Outcome-Changing Effect of Polarity Reversal in Hydrogen-Atom-Abstraction Reactions

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S Supporting Information

ABSTRACT: We have examined hydrogen-atom-abstraction reactions for combinations of electrophilic/nucleophilic radicals with electrophilic/nucleophilic substrates. We find that reaction between an electrophilic radical and a nucleophilic substrate is relatively favorable, and vice versa, but the reactions between a radical and a substrate that are both electrophilic or both nucleophilic are relatively unfavorable, consistent with the literature reports of Roberts. As a result, the regioselectivity for the abstraction from a polar substrate can be reversed by reversing the polarity of the attacking radical. Our calculations support Roberts' polarity-reversal-catalysis concept and suggest that addition of a catalyst of appropriate electrophilicity/nucleophilicity can lead to an enhancement of the reaction rate of approximately 5 orders of magnitude. By exploiting the control over regioselectivity associated with the polar nature of the radical and the substrate, we demonstrate the possibility of directing the regioselectivity of hydrogen abstraction from amino acid derivatives and simultaneously providing a significant rate acceleration.

INTRODUCTION

Free radicals are of great importance in many aspects of synthetic chemistry, industrial polymerization processes, and biological reactions.^{1,2} Radicals have been widely studied theoretically,³ and in particular, we have examined computationally their thermodynamic stabilities, as reflected for example in bond dissociation energies, in a series of recent studies.^{4–7} Thermodynamic stability is a major factor that affects the reactivity of radicals, through the Bell–Evans–Polanyi principle.⁸

However, thermodynamics does not provide the whole picture of radical reactivity. There are a number of additional important contributing factors, including polar effects operating along the reaction profile, which are determined by the electrophilic or nucleophilic character of the radicals and the substrates.^{9,10} Indeed, in recent investigations of abstraction of hydrogen from amino acid derivatives by $\bullet\text{Cl}$ and $\bullet\text{OH}$, we concluded that polar effects play a vital role in determining the regioselectivity of the abstractions.^{11–13} Specifically, polar effects with these electrophilic radicals direct the abstraction away from the thermodynamically preferred α -position, at which the electron-withdrawing substituents have a deactivating effect in the transition structure.

Exploitation of polar effects to achieve selectivity and catalysis in radical reactions has been described more generally in a review by Roberts.¹⁴ He noted, for example, that reaction between an electrophilic radical and a nucleophilic substrate is favorable, and vice versa, but reactions between a radical and a substrate that are both electrophilic or both nucleophilic are unfavorable. Such a principle has been employed in a number of reactions as detailed in ref 14. In one example that we will

further analyze in our study,¹⁵ a nucleophilic additive was used to facilitate the otherwise slow reaction between an electrophilic substrate and an electrophilic radical. The concept has further been employed in, for example, hydroacylation, dehalogenation, hydrosilylation, and carboxyalkylation reactions.¹⁴

As noted above, the contrathermodynamic regioselectivity observed in abstractions of hydrogen from amino acids and related small peptides by $\bullet\text{Cl}$ and $\bullet\text{OH}$ has been ascribed to polar effects.^{11–13} If this is indeed the case, reversing the polarity of the abstracting radical should have predictable consequences. In the study presented here, we test this proposition as part of a more general examination of the reverse polarity effect and its influence on regioselectivity and reactivity in hydrogen abstractions. We hope that this computational study, together with previous experimental observations, will provide the basis for a better understanding of polar effects in radical reactions, as well as for tuning radical reactions by exploiting the polar nature of various radicals and substrates.

COMPUTATIONAL DETAILS

Standard ab initio molecular orbital theory and density functional theory (DFT) calculations^{16,17} were conducted with Gaussian 09.¹⁸ The computational approach used in this study is based on a previous protocol that we have found to yield kinetic information of reasonable accuracy.^{19,20}

Gas-phase geometries of stationary points were obtained with the BHandH-LYP/6-31+G(d,p) procedure. Following

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each geometry optimization, harmonic frequency analysis was used to confirm the nature of each stationary point as an equilibrium structure or a transition structure. Improved single-point energies were evaluated using the B2K-PLYP/aug'-cc-pVTZ procedure.²¹ To obtain the zero-point vibrational energies (ZPVEs) and thermal corrections for enthalpies (ΔH_{298}) and entropies (S_{298}) at 298 K, we used BHandH-LYP/6-31+G(d,p) harmonic vibrational frequencies and appropriate literature scale factors.²² In cases in which solvent effects are taken into account, solvation corrections were obtained at the M05-2X/6-31G(d) level²³ using the SMD model.²⁴ The parameters for either acetic acid or carbon tetrachloride were used in the SMD calculations.

