3$]), 7.30 (d, J 2 Hz, C$_4$H[N$_1$]), 7.49 (d, J 9 Hz, C$_7$H[N$_1$]), 7.60-92 (cm, C$_6$H$_5$[N$_1$ & N$_3$] and [C$_4$H & C$_7$H][N$_3$]), 8.18 (s, C$_2$H[N$_3$]) and 8.24 (s, C$_2$H[N$_1$]).

Alkylation of 5-Methoxybenzimidazole Anion with Benzyl Chloride in Formamide

The standard alkylation and isolation procedure was followed using formamide as solvent. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed it to consist of ca 80% 5-methoxybenzimidazole and ca 20% alkyl products. The latter were resolved into 56.5±3% N$_1$ and 43.5% N$_3$ using the C$_2$H signals.
5. Alkylation of 4-Substituted benzimidazoles

A. 4-Nitrobenzimidazole

Preparation

Initially the 4-nitrobenzimidazole used was obtained as a byproduct of a 5-nitrobenzimidazole synthesis. Vacuum sublimation of this material at 160° gave an off white powder, m.p. 239-40° (lit. 240°) (Found: C, 51.73; H, 2.94; N, 25.51. \( \text{C}_7\text{H}_5\text{N}_3\text{O}_2 \) requires C, 51.53; H, 3.09; N, 25.76%).

P.m.r. (DMSO-d6): δ 7.50 (1H, t, \( J \) 8 Hz, \( \text{C}_6\text{H} \)), 8.25 (2H, d, \( J \) 8 Hz, \( \text{C}_5\text{H} \) & \( \text{C}_7\text{H} \)), 8.58 (1H, s, \( \text{C}_2\text{H} \)) and 13.44 (1H, bs, \( \text{N}_3\text{H} \)).

Mass spectrum: m/e 163(M⁺, 100), 133(7), 117(56), 105(8), 90(44) and 63(22).

Subsequently 4-nitrobenzimidazole was produced by selective reduction of 2,6-dinitroaniline to 3-nitro-o-phenylenediamine followed by cyclisation with formic acid to give 12% yield. Qualitative t.l.c. on silica gel using CHCl₃ as developing solvent indicated the 4-nitrobenzimidazole to be impure. However, column chromatography of the crude product (1.1 g) on silica gel (300 g) with CHCl₃ as eluting solvent gave, after recrystallisation from 95% ethanol, pure 4-nitrobenzimidazole (0.53 g, 48%) as orange-yellow crystals, m.p. 242° (Found: C, 51.40; H, 3.44; N, 25.66. \( \text{C}_7\text{H}_5\text{N}_3\text{O}_2 \) requires C, 51.53; H, 3.09; N, 25.76%).

The preparation of further 4-nitrobenzimidazole necessitated the synthesis of additional 2,6-dinitroaniline (20.2 g, 23%) by a literature procedure from chlorobenzene (50 ml). To gain a higher yield the 4-nitrobenzimidazole (8.0 g, 90%) was prepared by another method from the 2,6-dinitroaniline (10.0 g).
Column chromatography on the crude product using silica gel (600 g) and 10% methanol/CHCl₃ as eluting solvent gave pure 4-nitrobenzimidazole (4 g, 40%) as a yellow powder, m.p. 240° (Found: C, 51.30; H, 3.02; N, 25.37. C₇H₅N₃O₂ requires C, 51.53; H, 3.09; N, 25.76%).

Alkylation of 4-Nitrobenzimidazole Anion with Benzyl Chloromethyl Ether

The standard alkylation and isolation procedure was followed except that 1.2 equivalents of alkylation agent was used because it contained 10% benzyl chloride. The p.m.r. spectrum (DMSO-d⁶) of the isolated material showed it to consist of the expected alkylation products with ca 5% 4-nitrobenzimidazole and ca 10% of unknown materials appearing as spurious signals around that of CH₂C₆H₅. The proportions of the isomeric products were found to be 90.0±2% N¹ and 10.0% N³ using the NCH₂ signals run in CDCl₃ (CDCl₃ gave better separation than DMSO-d⁶ as solvent).

P.m.r. (DMSO-d⁶): δ 4.40 (s, CH₂C₆H₅[N³]), 4.66 (s, CH₂C₆H₅[N¹]), 5.99 (s, CH₂[N³]), 6.02 (s, CH₂[N¹]), 7.30-46 (cm, C₆H₅[N³]), 7.40 (s, C₆H₅[N¹]), 7.57 (t, J 8 Hz, C⁶H[N³]), 7.63 (t, J 8 Hz, C⁶H[N¹]), 8.12 (d, J 8 Hz, C⁵H[N³]), 8.24 (d, J 8 Hz, C⁷H[N¹ & N³]), 8.27 (d, J 8 Hz, C⁵H[N¹]), 8.80 (s, C²H[N³]) and 8.90 (s, C²H[N¹]).

P.m.r. (CDCl₃): δ 4.32 (2.54H, s, CH₂C₆H₅[N³]), 4.47 (1.46H, s, CH₂C₆H₅[N¹]), 5.67 (1.54H, s, CH₂[N³]), 5.80 (2.46H, s, CH₂[N¹]), 7.12-48 (cm, [C₆H₅ & C⁶H][N³]), 7.27 (s, C₆H₅[N¹]), 7.38 (t, J 8 Hz, C⁶H[N¹]), 7.83 (d, J 8 Hz, C⁷H[N¹]), 7.95 (d, J 8 Hz, C⁵H[N³]), 8.00 (1.29H, s, C²H[N³]), 8.11 (d, J 8 Hz, C⁷H[N³]) and 8.16 (0.71H, s, C²H[N¹]).

The reaction was repeated using 0.85 equivalents of...
alkylating agent to ensure that dialkylation and hence product interconversion did not occur. A p.m.r. spectrum (CDCl₃) of the isolated material showed it to consist of ca 35\% 4-nitrobenzimidazole and ca 65\% of its alkylated products. The latter were resolved into 38.5±6\% N₁ and 61.5\% N₃ using the NCH₂ signals. The CH₂C₆H₅ and C²H signals showed 36.5±5\% N₁, 63.5\% N₃ and 35.5±4\% N₁, 64.5\% N₃ respectively.

Alkylation of 4-Nitrobenzimidazole Anion with Chloromethyl Pivalate

The alkylation procedure was modified for this reaction and subsequent ones by diminishing the amounts of the reactants and solvent by 33\% (i.e. 1.00 mM to 0.67 mM etc.). Also the alkylating agent was reduced in amount to 0.95 equivalents (relative to the benzimidazole) to ensure that dialkylation and hence product interconversion did not occur. The standard isolation procedure was employed. The p.m.r. spectrum (DMSO-d⁶) of the isolated material showed it to consist of ca 40\% 4-nitrobenzimidazole and ca 60\% of one alkyl product. The latter was determined to be the N₁ isomer as described in Chapter 5.

P.m.r. (DMSO-d⁶): δ 1.08 (s, C(CH₃)₃), 6.40 (s, CH₂), 7.60 (t, J 8 Hz, C⁶H), 8.07 (d, J 8 Hz, C⁵H), 8.14 (d, J 8 Hz, C⁷H) and 8.69 (s, C₂H).

P.m.r. (CDCl₃): δ 1.15 (s, C(CH₃)₃), 6.20 (s, CH₂), 7.46 (t, J 8 Hz, C⁶H), 7.90 (d, J 8 Hz, C⁷H), 8.16 (d, J 8 Hz, C⁵H) and 8.34 (s, C²H).

The alkylation was repeated and a p.m.r. spectrum (DMSO-d⁶) was obtained of the reaction product immediately after the removal of DMF. Again only the N₁ product was present.
Alkylation of 4-Nitrobenzimidazole Anion with 4-Methoxybenzyl Chloride

The standard alkylation and isolation procedure was followed as described in the previous pivaloylmethylation reaction. The p.m.r. spectrum (DMSO-d<sub>6</sub>) of the isolated material showed it to contain ca 80% and ca 20% of the 4-methoxybenzyl chloride and 2-methoxybenzyl chloride (a ca 20% impurity in the first agent) alkylation products respectively. The methylene signals were used to resolve the 4-methoxybenzyl products into 65.5±5% N<sup>1</sup>, 34.5% N<sup>3</sup> and the 2-methoxybenzyl products into 61.0±4% N<sup>1</sup>, 39.0% N<sup>3</sup>.

P.m.r. (DMSO-d<sub>6</sub>): δ 3.42 (s, CH<sub>3</sub>[N<sup>1</sup>]), 3.52 (s, CH<sub>3</sub>[N<sup>3</sup>]), 3.68 (s, CH<sub>3</sub>[N<sup>3</sup>]), 3.70 (s, CH<sub>3</sub>[N<sup>1</sup>]), 5.56 (2.60H, s, CH<sub>2</sub>[N<sup>1</sup>]), 5.60 (1.40H, s, CH<sub>2</sub>[N<sup>3</sup>]), 5.78 (1.56H, s, CH<sub>2</sub>[N<sup>3</sup>]), 5.86 (2.44H, s, CH<sub>2</sub>[N<sup>1</sup>]), 6.80-7.40 (cm, C<sub>6</sub>H<sub>4</sub>[N<sup>1</sup> & N<sup>3</sup>]), 7.38 (t, J 8 Hz, C<sub>6</sub>H[N<sup>1</sup> & N<sup>3</sup>]), 7.85 (d, J 8 Hz, C<sub>5</sub>H[N<sup>3</sup>]), 8.01 (d, J 8 Hz, [C<sub>5</sub>H & C<sub>7</sub>H][N<sup>1</sup>]), 8.09 (d, J 8 Hz, C<sub>7</sub>H[N<sup>3</sup>]), 8.46 (s, C<sub>2</sub>H[N<sup>3</sup>]), 8.59 (s, C<sub>2</sub>H[N<sup>1</sup>]), 8.74 (s, C<sub>2</sub>H[N<sup>1</sup> & N<sup>3</sup>]).

