Mechanisms of the Intriguing Rearrangements of Activated Organic Species

A Thesis Submitted for the Degree
of
Doctor of Philosophy
of
The Australian National University

by

David Grant Harman

Department of Chemistry
Faculty of Science
Canberra

April 2003

Declaration

This thesis is an original work. None of the work has been previously submitted by me for the purpose of obtaining a degree or diploma in any university or other tertiary education institution. To the best of my knowledge, this thesis does not contain material previously published by another person, except where due reference is made in the text.

To those who tell me the truth in love,
particularly when I do not want to hear it.

Acknowledgements

Many people, too numerous to mention individually, assisted in the production of this thesis. Corporately I wish to thank them and to express my deep and sincere gratitude. I would briefly like to mention those to whom I am particularly indebted and I apologise to anyone whom I have inadvertently omitted.

Professor Athel Beckwith was my supervisor while I was working in the laboratories of the Research School of Chemistry. Athel and his wife Kaye made me feel welcome in Canberra. I'm grateful to have worked on such challenging projects and to have had such expert guidance. Athel's love for chemistry, his vast knowledge, his view of the bigger picture and the humility to admit when he didn't know something have been the source of much inspiration.

My RSC advisers were Professor Lew Mander, Professor Rod Rickards and Dr John MacLeod. I would like to thank them and other academic, technical and administrative staff for valuable advice and assistance. Mr Robert Longmore deserves a particular mention for his laboratory prowess, his willingness to share his expertise and his friendship. So does Mrs Joan Smith—RSC Librarian Extraordinaire—for her helpfulness, patience, encouragement and continual grace when loans were overdue.

Dr Steven Brumby helped me record the esr spectra. My brother, Mr Ian Harman, helped me with the computer program used to determine the rotational barriers in β-substituted ethyl radicals. Ms Peta Simmonds, Mrs Tin Culnane and Mr Chris Blake of the ANU NMR Centre helped me with two-dimensional and ^{17}O nmr. Drs Graham Heath, Richard Webster and Brett Yeomans assisted me with the recording and interpretation of cyclic voltammagrams.

I thank the Australian Government for a Commonwealth Postgraduate Research Award, known later as the Australian Postgraduate Research Award. I'm grateful to have received an Australian National University PhD Scholarship for six months upon the expiration of my APRA.

I'm one of the lucky few who have worked in both the Research School of Chemistry and the Department of Chemistry. Professor Jack Elix has been my supervisor during my time in the Department. I'd like to thank him for taking on a student from a field quite different to his own, for his efforts in correcting thesis drafts and for his gentle advice. Drs Christina Chai and Geoff Salem, my current advisers, I thank for their assistance. My passage into the Department was facilitated by past Heads Professor Jack Elix and Dr Gad Fischer. Thanks also to the current Head, Dr Geoff Salem, for his support. Mr Warren Griffiths provided tireless assistance with computer problems.

And last, but by no means the least, I'd like to acknowledge the unending support my parents Kay and Grant have given me in realms moral, spiritual and financial and for some proof reading.

Abstract

The β-acyloxyalkyl radical rearrangement has been known since 1967 but its mechanism is still not fully understood, despite considerable investigation. Since the migration of a β-trifluoroacetoxy group generally proceeds more rapidly and with more varied regiochemistry than its less electronegative counterparts, this reaction was studied in the hope of understanding more about the subtleties of the mechanism of the β-acyloxyalkyl radical rearrangement. The mechanism of the catalysed rearrangement of *N*-alkoxy-2(1*H*)-pyridinethiones was also explored because preliminary studies indicated that the transition state (TS) for this process was isoelectronic with TSs postulated for the β-acyloxyalkyl radical and other novel rearrangements.

A kinetic study of the rearrangement of the 2-methyl-2-trifluoroacetoxy-1-heptyl radical in solvents of different polarity was undertaken using a radical clock method. Arrhenius equations for the rearrangement in each solvent were: hexane, $\log_{10}[k_r\ (\mathrm{s}^{-1})] = 11.8\pm0.3 - (48.9\pm0.7)/\theta$; benzene, $\log_{10}[k_r\ (\mathrm{s}^{-1})] = 12.0\pm0.2 - (43.7\pm0.8)/\theta$; and propionitrile, $\log_{10}[k_r\ (\mathrm{s}^{-1})] = 11.9\pm0.2 - (42.0\pm0.3)/\theta$. Rate constants at 75˚C were: hexane, $k_r = 2.9 \times 10^4$; benzene, $k_r = 2.8 \times 10^5$; and propionitrile, $k_r = 4.0 \times 10^5\ \mathrm{s}^{-1}$. The equilibrium constant for the reversible rearrangement at 80°C in benzene was $15.1 < K < 52.9$.