In a number of cases, we employ the IRCmax method²⁵ to approximate a high-level reaction path to make direct comparisons with our previous studies.^{11–13} This is achieved by conducting high-level (B2K-PLYP/aug'-cc-pVTZ) single-point energy calculations on a reaction path obtained using the IRC procedure²⁶ at a lower level [BHandH-LYP/6-31+G(d,p)].

RESULTS AND DISCUSSION

Effect of Reversal of Polarities in Abstraction of Hydrogen from Acetylated Amino Acids. In our previous studies of abstraction of hydrogen from *N*-acetylamino acids by electrophilic radicals such as $\bullet\text{Cl}$ and $\bullet\text{OH}$,^{11–13} a key finding was the confirmation of the experimentally observed regioselectivity,²⁷ corresponding to reactions occurring predominantly at positions away from the α -position (Table 1).

Table 1. Calculated Condensed-Phase (Acetic Acid) Free Energy Barriers (kilojoules per mole) for Abstraction of Hydrogen from *N*-Acetylamino Acids by Various Radicals

	$\bullet\text{Cl}^a$	$\bullet\text{OH}^a$	$\text{NH}_3\text{Me}_2\text{B}^\bullet$
α	29.6	51.5	34.8
β	26.4	48.7	89.7
γ	23.5	46.6	99.6
δ	22.9	38.9	100.9
ϵ	23.3	39.0	94.3

^aResults for $\bullet\text{Cl}$ and $\bullet\text{OH}$ are from refs 11 and 13, respectively.

This observation was anomalous in that the α -abstraction is strongly favored thermodynamically because of captodative stabilization of the product α -radical. The behavior has been attributed to deactivating polar effects in the transition structures arising from destabilizing interactions between the electrophilic radicals and the electron-withdrawing α -substituents.^{11–13} This explanation can be tested by employing a nucleophilic radical instead of an electrophilic radical for the hydrogen abstraction, in which case a reversal in the regioselectivity might be anticipated.

We have therefore examined the abstraction reactions of our model acetylated amino acids [1 and 2 (Figure 1)] with the nucleophilic radical, $\text{NH}_3\text{Me}_2\text{B}^\bullet$.¹⁴ Consistent with our previous theoretical studies,^{11–13} we have used the variational IRCmax approach, together with a continuum solvation model (with parameters for acetic acid) to estimate the free energies of solvation, to afford barriers that could be compared with experimental solution-phase measurements.²⁷ We can see that, while the side-chain reactions with $\text{NH}_3\text{Me}_2\text{B}^\bullet$ are highly unfavorable, with barriers of approximately 90–100 kJ mol^{−1} (Table 1), hydrogen abstraction by this nucleophilic boron-

Figure 1. Model *N*-acetylamino acids used in this study.

centered radical at the α -position is considerably more facile, with a much smaller barrier of 34.8 kJ mol^{−1}. Our calculated bond dissociation energies for Cl-H (423.7 kJ mol^{−1}) and $\text{NH}_3\text{Me}_2\text{B-H}$ (417.2 kJ mol^{−1}) are quite similar, and therefore, the difference in the regioselectivities for $\text{NH}_3\text{Me}_2\text{B}^\bullet$ and $\bullet\text{Cl}$ can largely be attributed to their contrasting polar character. Thus, these results indeed support the proposition that the barriers for abstraction of hydrogen from acetylated amino acids are significantly influenced by polar effects, with the regioselectivity being reversed when the abstracting radical is changed from electrophilic ($\bullet\text{Cl}$ or $\bullet\text{OH}$) to nucleophilic [$\text{NH}_3\text{Me}_2\text{B}^\bullet$]. In this context, it is interesting to note that Nature uses thyl radicals for α -abstraction,^{28,29} instead of oxygen-centered radicals such as $\bullet\text{OH}$ that show side-chain reactivity. However, for thyl radical abstractions, the reversal of regioselectivity is likely not to be due to polar effects, but rather to the fact that the reaction free energy is favorable only for α -abstraction.³⁰

Generality of the Effect of Polar Interactions on the Regioselectivity of Hydrogen Abstraction. In the previous section, we demonstrated a change in regioselectivity for abstraction of hydrogen from *N*-acetylamino acids as a result of a change in the electrophilic/nucleophilic character of the abstracting radical. We may anticipate that such an effect would be applicable more generally, as suggested by Roberts,¹⁴ to the four cases spanned by the combination of an electrophilic or nucleophilic radical and an electrophilic or nucleophilic substrate, corresponding to the presence in the substrates of electron-withdrawing or electron-donating substituents, respectively (Table 2).