P.m.r. (CDCl<sub>3</sub>): δ 3.08 (s, CH<sub>3</sub>[N<sup>1</sup>]), 3.67 (s, CH<sub>3</sub>[N<sup>3</sup>]), 3.74 (s, CH<sub>3</sub>[N<sup>1</sup>]), 5.41 (s, CH<sub>2</sub>[N<sup>1</sup>]), 5.56 (s, CH<sub>2</sub>[N<sup>3</sup>]), 5.96 (s, CH<sub>2</sub>[N<sup>1</sup>]), 6.10 (s, CH<sub>2</sub>[N<sup>3</sup>]), 6.68-7.30 (cm, C<sub>6</sub>H<sub>4</sub>[N<sup>1</sup> & N<sup>3</sup>]), 7.28 (t, J 8 Hz, C<sub>6</sub>H[N<sup>1</sup> & N<sup>3</sup>]), 7.67 (d, J 8 Hz, C<sub>7</sub>H[N<sup>1</sup>]), 7.82 (d, J 8 Hz, C<sub>5</sub>H[N<sup>3</sup>]), 8.05 (d, J 8 Hz, C<sub>5</sub>H[N<sup>1</sup>]), 8.06 (d, J 8 Hz, C<sub>7</sub>H[N<sup>3</sup>]), 8.22 (s, C<sub>2</sub>H[N<sup>3</sup>]) and 8.34 (s, C<sub>2</sub>H[N<sup>1</sup>]).

The reaction was repeated but with pure 4-methoxybenzyl chloride. A p.m.r. spectrum (DMSO-d<sub>6</sub>) of the isolated material showed ca 40% 4-nitrobenzimidazole and ca 60% of its

* Signals of the 2-methoxybenzyl products.
alkylated products to be present. The latter were resolved into 64.0±3% $N^1$ and 36.0% $N^3$ using the methylene signals.

Averaging the results of the two 4-methoxybenzylolation reactions gave proportions of 65.0±4% $N^1$ and 35.0% $N^3$.

**Alkylation of 4-Nitrobenzimidazole Anion with Benzyl Chloride**

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed only the alkyl products to be present. These were resolved into 67.0±3% $N^1$ and 33.0% $N^3$ using the methylene signals.

\[ \text{P.m.r. (DMSO-d}_6 \text{): } \delta 5.71 (2.68H, s, CH}_2[N^1]), 5.78 (1.32H, s, CH}_2[N^3]), 7.42 (s, C}_6H}_5[N^1 \& N^3]), 7.48 (t, J 8 Hz, C]^6H[N^3]), 7.50 (t, J 8 Hz, C]^6H[N^1]), 7.98 (d, J 8 Hz, C]^5H[N^3]), 8.13 (d, J 8 Hz, [C]^5H \& C]^7H[N^1]), 8.20 (d, J 8Hz, C]^7H[N^3]), 8.84 (s, C]^2H[N^3]) and 8.86 (s, C]^2H[N^1]). \]

\[ \text{P.m.r. (CDCl}_3 \text{): } \delta 5.52 (s, CH}_2[N^1]), 5.70 (s, CH}_2[N^3]), 7.24-44 (cm, C]^6H[N^1 \& N^3]), 7.37 (s, C}_6H}_5[N^1 \& N^3]), 7.69 (d, J 8 Hz, C]^7H[N^1]), 7.93 (d, J 8 Hz, C]^5H[N^3]), 8.15 (d, J 8 Hz, C]^5H[N^1] \& C]^7H[N^3]), 8.20 (s, C]^2H[N^3]) and 8.32 (s, C]^2H[N^1]). \]

**Alkylation of 4-Nitrobenzimidazole Anion with 4-Nitrobenzyl Chloride**

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed it to consist of ca 60% 4-nitrobenzimidazole, ca 30% of its $N^1$ and $N^3$ alkylated products and ca 10% of an unknown material giving a signal near that of NCH$_2$. The alkyl products were resolved into 65.0±4% $N^1$ and 35.0% $N^3$ using the methylene signals. The C$^2H$ signals showed 67.5±4% $N^1$ and
32.5% $N^3$.

P.m.r. (DMSO-d$^6$): $\delta$ 5.86 (2.64H, s, $CH_2[N^1]$), 5.92 (1.36H, s, $CH_2[N^3]$), 8.74 (1.30H, s, $C^2H[N^3]$) and 8.86 (2.70H, s, $C^2H[N^1]$).

P.m.r. (CDCl$_3$): $\delta$ 5.66 (s, $CH_2[N^1]$), 5.86 (s, $CH_2[N^3]$), ca 8.30 (s, $C^2H[N^3]$) and 8.38 (s, $C^2H[N^1]$).

The remaining signals of the products were obscured by those of 4-nitrobenzimidazole and of the 4-nitrobenzyl aromatic protons.

The reaction was repeated using the standard procedure. The p.m.r. spectrum (DMSO-d$^6$) of the isolated material showed it to consist of ca 65% 4-nitrobenzimidazole, ca 25% alkylated compounds and ca 15% of the unidentified material. The alkylated compounds were resolved into 66.5±4% $N^1$ and 33.5% $N^3$ using the methylene signals.

Averaging the results of the two reactions gave an answer of 66.0±5% $N^1$ and 34.0% $N^3$.

Alkylation of 4-Nitrobenzimidazole Anion with Phenacyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$^6$) of the isolated material showed it to consist of ca 30% 4-nitrobenzimidazole and ca 70% of its alkylated products. The latter were resolved into 86.0±2% $N^1$ and 14.0% $N^3$ using the methylene signals which were separated by addition of CDCl$_3$ to the DMSO-d$^6$.

P.m.r. (DMSO-d$^6$): $\delta$ 6.33 (4H, s, $CH_2[N^1 \& N^3]$), 7.44-8.36 (cm, [$C^5H$, $C^7H$ & $C_6H_5$]$[N^1 \& N^3]$ and $C^6H[N^3]$), 7.55 (t, $J$ 8 Hz, $C^6H[N^1]$), 8.60 (s, $C^2H[N^3]$) and 8.69 (s, $C^2H[N^1]$).
Alkylation of 4-Nitrobenzimidazole Anion with Methyl Iodide

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-\(d^6\)) of the isolated material showed only alkylated products to be present. These were resolved into 53.5\(\frac{3}{2}\)% \(N^1\) and 46.5% \(N^3\) using the \(C^2H\) signals.

P.m.r. (DMSO-\(d^6\)): \(\delta\) 3.87 (s, \(CH_3[N^1]\)), 3.92 (s, \(CH_3[N^3]\)), 7.38 (t, \(J\) 8 Hz, \(C^6H[N^1] \& N^3\)), 7.93 (d, \(J\) 8 Hz, \(C^7H[N^1] \& C^5H[N^3]\)), 8.02 (d, \(J\) 8 Hz, \(C^5H[N^1] \& C^7H[N^3]\)), 8.32 (0.93H, s, \(C^2H[N^3]\)) and 8.41 (1.07H, s, \(C^2H[N^1]\)).

P.m.r. (CDC\(_1\)\(_3\)): \(\delta\) 3.93 (s, \(CH_3[N^1]\)), 4.02 (s, \(CH_3[N^3]\)), 7.36 (t, \(J\) 8Hz, \(C^6H[N^3]\)), 7.40 (t, \(J\) 8 Hz, \(C^6H[N^1]\)), 7.74 (d, \(J\) 8 Hz, \(C^7H[N^1]\)), 7.97 (s, \(C^2H[N^3]\)), 8.04 (d, \(J\) 8 Hz, \(C^5H[N^3]\)), 8.07 (d, \(J\) 8 Hz, \(C^7H[N^3]\)), 8.15 (d, \(J\) 8 Hz, \(C^6H[N^1]\)) and 8.16 (s, \(C^2H[N^1]\)).

Alkylation of 4-Nitrobenzimidazole Anion with Ethyl Bromide

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-\(d^6\)) of the isolated material showed it to consist of mainly the alkyl products and, in addition, a compound giving rise to a small doublet near the \(NCH_2\) signals. The alkylated products were resolved into 64.0±4% \(N^1\) and 36.0% \(N^3\) using the \(C^2H\) signals.

P.m.r. (DMSO-\(d^6\)): \(\delta\) 1.29 (t, \(J\) 7 Hz, \(CH_3[N^3]\)), 1.46 (t, \(J\) 7 Hz, \(CH_3[N^1]\)), 4.14 (d, unidentified), 4.41 (q, \(J\) 7 Hz, \(CH_2[N^1]\)), 4.45 (q, \(J\) 7 Hz, \(CH_2[N^3]\)), 7.42 (t, \(J\) 8 Hz, \(C^6H[N^3]\)), 7.46 (t, \(J\) 8 Hz, \(C^6H[N^1]\)), 7.97 (d, \(J\) 8 Hz, \(C^5H[N^3]\)), 8.06 (d, \(J\) 8 Hz, \(C^7H[N^1]\)), 8.10 (d, \(J\) 8 Hz, \(C^5H[N^1] \& C^7H[N^3]\)), 8.56 (0.72H, s, \(C^2H[N^3]\)) and 8.63 (1.28H, s, \(C^2H[N^1]\)).
Alkylation of 4-Nitrobenzimidazole Anion with Isopropyl Bromide

The standard alkylation and isolation procedure was followed and reaction was continued for 7 days. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed it to consist of ca 60% 4-nitrobenzimidazole and ca 40% of one alkyl product. As described in Chapter 5 this product was established to be the N$^1$ isomer.

P.m.r. (DMSO-d$_6$): $\delta$ 1.61 (d, $J$ 6 Hz, CH(CH$_3$)$_2$), 4.94 (m, $J$ 6 Hz, CH(CH$_3$)$_2$), 7.52 (t, $J$ 8 Hz, C$^6$H), 8.12 (d, $J$ 8 Hz, C$^5$H), 8.22 (d, $J$ 8 Hz, C$^7$H) and 8.75 (s, C$^2$H).

P.m.r. (CDCl$_3$): $\delta$ 1.70 (d, $J$ 6 Hz, CH(CH$_3$)$_2$), 4.78 (m, $J$ 6 Hz, CH(CH$_3$)$_2$), 7.46 (t, $J$ 8 Hz, C$^6$H), 7.83 (d, $J$ 8 Hz, C$^7$H), 8.22 (d, $J$ 8 Hz, C$^5$H) and 8.34 (s, C$^2$H).

Alkylation of 4-Nitrobenzimidazole Anion with tert-Butyl Bromide

The standard alkylation and isolation procedure was followed with reaction continuing for 4 days. The p.m.r. spectrum of the isolated material showed that there was no apparent product but a mass of unintelligible resonance signals present.

Relative Thermodynamic Stabilities of N$^1$- and N$^3$-Benzyl-4-Nitrobenzimidazoles

The material isolated from the benzylation of 4-nitrobenzimidazole (0.100 g, 0.40 mM) was dissolved in DMF (2 ml) and benzyl chloride (0.014 ml, 0.12 mM) added. The solution was heated at 125°C and at intervals 4 aliquots (0.5 ml) were removed. On removal of DMF a p.m.r. spectrum (CDCl$_3$) was run on each sample and the proportions of the monobenzyl products (Table 22), the only material present, were estimated using the methylene signals.
Table 22
Reversible Rebenzylation of N¹- and N³-
Benzyl-4-Nitrobenzimidazoles

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (hrs)</th>
<th>N¹ product (%)</th>
<th>N³ product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>67.0±3</td>
<td>33.0</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>81.0±3</td>
<td>19.0</td>
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<tr>
<td>2</td>
<td>240</td>
<td>89.0±3</td>
<td>11.0</td>
</tr>
<tr>
<td>3</td>
<td>384</td>
<td>88.0±3</td>
<td>12.0</td>
</tr>
<tr>
<td>4</td>
<td>624</td>
<td>88.0±4</td>
<td>12.0</td>
</tr>
</tbody>
</table>

A. Calculated for 30° (see Table 21).

B. 4-Carboxymethylbenzimidazole

Preparation

Initially a literature\textsuperscript{64} preparation of 4-carboxymethylbenzimidazole from 4-carboxybenzimidazole (see Exp. 5.C) was used. However, only small amounts of the desired product were formed and the starting material was regenerated.

Another approach was taken which involved refluxing the formate salt of 4-carboxybenzimidazole with thionyl chloride. After removal of the thionyl chloride and treatment of the residual material with methanol a polymeric material was obtained. Consequently, this approach was abandoned.

Finally 4-carboxymethylbenzimidazole was prepared by the following procedure. 4-Carboxybenzimidazole (2.0 g) was dissolved in absolute methanol (200 ml) and conc. sulphuric acid (1.5 ml) added. This solution was refluxed overnight and concentrated to a few mls before neutralising
by addition to a phosphate buffer of pH 8.5. At this pH the 4-carboxymethylbenzimidazole (1.8 g, 83%) precipitated as a white amorphous material, m.p. 204° (Found: C, 61.22; H, 4.75; N, 15.77. C₉H₈N₂O₂ requires C, 61.36; H, 4.58; N, 15.91%). P.m.r. (DMSO-d₆): δ 3.99 (3H, s, CH₃), 7.38 (1H, t, J 8 Hz, C⁵H), 7.93 (1H, d, J 8 Hz, C⁶H), 8.04 (1H, d, J 8 Hz, C⁷H), 8.38 (1H, s, C²H) and 12.72 (1H, vbs, N³H); P.m.r. (CDCl₃): δ 4.04 (3H, s, CH₃), 7.41 (1H, t, J 8 Hz, C⁵H), 8.03 (1H, d, J 8 Hz, C⁶H), 8.12 (1H, d, J 8 Hz, C⁷H), 8.25 (1H, s, C²H) and the N³H was not apparent. Mass spectrum: m/e 176(M⁺, 100%), 145(56), 144(72), 117(41), 116(37) and 90(23).

Alkylation of 4-Carboxymethylbenzimidazole Anion with Benzyl Chloromethyl Ether

The standard alkylation procedure was followed except for the use of 0.80 equivalents of alkylating agent but the isolation procedure was modified. After removal of DMF by co-distillation with toluene the residue was dissolved in CHCl₃ (5 ml) and the remaining solid filtered off. The solvent was then removed and the isolated material analysed by p.m.r. (CDCl₃). This material was found to consist of ca 10% benzylated and ca 55% benzyloxymethylated products of 4-carboxymethylbenzimidazole as well as ca 35% of the unreacted benzimidazole itself. The proportions of the benzyloxymethyl products were found to be 32.5±2% N¹ and 67.5% N³ using the NCH₂ signals.

P.m.r.* (DMSO-d₆): 3.92 (s, CH₃[N³]), 3.96 (s, CH₃[N¹]), 4.36 (s, CH₂[N¹ & N³]), 5.91 (s, CH₂[N¹]), 6.01

* Signals of benzyloxymethyl products.
Alkylation of 4-Carboxymethylbenzimidazole Anion with Benzyl Chloride

The alkylation and isolation procedure of the previous reaction was followed using 0.95 equivalents of alkylating agent. The p.m.r. spectrum (CDCl₃) of the isolated material showed it to consist of ca 8% 4-carboxymethylbenzimidazole and ca 92% of its benzylated products. The latter were resolved into 72.0 ± 2% N₁ and 28.0% N₃ using the methylene signals.

P.m.r. (DMSO-d₆): δ 3.76 (s, CH₃[N³]), 3.93 (s, CH₃[N¹]), 5.64 (s, CH₂[N¹]), 5.81 (s, CH₂[N³]), 7.22-42 (cm, C₆H[N¹ & N³]), 7.36 (s, C₆H₅[N¹ & N³]), 7.65 (d, J 8 Hz, C₅H[N³]), 7.86 (d, J 8 Hz, [C₅H & C₇H][N¹]), 8.03 (d, J 8 Hz, C₇H[N³]) and 8.69 (s, C²H[N¹] & N³).

P.m.r. (CDCl₃): δ 3.81 (s, CH₃[N³]), 4.12 (s, CH₃[N¹]), 5.44 (s, CH₂[N¹]), 5.85 (s, CH₂[N³]), 7.13-53 (cm, [C₆H & C₆H₅][N¹ & N³]), 7.60 (d, J 8 Hz, C₇H[N¹]), 7.89 (d, J 8 Hz, C₅H[N³]), 8.11-29 (cm, C₇H[N³]), 8.17 (d, J 8 Hz, C₅H[N¹]), 8.18 (s, C²H[N³]) and 8.28 (s, C²H[N¹]).

* Signals of benzyloxy methyl products.
Alkylation of 4-Carboxymethylbenzimidazole Anion with Phenacyl Chloride

The same alkylation and isolation procedure was followed as in the previous reaction. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed it to consist of ca 85% 4-carboxymethylbenzimidazole and ca 15% of its phenacylated products. The latter were resolved into 67.0±4% N$^1$ and 33.0% N$^3$ using the methylene signals (CDCl$_3$/DMSO-d$_6$ mixture).

P.m.r. (DMSO-d$_6$): δ 6.29 (2.70H, s, CH$_2$[N$^1$]), 6.35 (1.30H, s, CH$_2$[N$^3$]) and the other signals were obscured by those of 4-carboxymethylbenzimidazole and the phenacyl aromatic protons.

The reaction was repeated and gave similar amounts of 4-carboxymethylbenzimidazole and its phenacyl products. The latter were resolved into 68.0±3% N$^1$ and 32% N$^3$ using the methylene signals (DMSO-d$_6$/CDCl$_3$).

The results of the 2 reactions were averaged to give 67.5±4% N$^1$ and 32.5% N$^3$.

Relative Thermodynamic Stabilities of N$^1$- and N$^3$-Benzyl-4-Carboxymethylbenzimidazole

The product mixture (0.100 g, 0.38 mM) isolated from the benzylation of 4-carboxymethylbenzimidazole was dissolved in DMF (1.5 ml) and benzyl chloride added (0.015 ml, 0.13 mM). The solution was heated at 125° for 4 days, DMF was removed, and a p.m.r. spectrum (CDCl$_3$) was run on the residue. This was found to contain decomposed materials in addition to the monobenzyl products in the proportions of 91.0±4% N$^1$ and 9.0% N$^3$ (methylene signals).

Another sample was taken after a further 5 days and
the p.m.r. spectrum (CDCl₃) showed only decomposed material
to be present.

C. 4-Carboxybenzimidazole

The sulphate salt of 4-carboxybenzimidazole (2.0 g, 28%) was prepared by oxidising ⁶⁴ 4-methylbenzimidazole (4.5 g) (see Exp. 5.D.). The product was dissolved in boiling water/decocolourising charcoal and then the free acid was precipitated at pH 4 as a white powder, m.p. 297-307° (Found: C, 59.07; H, 4.19; N, 17.07. C₉H₈N₂O₂ requires C, 59.25; H, 3.73; N, 17.28%). P.m.r. (DMSO-d⁶): δ 7.43 (1H, t, J 8 Hz, C⁵H), 7.98 (1H, d, J 8 Hz, C⁷H), 8.08 (1H, d, J 8 Hz, C⁶H) and 8.25 (1H, s, C²H). As the carboxyl and imino protons exchange with water their signals were not detected. Mass spectrum: m/e 162(M⁺, 86%), 144(99), 117(31), 116(100) and 90(32).