Table 2. Anticipated Regioselectivity for Hydrogen Abstraction by an Electrophilic or Nucleophilic Radical from an Electrophilic or Nucleophilic Substrate

radical	substrate	substituent on substrate	expected preferred site of reaction
electrophilic	nucleophilic	electron-donating	close to substituent
electrophilic	electrophilic	electron-withdrawing	away from substituent
nucleophilic	nucleophilic	electron-donating	away from substituent
nucleophilic	electrophilic	electron-withdrawing	close to substituent

To assess the validity of these qualitative predictions, we have examined the reactions of two hypothetical substrates, namely, nucleophilic 3 and electrophilic 4 (Figure 2). The formally anionic Me_3B^- group in 3 serves as a strongly electron-donating substituent, while the cationic Me_3N^+ group in 4 is expected to be strongly electron-withdrawing. For the radicals, we again use $\text{NH}_3\text{Me}_2\text{B}^\bullet$ as the nucleophilic radical. For an electrophilic radical, there are a large number of options, including $\bullet\text{Cl}$, $\bullet\text{OH}$, and $\bullet\text{OOH}$. Among these, $\bullet\text{Cl}$ is the most electrophilic,

Figure 2. Nucleophilic (3) and electrophilic (4) substrates containing strongly electron-donating (Me_3B^-) and strongly electron-withdrawing (Me_3N^+) groups, respectively, as well as nucleophilic [$\text{NH}_3\text{Me}_2\text{B}^\bullet$] and electrophilic ($\bullet\text{Cl}$) abstracting radicals. The combination of these substrates and radicals gives rise to the four scenarios shown in Table 2.

and we have selected this as the electrophilic radical in the reactions with 3 and 4.

The gas-phase free energy barriers for the reactions between substrates 3 and 4 and radicals $\bullet\text{Cl}$ and $\text{NH}_3\text{Me}_2\text{B}^\bullet$ are shown in Table 3. We first note that some of the barriers are highly

Table 3. Calculated Gas-Phase Free Energy Barriers (kilojoules per mole) for Abstraction of Hydrogen from Substrates 3 and 4 (Figure 2) by Radicals $\bullet\text{Cl}$ and $\text{NH}_3\text{Me}_2\text{B}^\bullet$

	3 with $\bullet\text{Cl}$	4 with $\bullet\text{Cl}$	3 with $\text{NH}_3\text{Me}_2\text{B}^\bullet$	4 with $\text{NH}_3\text{Me}_2\text{B}^\bullet$
α	−70.5	52.6	88.3	42.3
β	−51.6	37.1	77.5	43.4
γ	−24.8	13.9	75.7	57.4
δ	−15.0	6.4	61.0	63.5
ϵ	−11.9	7.9	64.5	69.8

negative. Examination of a selection of the reaction paths that correspond to these negative barriers at the BHandH-LYP/6-31+G(d,p) level, i.e., the method used for geometry optimizations, shows that the reaction paths in these cases involve complexes that lie lower in energy than the separated reactants and lower in energy than the transition structures. The effect of such reactant complexes has been discussed in our previous studies,^{11,12} and here we simply note that, in the examples presented here, they somewhat moderate the trend but do not lead to qualitative changes.

For the reactions of the electrophilic $\bullet\text{Cl}$ with nucleophilic substrate 3, the barrier at the α -position is the most negative ($-70.5 \text{ kJ mol}^{-1}$). The barrier becomes less negative as the site of reaction progressively moves away from the negatively charged Me_3B^- substituent ($-11.9 \text{ kJ mol}^{-1}$ at the ϵ -position). This is consistent with the qualitative prediction of Table 2. The opposite trend is seen for hydrogen abstraction by electrophilic $\bullet\text{Cl}$ from electrophilic substrate 4, where the α -barrier is the largest (52.6 kJ mol^{-1}), and the barrier generally decreases for reactions occurring more remotely from the positively charged Me_3N^+ group (7.9 kJ mol^{-1} for ϵ -abstraction). This is again consistent with the qualitative prediction of Table 2. On the other hand, with the nucleophilic radical $\text{NH}_3\text{Me}_2\text{B}^\bullet$ as the abstracting species, the α -barrier is the largest when nucleophilic 3 is the substrate (88.3 and 64.5 kJ mol^{-1} for α - and ϵ -abstractions, respectively), but it is the lowest with electrophilic 4 (42.3 kJ mol^{-1} at the α -position and 69.8 kJ mol^{-1} at the ϵ -position). These results are also consistent with the predictions shown in Table 2 and further demonstrate the importance of polar effects in radical reactions.