Alkylation of 4-Carboxybenzimidazole Dianion with Benzyl Chloromethyl Ether

The standard alkylation procedure was followed using 2.10 and 0.80 equivalents (based on the amount of benzimidazole) of sodium hydride and the alkylating agent respectively. For the reactions of the 4-carboxy compound the isolation procedure was modified after DMF was removed by co-distillation with toluene. The solid residue was dissolved in water and the pH adjusted to 4.0. The solution was extracted with CHCl₃, the extracts dried (Na₂SO₄) and the solvent removed. A p.m.r. spectrum was run on the residual material. Also the material in the aqueous solution was checked by p.m.r. after solvent removal and in all cases no
alkylated products were found.

For the reaction with benzyl chloromethyl ether the p.m.r. spectrum (DMSO-d<sup>6</sup>) of the CHCl<sub>3</sub> extracted material showed it to consist of ca 85% of a benzyloxymethyl product and ca 15% of a benzyl product. Both products were determined to be the N<sup>1</sup> isomer as described in the following section on the benzylation of 4-carboxybenzimidazole dianion.

P.m.r. (DMSO-d<sup>6</sup>): δ 4.53 (s, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.86 (s, CH<sub>2</sub>), 7.29 (s, C<sub>6</sub>H<sub>5</sub>), 7.44 (t, J 8 Hz, C<sup>6</sup>H), 7.91 (d, J 8 Hz, C<sup>5</sup>H), 7.95 (d, J 8 Hz, C<sup>7</sup>H) and 8.71 (s, C<sup>2</sup>H).

Alkylation of 4-Carboxybenzimidazole Dianion with Benzyl Chloride

The same alkylation and isolation procedure was used as in the previous alkylation using 0.95 equivalents of alkylation agent. The p.m.r. spectrum (DMSO-d<sup>6</sup>) of the isolated material showed it to consist of only one alkyl product.

P.m.r. (DMSO-d<sup>6</sup>): δ 5.60 (s, CH<sub>2</sub>), 7.15-7.47 (cm, C<sup>6</sup>H), 7.30 (s, C<sub>6</sub>H<sub>5</sub>), 7.82 (d, J 8 Hz, C<sup>5</sup>H & C<sup>7</sup>H) and 8.74 (s, C<sup>2</sup>H).

The reaction was repeated under identical conditions using 1.40 equivalents of sodium hydride. The excess base was used to deprotonate any water molecules present and thus ensure that they did not selectively bind to the benzimidazole and affect alkylation preferences. The result was unchanged.

The single alkyl product was identified as N<sup>1</sup> as described in Chapter 5. This process was facilitated by the hydrolysis of the benzyl products of 4-carboxymethylbenzimidazole to the corresponding 4-carboxy compounds. The

* Signals for the benzyloxymethyl compound.
material isolated from the benzylation of 4-carboxymethylbenzimidazole was dissolved in aqueous solution of pH 11 and refluxed overnight. The pH was then adjusted to 4.0 and the products isolated as in the normal 4-carboxybenzimidazole alkylation. The p.m.r. spectrum (DMSO-d$_6$) showed the 2 benzyl products of 4-carboxybenzimidazole to be present.

P.m.r. (DMSO-d$_6$): $\delta$ 5.61 (s, CH$_2$[N$^1$]), 5.86 (s, CH$_2$[N$^3$]), 7.20-40 (cm, C$_6$H$_5$[N$^1$ & N$^3$]), 7.33 (s, C$_6$H$_5$[N$^1$ & N$^3$]), 7.67 (d, $\ J$ 8 Hz, C$_5$H[N$^3$]), 7.84 (d, $\ J$ 8 Hz, C$_7$H[N$^3$]), 7.85 (d, $\ J$ 8 Hz, [C$_5$H & C$_7$H][N$^1$]), 8.55 (s, C$_2$H[N$^3$]) and 8.74 (s, C$_2$H[N$^1$]).

Alkylation of 4-Carboxybenzimidazole Dianion with Phenacyl Chloride

The same alkylation and isolation procedure was used as for the previous alkylation. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed that no alkyl products had formed and that the starting materials had apparently decomposed.

The alkylation was repeated under similar conditions with an extended reaction time (6 days). The results were unchanged.

Relative Thermodynamic Stabilities of N$^1$- and N$^3$-Benzyl-4-Carboxybenzimidazoles

N$^1$-Benzyl-4-carboxybenzimidazole (0.100 g, 0.62 mM) was dissolved in DMF (2 ml) and benzyl chloride (0.020 ml, 0.17 mM) added. The solution was heated at 125° and after 6 days a sample was taken and the DMF removed. The p.m.r.
spectrum (DMSO-d\textsubscript{6}) of the isolated material was broadened and showed only the starting material to be present. The reaction was abandoned at this stage.

D. 4-Methylbenzimidazole

Preparation

4-Methylbenzimidazole was prepared using a literature method\textsuperscript{64}. 3-Nitro-2-aminotoluene (14.4 g) was reduced to 2,3-diaminotoluene (9.0 g, 78\%) which was then cyclised with formic acid to the desired product (6.5 g, 67\%). Recrystallisation from water afforded white flakes, m.p. 145\textdegree (lit.\textsuperscript{17} 145\degree) (Found: C, 72.61; H, 5.94; N, 21.66. C\textsubscript{8}H\textsubscript{8}N\textsubscript{2} requires C, 72.70; H, 6.10; N, 21.20\%). P.m.r. (DMSO-d\textsubscript{6}): \(\delta\) 2.61 (3H, s, \textsubscript{CH\textsubscript{3}}), 7.07 (1H, d of d, \(J\) 7 \& 2 Hz, C\textsubscript{5}H), 7.20 (1H, t, \(J\) 7 Hz, C\textsubscript{6}H), 7.54 (1H, d of d, \(J\) 7 Hz, C\textsubscript{7}H), 8.36 (1H, s, C\textsubscript{2}H) and 12.61 (1H, s, N\textsubscript{1}H); P.m.r. (CDCl\textsubscript{3}): \(\delta\) 2.65 (3H, s, \textsubscript{CH\textsubscript{3}}), 7.15 (1H, d of d, \(J\) 7 \& 2 Hz, C\textsubscript{5}H), 7.26 (1H, t, \(J\) 7 Hz, C\textsubscript{6}H), 7.58 (1H, d of d, \(J\) 7 \& 2 Hz, C\textsubscript{7}H), 8.28 (1H, s, C\textsubscript{2}H) and 11.92 (1H, bs, N\textsubscript{1}H). Mass spectrum: m/e 132(M\textsuperscript{+}, 100\%), 131(90), 104(19) and 77(25).

Alkylation of 4-Methylbenzimidazole Anion with Benzyl Chloromethyl Ether

The standard alkylation and isolation procedure (as described in the anionic 4-nitrobenzimidazole/chloromethyl pivalate reaction) was followed using 0.90 equivalents of alkylation agent. The p.m.r. spectrum (CDCl\textsubscript{3}) of the isolated material showed there to be present ca 15\% 4-methylbenzimidazole, ca 5\% of its benzyl products, ca 55\% of its benzyloxyethyl products and ca 25\% of benzyl chloromethyl ether decomposition.
products. The benzyloxymethyl products were determined to consist of 57.5±4% N¹ and 42.5% N³ using the NCH² signals.

P.m.r. (DMSO-d⁶): δ 2.62 (s, CH₃[N¹]), 2.72 (s, CH₃[N³]), 4.54 (s, CH₂C₆H₅[N¹ & N³]), 5.80 (s, CH₂[N¹]), 5.85 (s, CH₂[N³]), 7.14-66 (cm, [C⁵H, C⁶H & C⁷H][N¹ & N³]), 7.35 (s, C₆H₅[N¹ & N³]) and 8.44 (s, C²H[N¹ & N³]).

P.m.r. (CDC1₃): δ 2.62 (s, CH₃[N³]), 2.70 (s, CH₃[N¹]), 4.41 (s, CH₂C₆H₅[N¹ & N³]), 5.50 (2.30H, s, CH₂[N¹]), 5.55 (1.70H, s, CH₂[N³]), 7.10-59 (cm, [C⁵H & C⁷H][N¹] and [C⁵H & C⁶H][N³]), 7.28 (s, C₆H₅[N³]), 7.32 (s, C₆H₅[N¹]), 7.51 (d, J 7 Hz, C⁵H[N¹]), 7.68 (d, J 7 Hz, C⁷H[N³]), 7.80 (s, C²H[N³]) and 7.92 (s, C²H[N¹]).

Alkylation of 4-Methylbenzimidazole Anion with Benzyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (CDC1₃) of the isolated material showed ca 10% 4-methylbenzimidazole and ca 90% of its benzylated products to be present. The latter were shown to consist of 77.0±4% N¹ and 23.0% N³ using the methylene signals.

P.m.r. (DMSO-d⁶): δ 2.41 (s, CH₃[N³]), 2.60 (s, CH₃[N¹]), 5.52 (s, CH₂[N¹]), 5.73 (s, CH₂[N³]), 7.01-59 (cm, [C⁵H, C⁶H & C⁷H][N¹ & N³] and C₆H₅[N³]), 7.36 (s, C₆H₅[N¹]) and 8.45 (s, C²H[N¹ & N³]).

P.m.r. (CDC1₃): δ 2.41 (s, CH₃[N¹]), 2.72 (s, CH₃[N³]), 5.24 (3.04H, s, CH₂[N¹]), 5.47 (0.96H, s, CH₂[N³]), 7.14 (s, C₆H₅[N¹]), 7.16-50 (cm, [C⁵H, C⁶H & C⁷H][N¹ & N³] and C₆H₅[N³]) and 7.92 (s, C²H[N¹ & N³]).

* Signals of benzyloxymethyl products.
Alkylation of 4-Methylbenzimidazole Anion with Phenacyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (CDCl₃) of the isolated material showed ca 50% decomposed phenacyl chloride, ca 30% 4-methylbenzimidazole and ca 20% of its phenacyl products. The latter were resolved into 86.5±4% N¹ and 13.5% N³ using the methylene signals.

P.m.r. (DMSO-d⁶): δ 2.63 (s, CH₃[N¹]), 6.09 (s, CH₂[N¹]) and 6.26 (s, CH₂[N³]).

P.m.r. (CDCl₃): δ 2.41 (s, CH₃[N³]), 2.68 (s, CH₃[N¹]), 5.53 (3.46H, s, CH₂[N¹]) and 5.73 (0.54H, s, CH₂[N³]).

The remaining signals were unassignable due to interference by signals of other materials.

Relative Thermodynamic Stabilities of N¹- and N³-Benzyl-4-Methylbenzimidazole

The product isolated from the 4-methylbenzimidazole benzylation was washed with alkalie to remove residual 4-methylbenzimidazole and then 0.110 g (0.50 mM) was dissolved in DMF (2 ml). Benzyl chloride (0.022 ml, 0.20 mM) was added to the solution which was then heated at 125° and 4 aliquots (0.5 ml) were removed at intervals. The DMF was removed from the samples and p.m.r. spectra (CDCl₃) were run. These revealed the presence of ca 40% dibenzyl material and ca 60% monobenzyl products and the spectra were found to become increasingly broadened with successive samples until the 4th spectrum was uninterpretable. The proportions of the monobenzyl products are shown in Table 23 as determined using the methylene signals.
Table 23
Reversible Rebenzylation of
N$^1$- and N$^3$-Benzyl-4-Methylbenzimidazole

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (hrs)</th>
<th>N$^1$ product$^A$ (%)</th>
<th>N$^3$ product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>77.0±4</td>
<td>23.0</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
<td>98$^{+1}_{-3}$</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>192</td>
<td>99$^{+0}_{-3}$</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>336</td>
<td>99$^{+0}_{-3}$</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>576</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

A. Calculated for 30°.

E. 4-Methoxybenzimidazole

Preparation
m-Nitroanisole (14.0 g) was nitrated$^{65}$ to yield the desired 2,3-dinitroanisole (3.1 g) together with a mixture (14.2 g) of this product and 3,4-dinitroanisole (total yield 95%). Column chromatography of the mixture (9.0 g) using silica gel (900 g) and ether as eluting solvent gave successively 3,4-dinitroanisole (3.1 g), a mixture of the 2 isomers (2.2 g) and 2,3-dinitroanisole (3.0 g). The 2,3-dinitroanisole (6.1 g) was then reduced$^{66}$ to give 2,3-diaminoanisole (4.0 g, 94%). The diamine was dissolved in a mixture of 90% formic acid (6.1 ml) and 4 molar hydrochloric acid (80 ml) and heated on a water bath for 2 hrs. On cooling the solution was neutralised with 4 molar sodium hydroxide solution and the precipitate was recrystallised from water to give 4-methoxybenzimidazole (2.9 g, 70%) as fine purple
crystals, m.p. 171-2° (lit. 167 169-70°) (Found: C, 64.34; H, 5.22; N, 18.78. C₈H₈N₂O requires C, 64.85; H, 5.44; 18.91%). P.m.r. (DMSO-d₆): δ 3.98 (3H, s, CH₃), 6.80 (1H, d of d, J 8 & 2 Hz, C⁵H), 7.17 (1H, t, J 8 Hz, C⁶H), 7.27 (1H, d of d, J 8 & 2 Hz, C⁷H), 8.20 (1H, s, C²H) and 12.72 (1H, bs, NH); P.m.r. (CDC₁₃): δ 4.00 (3H, s, CH₃), 6.73 (1H, d of d, J 8 & 2 Hz, C⁵H), 6.82 (1H, bs, N¹H), 7.19 (1H, t, J 8 Hz, C⁶H), 7.27 (1H, d of d, J 8 Hz, C⁷H) and 8.03 (1H, s, C²H). Mass spectrum: m/e 148(M⁺, 100%), 133(50), 119(18), 118(20), 105(55) and 78(15).

Alkylation of 4-Methoxybenzimidazole Anion with Benzyl Chloromethyl Ether

The standard alkylation and isolation procedure was followed using 0.90 equivalents of alkylation agent. The p.m.r. spectrum (DMSO-d₆) of the isolated material showed there to be present ca 40% 4-methoxybenzimidazole, ca 5% benzylation products and ca 55% benzyloxymethylation products. The latter were found to consist of 29.0±4% N¹ and 71.0% N³ using the NCH₂ signals.

P.m.r. (DMSO-d₆): δ 3.98 (s, CH₃[N³]), 4.03 (s, CH₃[N¹]), 4.56 (s, CH₂C₆H₅[N¹]), 4.62 (s, CH₂C₆H₅[N³]), 5.81 (1.26H, s, CH₂[N¹]), 5.92 (2.74H, s, CH₂[N³]), 6.81 (d, J 8 Hz, C⁵H[N¹]), 6.94 (d, J 8 Hz, C⁵H[N³]), 7.14 (cm, [C⁶H, C⁷H & C₆H₅][N¹ & N³]), 8.43 (s, C²H[N¹]) and 8.45 (s, C²H[N³]).

Alkylation of 4-Methoxybenzimidazole Anion with Benzyl Chloride

The standard alkylation and isolation procedure was followed. A p.m.r. analysis (DMSO-d₆) showed the isolated material to consist of ca 25% 4-methoxybenzimidazole, the
remainder being the 2 alkyln products. The proportions of the latter were found to be 43.5±2% N\textsuperscript{1} and 56.5% N\textsuperscript{3} using the methylene signals.

\textbf{P.m.r. (DMSO-d\textsuperscript{6}):} \delta 3.86 (s, CH\textsubscript{3}[N\textsuperscript{3}]), 3.96 (s, CH\textsubscript{3}[N\textsuperscript{1}]), 5.52 (1.72 H, s, CH\textsubscript{2}[N\textsuperscript{1}]), 5.66 (2.28H, s, CH\textsubscript{2}[N\textsuperscript{3}]), 6.77 (d, J 8 Hz, C\textsuperscript{5}H[N\textsuperscript{1}]), 6.82 (d, J 8 Hz, C\textsuperscript{5}H[N\textsuperscript{3}]), 7.16-40 (cm, [C\textsuperscript{6}H & C\textsuperscript{7}H][N\textsuperscript{1} & N\textsuperscript{3}]), 7.37 (s, C\textsubscript{6}H\textsubscript{5}[N\textsuperscript{1} & N\textsuperscript{3}]) and 8.42 (bs, C\textsuperscript{2}H[N\textsuperscript{1} & N\textsuperscript{3}]).

\textbf{P.m.r. (CDCl\textsubscript{3}):} \delta 3.90 (s, CH\textsubscript{3}[N\textsuperscript{3}]), 4.07 (s, CH\textsubscript{3}[N\textsuperscript{1}]), 5.38 (s, CH\textsubscript{2}[N\textsuperscript{1}]), 5.66 (s, CH\textsubscript{2}[N\textsuperscript{3}]), 6.78 (d, J 8 Hz, C\textsuperscript{5}H[N\textsuperscript{1} & N\textsuperscript{3}]), 7.25 (t, J 8 Hz, C\textsuperscript{6}H[N\textsuperscript{3}]), 7.29 (t, J 8 Hz, C\textsuperscript{6}H[N\textsuperscript{1}]), 7.29-55 (cm, [C\textsuperscript{7}H & C\textsubscript{6}H\textsubscript{5}][N\textsuperscript{1} & N\textsuperscript{3}]), 7.90 (s, C\textsuperscript{2}H[N \textsuperscript{1}]) and 7.94 (s, C\textsuperscript{2}H[N\textsuperscript{3}]).

The procedure was repeated and gave 42.5±2% N\textsuperscript{1} and 57.5% N\textsuperscript{3}.

The average result of the 2 reactions was calculated to be 43.0±3% N\textsuperscript{1} and 57.0% N\textsuperscript{3}.

\textbf{Alkylation of 4-Methoxybenzimidazole Anion with Phenacyl Chloride}

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d\textsuperscript{6}) of the isolated material showed it to contain ca 20% 4-methoxybenzimidazole and ca 80% of the 2 alkyln products. The latter were found to consist of 38.5±4% N\textsuperscript{1} and 61.5% N\textsuperscript{3} using the methylene signals (CDCl\textsubscript{3}).

\textbf{P.m.r. (DMSO-d\textsuperscript{6}):} \delta 3.96 (s, CH\textsubscript{3}[N\textsuperscript{1}]), 3.98 (s, CH\textsubscript{3}[N\textsuperscript{3}]), 6.06 (s, CH\textsubscript{2}[N\textsuperscript{1} & N\textsuperscript{3}]), 6.77 (d, J 8 Hz, C\textsuperscript{5}H[N\textsuperscript{1} & N\textsuperscript{3}]), 7.12-40 (cm, [C\textsuperscript{6}H & C\textsuperscript{7}H][N\textsuperscript{1} & N\textsuperscript{3}]) and 7.60-8.24 (cm, [C\textsuperscript{2}H & C\textsubscript{6}H\textsubscript{5}][N\textsuperscript{1} & N\textsuperscript{3}]).
P.m.r. (CDC\textsubscript{13}): δ 3.96 (s, CH\textsubscript{3}[N\textsuperscript{1}]), 4.01 (s, CH\textsubscript{3}[N\textsuperscript{3}]), 5.50 (1.56H, s, CH\textsubscript{2}[N\textsuperscript{1}]), 5.75 (2.44H, s, CH\textsubscript{2}[N\textsuperscript{3}]), 6.66-74 (cm, C\textsuperscript{5}H[N\textsuperscript{1} & N\textsuperscript{3}]), 7.16-34 (cm, [C\textsuperscript{6}H & C\textsuperscript{7}H][N\textsuperscript{1} & N\textsuperscript{3}]) and 7.50-8.10 (cm, [C\textsuperscript{2}H & C\textsubscript{6}H\textsubscript{5}][N\textsuperscript{1} & N\textsuperscript{3}]).