Polarity-Reversal Catalysis. We now examine how polar effects can be exploited to accelerate chemical reactions. The concept of polarity-reversal catalysis was proposed by Roberts,¹⁴ to make use of the different reactivity patterns in hydrogen-abstraction reactions depending on the nucleophilicities and electrophilicities for the radical and substrate. To connect Roberts' observations with data that are more quantitative in nature, we have conducted detailed high-level calculations on a model system, closely related to a system that he examined.

Consider abstraction of hydrogen from CH_3CN by $\text{MeO}^\bullet$ [reactants A yielding products C (Figure 3)]:

Figure 3. Calculated gas-phase free energy profile (kilojoules per mole) for uncatalyzed [A to C (reaction 1)] and catalyzed [A to B to C (reactions 2 and 3)] hydrogen abstractions by $\text{MeO}^\bullet$ from CH_3CN . The catalyst $\text{NH}_3\text{Me}_2\text{B-H}$ is denoted NB-H.

This is a reaction of an electrophilic radical ($\text{MeO}^\bullet$) with an electrophilic substrate (CH_3CN), so it might be expected to involve a significant barrier. Indeed, we find that the reaction has to overcome a gas-phase free energy barrier of 77.7 kJ mol^{-1} (Figure 3), despite being exergonic by 29.8 kJ mol^{-1} .

A nucleophilic substrate added as a catalyst might be expected to undergo more facile abstraction by the electrophilic $\text{MeO}^\bullet$. We use $\text{NH}_3\text{Me}_2\text{BH}$ as the nucleophilic substrate:

and indeed the free energy barrier for abstraction by $\text{MeO}^\bullet$ from $\text{NH}_3\text{Me}_2\text{BH}$ is just 31.2 kJ mol^{-1} . The reaction free energy to give intermediates B is $-14.4 \text{ kJ mol}^{-1}$ (Figure 3).

As the second step in the two-stage catalyzed process, $\text{NH}_3\text{Me}_2\text{B}^\bullet$ (a nucleophilic radical) formed in reaction 2 abstracts a hydrogen from CH_3CN (an electrophilic substrate) to again give products C (Figure 3):

This nucleophilic radical/electrophilic substrate combination might also be expected to have a small barrier. Indeed, we calculate a barrier of just 37.3 kJ mol^{-1} and an exergonicity of $-15.4 \text{ kJ mol}^{-1}$.

Our calculations thus show, consistent with Roberts' observations, that the barriers (31.2 and 37.3 kJ mol^{-1}) for the two steps of the catalyzed process (reactions 2 and 3, respectively) are substantially smaller than the barrier (77.7 kJ mol^{-1}) for uncatalyzed reaction 1. The benefit of adding the

Figure 4. Comparison of calculated condensed-phase (CCl_4) free energy profiles (kilojoules per mole) for abstraction of hydrogen by $\text{MeO}^\bullet$ from acetylated amino acids 2 in the absence of a catalyst (---) and in the presence of the nucleophilic catalyst $\text{NH}_3\text{Me}_2\text{BH}$ (denoted NB-H) (—): (A) from the α -position and (B) from the ϵ -positions.

polarity-reversal catalyst corresponds to a striking rate enhancement of approximately 5 orders of magnitude at room temperature!

How does such a result compare with experiment? There are no explicit measured rate data reported in the study by Roberts.¹⁵ Nonetheless, their results indicate that, for the reaction of *tert*-butoxyl radical with a mixture of CH_3CN and oxirane, there was no reaction with CH_3CN . In contrast, when an amine–borane was present in the mixture, the reaction occurred exclusively with CH_3CN . If we assume that in each case, the minor reaction path represents <1% of the overall reaction, then such a complete reversal of the selectivity corresponds to an enhancement in the rate for the CH_3CN reaction of at least 4 orders of magnitude. This is fully consistent with our theoretical results.