The procedure was repeated and gave 40.0±2% N\textsuperscript{1} and 60.0% N\textsuperscript{3}.

The average result of the 2 alkylations was estimated to be 39.0±3% N\textsuperscript{1} and 61.0% N\textsuperscript{3}.

Relative Thermodynamic Stabilities of N\textsuperscript{1}- and N\textsuperscript{3}-Benzyl-4-methoxybenzimidazole

The product isolated from the 4-methoxybenzimidazole benzylation was washed in alkalie and 0.237 g (1.00 mM) was dissolved in DMF (6.0 ml). Benzyl chloride (0.069 ml, 0.60 mM) was added to the solution which was then heated at 125°.

Three samples (2.0 ml) were taken at intervals and after solvent removal were analysed by p.m.r. (CDC\textsubscript{13}). Each p.m.r. spectra indicated the presence of ca 25% dialkyl material, ca 50% monoalkyl isomers and ca 25% of a material giving signals in the methylene region. Table 24 lists the proportions of the monobenzyl compounds as evaluated using the methylene signals.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time (hrs)</th>
<th>N\textsuperscript{1} Product\textsuperscript{A} (%)</th>
<th>N\textsuperscript{3} Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>43.0±3</td>
<td>57.0</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>70.5±5</td>
<td>29.5</td>
</tr>
<tr>
<td>2</td>
<td>264</td>
<td>76.0±5</td>
<td>24.0</td>
</tr>
<tr>
<td>3</td>
<td>576</td>
<td>83.0±5</td>
<td>17.0</td>
</tr>
</tbody>
</table>

\textsuperscript{A} Calculated for 30°.
F. 4-Aminobenzimidazole

Preparation

4-Aminobenzimidazole (2.0 g) was prepared from 4-nitrobenzimidazole (3.1 g, 79%) by following a literature hydrogenation procedure\textsuperscript{61}. Recrystallisation from water yielded 1.0 g (50%) of mauve crystals, m.p. 111-12° (lit.\textsuperscript{17} 120-1°) (Found: C, 61.49; H, 5.37; N, 31.06. C\textsubscript{7}H\textsubscript{7}N\textsubscript{3} requires C, 63.1; H, 5.30; N, 31.56%). P.m.r. (DMSO-d\textsubscript{6}): δ 6.39 (1H, d of d, J 7.5 & 1 Hz, C\textsuperscript{5}H), 6.77 (1H, d of d, J 7.5 & 1 Hz, C\textsuperscript{7}H), 6.90 (1H, t, J 7.5 Hz, C\textsuperscript{6}H) and 8.04 (1H, s, C\textsuperscript{2}H). The N\textsuperscript{1}H and NH\textsubscript{2} signals were not observed due to proton exchange with H\textsubscript{2}O. Mass spectrum: m/e 133(M\textsuperscript{+}, 100), 132(9), 104(21), 105(21) and 79(12).

Alkylation of 4-Aminobenzimidazole Anion with Benzyl Chloromethyl Ether

The standard alkylation and isolation procedure was followed using 0.90 equivalents of alkylating agent. The p.m.r. spectrum (DMSO-d\textsubscript{6}) of the isolated product showed there to be present benzylated (ca 10%), benzylloxymethylated (ca 60%) and decomposed (ca 10%) 4-aminobenzimidazole as well as possibly another alkyl product. The benzylloxymethyl products were found to consist of 80.0±4% N\textsuperscript{1} and 20.0% N\textsuperscript{3} using the NCH\textsubscript{2} signals (DMSO-d\textsubscript{6}/CDC\textsubscript{13} mixture).

P.m.r. (DMSO-d\textsubscript{6}): δ 4.33 (s, CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}[N\textsuperscript{1}]), 4.58 (s, CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}[N\textsuperscript{3}]), 5.70 (3.20H, s, CH\textsubscript{2}[N\textsuperscript{1}]), 5.84 (0.80H, s, CH\textsubscript{2}[N\textsuperscript{3}]), 6.46 (d[?], unidentified compound), 6.54 (d, J 8 Hz, C\textsuperscript{5}H[N\textsuperscript{1}]), 6.62 (t, J 8 Hz, C\textsuperscript{6}H[N\textsuperscript{3}]), 6.89 (d, J 8 Hz, C\textsuperscript{7}H[N\textsuperscript{1}]), 6.99 (d, J 5 Hz, C\textsuperscript{7}H[N\textsuperscript{1}]), ca 6.99 (d, J 5 Hz, C\textsuperscript{7}H[N\textsuperscript{3}]) and 7.37 (s, C\textsubscript{6}H\textsubscript{5}[N\textsuperscript{1} & N\textsuperscript{3}]).
These compounds were separated by preparative t.l.c. on silica gel using 10% methanol/CHCl₃ for development. The N³ product had the higher $R_f$.

N¹ product - P.m.r. (DMSO-d⁶): $\delta$ 4.33 (s, CH₂C₆H₅), 5.70 (s, CH₂), 6.54 (d, $J$ 8 Hz, C⁵H), 6.89 (d, $J$ 8 Hz, C⁷H), 7.06 (t, $J$ 8 Hz, C⁶H), 7.36 (s, C₆H₅) and 8.24 (s, C²H).

N³ product - P.m.r. (DMSO-d⁶): $\delta$ 4.58 (s, CH₂C₆H₅), 5.84 (s, CH₂), 6.62 (t, $J$ 5 Hz, C⁶H), 6.99 (d, $J$ 5 Hz, C⁷H), ca 6.99 (d, $J$ 5 Hz, C⁵H), 7.37 (s, C₆H₅) and 8.24 (s, C²H).

The unidentified alkyl product was not isolated and was only evident by p.m.r. (DMSO-d⁶) as a doublet ($\delta$ 6.46) and a singlet ($\delta$ 8.84) in the reaction mixture.

Alkylation of 4-Aminobenzimidazole Anion with Chloromethyl Pivalate

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d⁶) of the isolated material revealed the 2 alkyl products to be present along with small amounts of 4-aminobenzimidazole decomposition products. The relative proportions of the alkyl products were found to be 45.5±3% N¹ and 54.5% N³ using the methylene signals. The products were separated as per those of the reaction with benzyl chloromethyl ether, the N³ having the higher $R_f$.

N¹ product - P.m.r. (DMSO-d⁶): $\delta$ 1.10 (s, C(CH₃)₃), 6.22 (s, CH₂), 6.49 (d, $J$ 8 Hz, C⁵H), 6.83 (d, $J$ 8 Hz, C⁷H), 7.06 (t, $J$ 8 Hz, C⁶H) and 8.20 (s, C²H).

N³ product - P.m.r. (DMSO-d⁶): $\delta$ 1.10 (s, C(CH₃)₃), 6.38 (s, CH₂), 6.66 (t, $J$ 5 Hz, C⁶H), 7.02 (d, $J$ 5 Hz, C⁵H & C⁷H) and 8.22 (s, C²H).
Alkylation of 4-Aminobenzimidazole Anion using 4-Methoxybenzyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed it to contain ca 10% 4-aminobenzimidazole breakdown product the remaining material being a single alkyl product. As described in Chapter 5 this isomer was considered to be N$_1$.

P.m.r. (DMSO-d$_6$): δ 3.50 (s, CH$_3$), 5.31 (s, CH$_2$), 6.48 (d, $J$ 8 Hz, C$_5$H), 6.73 (d, $J$ 8 Hz, C$^7$H), 6.92 (d, $J$ 8 Hz, o protons in C$_6$H$_4$), 6.96 (t, $J$ 8 Hz, C$_6$H), 7.30 (d, $J$ 8 Hz, m protons in C$_6$H$_4$) and 8.24 (s, C$_2$H).

Alkylation of 4-Aminobenzimidazole Anion with Benzyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed ca 15% decomposed 4-aminobenzimidazole, 70% N$_1$/N$_3$ benzylaition products and ca 15% of possibly another alkyl product. The relative proportions of N$_1$ and N$_3$ benzylaition products were found to be 91.0$^{+3}_{-4}$% and 9.0% respectively using the methylene signals (DMSO-d$_6$/CDCl$_3$ mixture).

P.m.r. (DMSO-d$_6$): δ 5.40 (3.64H, s, CH$_2$[N$_1$]), 5.54 (0.36 H, s, CH$_2$[N$_3$]), 5.84 (s, CH$_2$(?), unidentified product), 6.47 (d, $J$ 8 Hz, C$_5$H[N$_1$]), 6.67 (d, $J$ 8 Hz, C$^7$H[N$_1$]), 6.94 (t, $J$ 8 Hz, C$_6$H$_5$[N$_1$]), 7.20 (s, C$_6$H$_5$[N$_3$]), 7.31 (s, C$_6$H$_5$[N$_1$]), 8.20 (s, C$_2$H[N$_1$]) and 8.68 (s, C$_2$H(?), unidentified product).

The procedure was repeated and gave 88.0±3% N$_1$ and 12.0% N$_3$. The N$_1$ and N$_3$ benzylaition products were separated by preparative t.l.c. on silica gel using CHCl$_3$ as the
developing media. The $N^3$ had the higher $R_f$ and it was not possible to isolate the unidentified material.

$N^1$ product - P.m.r. (CDCl$_3$): $\delta$ 5.29 (s, CH$_2$), 6.57 (d, $\delta$ 8 Hz, C$_5^H$), 6.73 (d, $\delta$ 8 Hz, C$_7^H$), 7.10 (t, $\delta$ 8 Hz, C$_6^H$), 7.10-35 (cm, C$_6^H_5$) and 7.88 (s, C$_2^H$).

$N^3$ product - P.m.r. (CDCl$_3$): $\delta$ 5.33 (s, CH$_2$), 6.43 (d, $\delta$ 8 Hz, C$_5^H$), 6.69 (d, $\delta$ 8 Hz, C$_7^H$), 7.12 (t, $\delta$ 8 Hz, C$_6^H$), 7.23-67 (cm, C$_6^H_5$) and 7.87 (s, C$_2^H$).

The results of the 2 reactions were averaged to give 89.5±5% $N^1$ and 10.5% $N^3$.

Alkylation of 4-Aminobenzimidazole Anion with 4-Nitrobenzyl Chloride

The standard alkylation and isolation procedure was employed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material indicated the presence of ca 40% decomposed 4-aminobenzimidazole and ca 60% of the $N^1$ alkylation product.

P.m.r. (DMSO-d$_6$): $\delta$ 5.58 (s, CH$_2$), 6.48 (d, $\delta$ 8 Hz, C$_5^H$), 6.65 (d, $\delta$ 8 Hz, C$_7^H$), 6.96 (t, $\delta$ 8 Hz, C$_6^H$) and 7.46-8.38 (cm, C$_2^H$ & C$_6^H_5$).

Alkylation of 4-Aminobenzimidazole Anion with Phenacyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum of the isolated material showed that no apparent alkylation had occurred and that the reactants had decomposed. The reaction was repeated and allowed to continue for 2 days but the results were unchanged.
Alkylation of 4-Aminobenzimidazole Anion with Methyl Iodide

The standard alkylation and isolation procedure was followed. A p.m.r. analysis (DMSO-d$_6$) showed there to be present ca 80% alkyl isomers and ca 20% of breakdown products from 4-aminobenzimidazole. The minor (N$^3$) of the 2 alkyl isomers was only evident as a small methyl signal slightly downfield of the corresponding N$^1$ one. These signals were used to estimate the relative proportions of the products to be $86.0_{-4}^{+3}\%$ N$^1$ and $14.0_{-4}^{+4}\%$ N$^3$.

P.m.r. (DMSO-d$_6$): $\delta$ 3.78 (s, CH$_3$[N$^1$]), 3.88 (s, CH$_3$[N$^3$]), 6.48 (d, $J$ 8 Hz, C$_5^H$[N$^1$]), 6.76 (d, $J$ 8 Hz, C$_7^H$[N$^1$]), 7.04 (t, $J$ 8 Hz, C$_6^H$[N$^1$]) and 8.01 (s, C$_2^H$[N$^1$]).

G. 4-Acetamidobenzimidazole

Preparation

A solution of 4-aminobenzimidazole (3.3 g) in acetic anhydride (50 ml) was refluxed for 2 hours followed by distillation of the acetic anhydride. 4-Acetamidobenzimidazole was precipitated by subsequent additions of ethanol (20 ml) and sodium hydroxide (pH 11.0). Recrystallisation from water gave white flakes (3.8 g, 80%), m.p. 285$^\circ$ (Found: C, 62.02; H, 5.47; N, 24.23. C$_9$H$_9$N$_3$O requires C, 61.70; H, 5.18; N, 23.99%). U.v.: $\lambda_{max}$ 217(+), 269(--), $\lambda_{min}$ 238(+); pH 1 $\lambda_{max}$ 218(+), 271(--), $\lambda_{min}$ 238(+). P.m.r. (DMSO-d$_6$): $\delta$ 2.16 (3 H, s, CH$_3$), 7.17 (1H, t, $J$ 7 Hz, C$_6^H$), 7.37 (1H, d of d, $J$ 7 & 2 Hz, C$_7^H$), 7.77 (1H, d of d, $J$ 7 & 2 Hz, C$_5^H$), 8.25 (1H, s, C$_2^H$), 10.08 (1H, bs, NHCO) and 12.56 (1H, bs, N$_1^H$H). Mass spectrum: m/e 175(M$^+$, 56%), 133(100), 105(16) and 78(10).
Alkylation of 4-Acetamidobenzenimidazole Anion with Benzy1 Chloromethyl Ether

The standard alkylation and isolation procedure was followed using 0.90 equivalents of alkylating agent. The p.m.r. spectrum (CDCl₃) of the isolated material indicated the presence of ca 50% N¹/N³ benzyloxymethylation products, ca 10% N¹/N³ benzylation products and ca 40% unidentified compounds. The proportions of the N¹ and N³ benzyloxymethylated products were found to be respectively 89.5±3% and 10.5% using the methyl signals. These two products were separated by column chromatography on alumina (50 g) with 6% methanol/CHCl₃ as the eluting media. The N¹ compound had the higher Rf.

N¹ product - P.m.r. (DMSO-d⁶): δ 2.22 (s, CH₃), 4.55 (s, CH₂C₆H₅), 5.80 (s, CH₂), 7.24-44 (cm, C⁶H & C⁷H), 7.34 (s, C₆H₅), 8.17 (d, J 7 Hz, C⁵H), 8.48 (s, C²H) and 10.02 (s, NHCO); P.m.r. (CDCl₃): δ 2.20 (s, CH₃), 4.42 (s, CH₂C₆H₅), 5.50 (s, CH₂), 7.16-42 (cm, C⁶H & C⁷H & C₆H₅), 7.84 (s, C²H), 8.33 (d, J 7 Hz, C⁵H) and 8.99 (s, NHCO). U.v.: λₘₐₓ 220(+), 273(--), 282(sh,--) and 290(sh,--), λₘᵢₙ 241(+) ; pH 1 λₘₐₓ 222(++) , 273(--) and 279(sh,--), λₘᵢₙ 245(- ).

N³ product - P.m.r. (DMSO-d⁶): δ 2.08 (s, CH₃), 4.51 (s, CH₂C₆H₅), 5.80 (s, CH₂), 7.24-44 (cm, C⁵H & C⁶H & C⁷H), 7.34 (s, C₆H₅), 8.48 (s, C²H) and 9.92 (s, NHCO); P.m.r. (CDCl₃): δ 2.05 (s, CH₃), 4.54 (s, CH₂C₆H₅), 5.60 (s, CH₂), 7.16-42 (cm, C⁶H & C⁷H & C₆H₅), 7.58 (bs, C²H), 7.95 (d, J 7 Hz, C⁵H) and 8.90 (s, NHCO). U.v.: λₘₐₓ 223(+), 257(--), 274(sh,+), 281(sh,-) and 292(sh,-), λₘᵢₙ 239(--); pH 1 λₘₐₓ 224(+), 274(+) and 277(sh,++), λₘᵢₙ 244(--).

Signals at 5.80 (s), 7.68 (d, J 6 Hz), 7.99 (d, J 8 Hz) and 10.12 (s) in the spectrum (CDCl₃) of the product
mixture may have indicated a 3rd benzyloxy methylated compound but this was not isolated.

Alkylation of 4-Acetamidobenzimidazole Anion with Chloromethyl Pivalate

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed 2 alkyl products to be present in the proportions 88.0±3% and 12.0% as determined by the methylene signals. Qualitative t.l.c. on silica using 10% methanol/CHCl$_3$ as developing media indicated 3 species to be present at $R_f$ ca 0.7, ca 0.55 and ca 0.3. Using a similar preparative t.l.c. procedure the materials of highest and lowest $R_f$ were isolated and found to correspond to the major and minor products as indicated by p.m.r.

The reaction was repeated under similar conditions and p.m.r. (DMSO-d$_6$) again indicated 2 alkyl products were present. They were in the proportions 91.0±3% and 9.0% as determined by the methylene signals (DMSO-d$_6$/CDCl$_3$ mixture). However, only one compound was common to both reactions; the major of the first reaction corresponded to the minor of the second. A similar qualitative t.l.c. procedure as was previously used, indicated 3 species to be present which corresponded in $R_f$ to the 3 of the first reaction. Using the equivalent preparative t.l.c. system the 2 compounds of higher $R_f$ were isolated. Of these, that of greatest $R_f$ proved to be the minor product and the other the major.

In Chapter 5 the major/minor products of reactions 1 and 2 are indicated to be $N^1/N^4$ (?) and $N^3/N^1$ respectively.
Reaction 1

N¹ product - P.m.r. (DMSO-d⁶): δ 1.10 (s, C(CH₃)₃), 2.21 (s, CH₃), 6.33 (s, CH₂), 7.30 (t, J 8 Hz, C⁶H), 7.44 (d, J 8 Hz, C⁷H), 8.11 (d, J 8 Hz, C⁵H), 8.43 (s, C²H) and 9.99 (s, NHCO). U.v.: λ_max 222(+), 264(sh,--), 271(--), 282(sh,--) and 291(sh,--), λ_min 240(-); pH 1 λ_max 225(++, 262(sh,--), 271(--), 280(sh,--) and 290(sh,-), λ_min 241(-).

N⁴(?) product - P.m.r. (DMSO-d⁶): δ 1.05 (s, C(CH₃)₃), 5.82 (s, CH₂), 7.81 (d, J 8 Hz, C⁵H & C⁷H) and 8.53 (s, C²H). U.v.: λ_max 230(+), 253(sh,++), 269(sh,-), 276(sh,+) and 280(sh,--), λ_min -; pH 1 λ_max 230(+), 255(++) and 273(sh,+), λ_min 242(+).