Application to the Functionalization of Acetylated Amino Acids. We have shown in earlier sections that the regioselectivity for abstraction of hydrogen from *N*-acetylated amino acids with $\text{NH}_3\text{Me}_2\text{B}^\bullet$ is the opposite of that with $\bullet\text{OH}$ (Table 1). We have also demonstrated how addition of a catalyst of appropriate electrophilicity/nucleophilicity can very significantly accelerate the reaction (Figure 3). In this section, we exploit both these features in the context of functionalizing amino acids and show how polarity-reversal catalysis can lead to both an acceleration in the rate of reaction and a change in the regioselectivity.

Figure 4 compares the reaction pathways for α -abstraction and ϵ -abstraction by the electrophilic $\text{MeO}^\bullet$ from the acetylated amino acid 2 in a CCl_4 solution, in the absence and presence of the nucleophilic catalyst $\text{NH}_3\text{Me}_2\text{BH}$. In the uncatalyzed reaction, the barrier for abstraction from the α -position (83.0 kJ mol^{-1}) is considerably greater than that at the ϵ -position (69.1 kJ mol^{-1}). Thus, the direct reaction of 2 with $\text{MeO}^\bullet$ should preferentially lead to production of the ϵ -radical.

When the $\text{NH}_3\text{Me}_2\text{BH}$ catalyst is added, there is a two-step reaction, in a manner similar to that depicted in Figure 3. Our calculations indicate that the first step, which involves reaction of $\text{MeO}^\bullet$ with $\text{NH}_3\text{Me}_2\text{BH}$ and is common to both the α - and ϵ -abstractions, has a barrier of just 42.4 kJ mol^{-1} . Importantly, this is significantly smaller than the barrier for direct hydrogen abstraction by $\text{MeO}^\bullet$ at either the α -position (83.0 kJ mol^{-1}) or the ϵ -position (69.1 kJ mol^{-1}) of 2. It is therefore likely to result in the production of $\text{NH}_3\text{Me}_2\text{B}^\bullet$ as a major reactive

hydrogen-abstracting species. In the second step, abstraction by $\text{NH}_3\text{Me}_2\text{B}^\bullet$ from the α -position of 2 has a barrier (40.1 kJ mol^{-1}) much lower than that of abstraction from the ϵ -position (90.9 kJ mol^{-1}). Accordingly, in the presence of $\text{NH}_3\text{Me}_2\text{B-H}$ as a catalyst, α -abstraction is calculated to be the predominant pathway, with a barrier lower than that of either the catalyzed or uncatalyzed ϵ -abstraction.

Thus, the inclusion of $\text{NH}_3\text{Me}_2\text{BH}$ as a catalyst in the reaction of $\text{MeO}^\bullet$ with acetylated amino acids leads to an acceleration in the rate of reaction and a change in regioselectivity due to the polarity-reversal-catalysis effect.

CONCLUDING REMARKS

In this study, we have examined hydrogen-abstraction reactions involving the various combinations of electrophilic/nucleophilic radicals with electrophilic/nucleophilic substrates, to demonstrate how polar effects can be exploited in radical reactions. For the four combinations of radical and substrate that we have examined, viz. (1) electrophilic radical/nucleophilic substrate, (2) electrophilic radical/electrophilic substrate, (3) nucleophilic radical/nucleophilic substrate, and (4) nucleophilic radical/electrophilic substrate, we find that examples 1 and 4 are indeed favorable while examples 2 and 3 are unfavorable, as proposed by Roberts. As a result, different regioselectivities are observed, with reactions for combinations 1 and 4 having a preference to occur close to the polar substituent, while the opposite is true for combinations 2 and 3.

Our calculations reinforce the polarity-reversal-catalysis concept of Roberts and provide a quantification of the effect of using the nucleophilic catalyst $\text{NH}_3\text{Me}_2\text{BH}$ together with an initial electrophilic radical $\text{MeO}^\bullet$ in hydrogen-abstraction reactions. Our results suggest that such a system can have a rate that is approximately 5 orders of magnitude faster than its uncatalyzed counterpart.

We have also performed calculations on abstractions of hydrogen from model amino acids and show how the polarity-reversal-catalysis concept can be exploited in these systems. In particular, we find that through addition of an appropriate catalyst, it is possible to modify the regioselectivity and to accelerate the rate of reaction.

■ ASSOCIATED CONTENT

■ Supporting Information

Optimized geometries [BHandH-LYP/6-31+G(d,p)] of the relevant species, zero-point vibrational energies, thermal corrections to enthalpies, entropies, and B2K-PLYP/aug'-cc-pVTZ electronic energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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