Reaction 2

N¹ product - P.m.r. (DMSO-d⁶): δ 1.09 (s, C(CH₃)₃), 2.18 (s, CH₃), 6.32 (s, CH₂), 7.32 (t, J 8 Hz, C⁶H), 7.44 (d, J 8 Hz, C⁷H), 8.04 (d, J 8 Hz, C⁵H), 8.43 (s, C²H) and 9.97 (s, NHCO). U.v.: λ_max 220(+), 263(sh,--), 271(--), 281(sh,--) and 291(sh,-), λ_min 241(-); pH 1 λ_max 224(++, 261(sh,--), 271(--), 278(sh,--) and 291(sh,-), λ_min 243(-).

N³ product - P.m.r. (DMSO-d⁶): δ 1.04 (s, C(CH₃)₃), 2.11 (s, CH₃), 6.33 (s, CH₂), 7.24 (t, J 8 Hz, C⁶H), 7.34 (d, J 8 Hz, C⁷H), 7.66 (d, J 8 Hz, C⁵H), 8.40 (s, C²H) and 10.00 (s, NHCO). U.v.: λ_max 223(+), 251(--), 274(sh,++) and 282(sh,-), λ_min 232(--); pH 1 λ_max 225(+), 257(--), 270(sh,++) and 278(sh,++), λ_min 236(--).

The reaction was performed a 3rd time under similar conditions but with 1.40 equivalents of sodium hydride. The results were 80.0±5% N¹ and 20.0% N⁴(?).
Alkylation of 4-Acetamidobenzimidazole Anion with Benzyl Chloride

The standard alkylation and isolation procedure was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material indicated only the N$^1$ and N$^3$ benzylated products to be present. The relative proportions were determined to be 96.0$^{+2%}_{-3%}$ N$^1$ and 4.0$^%$ N$^3$ using the methylene signals.

P.m.r. (DMSO-d$_6$): $\delta$ 1.98 (s, CH$_3$[N$^3$]), 2.20 (s, CH$_3$[N$^1$]), 5.53 (s, CH$_2$[N$^1$]), 5.61 (s, CH$_2$[N$^3$]), 7.19 (t, $J$ 8 Hz, C$_6^H$), 7.20-44 (cm, C$_7^H$[N$^1$]), 7.36 (s, C$_6^H_5$[N$^1$]), 8.06 (d, $J$ 8 Hz, C$_5^H$[N$^1$]), 8.48 (s, C$_2^H$[N$^1$]), 9.96 (s, NHCO [N$^1$]) and the remaining N$^3$ signals were too small and obstructed for detection.

The 2 products were separated by preparative t.l.c. on silica gel using 10% methanol/CHCl$_3$ as developing media. The N$^1$ product had the higher R$_f$.

N$^1$ product - P.m.r. (CDCl$_3$): $\delta$ 2.26 (s, CH$_3$), 5.38 (s, CH$_2$), 7.11 (cm, C$_7^H$ & C$_6^H_5$), 7.12 (t, $J$ 8 Hz, C$_6^H$), 7.92 (s, C$_2^H$), 8.30 (d, $J$ 8 Hz, C$_5^H$) and 8.67 (s, NHCO).

U.v.: $\lambda_{\text{max}}$ 222(+), 274(---), 281(sh,--) and 290(sh,--), $\lambda_{\text{min}}$ 242(+); pH 1 $\lambda_{\text{max}}$ 224(+), 273(---) and 279(sh,--), $\lambda_{\text{min}}$ 243(+).

N$^3$ product - P.m.r. (CDCl$_3$): $\delta$ 2.02 (s, CH$_3$), 5.52 (s, CH$_2$), 7.20 (s, C$_6^H_5$) and the remaining signals too minute for detection. U.v.: $\lambda_{\text{max}}$ 227(+), 257(--), and 284(sh,--), $\lambda_{\text{min}}$ 239(-); pH 1 $\lambda_{\text{max}}$ 223(+), 262(sh,--), 270(++) and 277(sh, ++), $\lambda_{\text{min}}$ 242(--).

Alkylation of 4-Acetamidobenzimidazole Anion with Phenacyl Chloride

The standard alkylation and isolation procedure
was followed. The p.m.r. spectrum (DMSO-d$_6$) of the isolated material showed there to be present ca 30% decomposed phenacyl chloride, ca 10% 4-acetamidobenzimidazole and ca 60% phenacylation products of the latter. The phenacylation products were found to consist of 90.0±3% N$^1$ and 10.0% N$^3$ using the methylene signals. The products were separated by preparative t.l.c. on silica gel using 10% methanol/CHCl$_3$ as developing media. The N$^1$ compound had the higher R$_f$.

N$^1$ product - P.m.r. (DMSO-d$_6$): δ 2.22 (s, CH$_2$), 6.09 (s, CH$_2$), 7.29 (d, $J$ 8 Hz, C$^7$H), 7.31 (t, $J$ 8 Hz, C$^6$H), 7.75-8.24 (cm, C$_6$H$_5$), 8.05 (d, $J$ 8 Hz, C$^5$H), 8.44 (s, C$_2$H) and 9.97 (bs, NHCO). U.v.: $\lambda_{\text{max}}$ 223(sh,+), 252(sh,+), 273 and 290(sh,--), $\lambda_{\text{min}}$--; pH 1 $\lambda_{\text{max}}$ 225(sh,+), 251(+) and 272(sh,--), $\lambda_{\text{min}}$--.

N$^3$ product - P.m.r. (DMSO-d$_6$): δ 1.57 (s, CH$_3$), 6.06 (s, CH$_2$), 7.75-8.24 (cm, C$_6$H$_5$), 9.75 (s, NHCO) and other signals too minute to detect. U.v.: $\lambda_{\text{max}}$ 219(sh,+), 249(-), 269(sh,++) and 275(sh,++), $\lambda_{\text{min}}$--; pH 1 $\lambda_{\text{max}}$ 223(sh,+), 250(-), 269(sh,++) and 277(sh,++), $\lambda_{\text{min}}$--.

Relative Thermodynamic Stabilities of N$^1$- and N$^3$-Benzy1-4-Acetamidobenzimidazole

The N$^3$ product (0.010 g, 0.038 mM) from the benzylation of anionic 4-acetamidobenzimidazole was dissolved in DMF (0.5 ml) and benzyl chloride (0.005 ml, 0.043 mM) added. The solution was heated at 125° for 4 days before the products were isolated and analysed. P.m.r. (CDCl$_3$) and qualitative t.l.c. (silica gel/10% methanol:CHCl$_3$) showed that the N$^1$ product was mainly present with small amounts of N$^3$. A more quantitative evaluation was not possible.
The N¹ product (0.150 g, 0.566 mM) from the benzylolation of anionic 4-acetamidobenzimidazole was dissolved in DMF (2 ml) and benzyl chloride (0.62 ml, 0.174 mM) was added. The solution was heated at 125° for 4 days before the products were isolated and analysed. The p.m.r. spectrum (CDCl₃) indicated only N¹ to be present. Qualitative t.l.c. (silica gel/10% methanol:CHCl₃) showed N¹ and a trace of N³ (possibly present in the starting material).
Theoretical Calculations

The procedure followed in performing the benzimidazole molecular orbital calculations is described in the following extract. It is taken from an article by the original workers\textsuperscript{27} which is yet to be submitted for publication.

"Standard self-consistent-field molecular orbital calculations were performed with a modified version of the Gaussian 70 system of programmes using the minimal STO-3G basis set.

![Diagram of structural parameters for benzimidazole and its anion](image)

Figure 1

Structural parameters for the unsubstituted benzimidazole and its anion were derived from crystallographic data. In both cases a regular hexagon was used for the benzene
ring with bond lengths the average of those in the experimental structure. The crystallographic values were used directly for the hetero-ring of benzimidazole itself, while for its anion there values were averaged (to give $C_{2v}$ symmetry).

Less reliance can be given to crystallographic C-H and N-H lengths so standard values were used for these. The resultant model geometries are summarised in Figure 1.

The calculations were performed for benzimidazoles with amino, nitro or cyano substituents in either the 4 or 5 position. The basic structure of the substituted benzimidazoles was taken from Figure 1 (in the extract) with standard parameters being used for the substituents. For the anionic systems, calculations were made of (i) Molecular Electrostatic Potential minima ($V_{\text{min.}}$); (ii) the electron population, $2p(z)$, of the nitrogen atoms' π type p-orbital; (iii) the $2p(y)$ electron population of the nitrogen atoms; (iv) the total electron population, $q_{\text{tot.}}$, of the nitrogens; (v) the overlap population within bonds $1,2(\pi_{N1-C2})$ and $2,3(\pi_{C2-N3})$; (vi) coefficients of the $2p(z)$ orbitals on the nitrogens in the highest occupied molecular orbitals (H.O.M.O.); and (vii) Protonation Energy of the nitrogens.

Also calculations were made of the linear correlation coefficients between the $N1/N3$ M.E.P. minima differences for each system and the corresponding differences in the other parameters. The coefficients, plus other calculated results, are presented in the following table taken from the same source as the extract.
### Theoretical Parameters Associated with the Site of Protonation in Benzimidazole Anions

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<th>Substituent</th>
<th>Site</th>
<th>( V_{\text{min.}} ) (kcal/mole)</th>
<th>( 2p(z) )</th>
<th>( 2p(y) )</th>
<th>( q_{\text{tot.}} )</th>
<th>( \pi\text{-N} )</th>
<th>C.H.O.M.O.</th>
<th>( E_{\text{prot.}} ) (kcal/mole)</th>
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</tr>
<tr>
<td>Correlation Coefficient with ( \delta V_{\text{min.}} )</td>
<td>(1.000)</td>
<td>0.050</td>
<td>0.908</td>
<td>0.820</td>
<td>0.639</td>
<td>0.283</td>
<td>0.978</td>
<td></td>
</tr>
</tbody>
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References

(Literature citation: Australian Journal of Chemistry)