A regiochemical study with oxygen-labelled radicals revealed that trifluoroacetoxy group migration occurs with 66-83% label transposition (3,2 shift). The proportion of 3,2 shift is decreased by polar solvent, high temperature and low concentration of the reducing agent. Results of labelling experiments were consistent with cooperative 1,2 and 3,2 shifts, the former having Ea 9.5 kJmol^{-1} higher than the latter in benzene solution.

An esr study of nine β-oxygenated radicals revealed that the temperature-dependent equilibrium conformation is controlled by a balance between steric and stereoelectronic effects. The influence of the latter is increased by electron-attracting β-substituents. Barriers to C_α–C_β rotation in β-*oxy*ethyl radicals are approximately the same as for the propyl radical. Consequently, there is no significant through-space interaction between the β-substituent and the unpaired electron.

Experimental results were consistent with a mechanism involving a combination of polarized 1,2 and 3,2 concerted shifts. The results may also be rationalised by the intermediacy of a contact ion pair, as well as combinations of the three options.

The rearrangement of *N*-alkoxy-2(1*H*)-pyridinethiones is catalysed by oxidants, Lewis acids and protic acids. Pseudo first order kinetics are observed and there are moderate solvent effects. The migration of a 1,1-dideuteroallyl group occurs almost exclusively in a 1,4 sense. Migration of an enantiomerically enriched 1-phenylethyl group proceeds with predominant retention of configuration in chloroform, but with virtual racemisation in acetonitrile. Migrating groups do not become diffusively free during the rearrangement. Substituents which stablise positive charge at C1 migrate more rapidly. The bulk of evidence indicates that a catalyst activates the pyridinethione for rearrangement by promoting aromatisation. Mass-spectrometric analysis of an isolated intermediate and kinetic results are consistent with an intermolecular mechanism.

Abbreviations and symbols

A	adenine
A	Arrhenius frequency factor
abs.	absolute
Ac	acetyl
ACS	American Chemical Society
AIBN	azobis(isobutyronitrile)
AM1	Austin Model 1
AM1-SM2	Solvation Model 2 based on the Austin Model 1
amu	atomic mass units
ANU	Australian National University
Ar	aryl
ASTM	American Society for Testing and Materials
B3LYP	Becke three parameter hybrid function, using the Lee-Yang-Parr correction
bp	boiling point
BP1	GC stationary phase consisting of dimethylpolysiloxane
BP5	GC stationary phase consisting of 5% phenyl / 95% dimethylpolysiloxane
BP10	GC stationary phase consisting of 14% cyanopropylphenyl / 86% dimethyl polysiloxane
BP20	GC stationary phase consisting of polyethylene glycol
BSTFA	bis(trimethylsilyl)trifluoroacetamide
Bu	*n*-butyl
cal	calorie
calc.	calculated
CIDNP	chemically induced dynamic nuclear polarisation
CIMS	chemical ionisation mass spectrometry
CIP	contact ion pair
conc.	concentrated *or* concentration
COSY	correlated nmr spectroscopy
CT	charge transfer
Δ	heat applied
DMAP	dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPO	5,5-dimethyl-1-pyrroline *N*-oxide

DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ε	dielectric constant
Ea	Arrhenius activation energy
e.e	enantiomer(ic) excess
EI	electron impact
EIMS	electron impact mass spectrum/spectrometry
eq.	equivalent(s) *or* equation
esr	electron spin resonance spectroscopy
Et	ethyl
E_T	Dimroth-Reichardt parameter for the ionising power of a solvent
Fc	ferrocenium
F_r	fraction of retention of configuration upon rearrangement
FTIR *or* ftir	fourier transform infrared spectroscopy
G3(MP2)	Gaussian 3 theoretical calculations applied to a geometry determined by second order Moller-Plesset pertubation theory
GC	gas chromatography
GCMS	gas chromatography / mass spectrometry
HETCOR	heteronuclear correlated nmr spectroscopy
hfs	hyperfine splitting
HP1	GC stationary phase consisting of dimethylpolysiloxane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
I.D.	inner diameter
INDO	molecular orbital theory incorporating the intermediate neglect of differential overlap
ir	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	symbol for nmr coupling constant
K	equilibrium constant
k	rate constant
KIE	kinetic isotope effect
lit.	literature value
LR HETCOR	long-range (2 and 3 bond) ^{13}C-^{1}H shift-correlated heteronuclear nmr
m-CPBA	*m*-chloroperbenzoic acid
m/z	mass to charge ratio
Me	methyl
min(s)	minute(s)

MO	molecular orbital
mp	melting point
MS	mass spectrometry
Ms	methanesulfonyl
MW	molecular weight
n.d.	not detected
n-Pr	*n*-propyl
n.r.	not resolved
Nu	nucleophile
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NMA	*N*-methylacetamide
nmr	nuclear magnetic resonance spectroscopy
PFK	perfluorokerosene
PFMC	perfluoromethylcyclohexane
Ph	phenyl
PM3	third parametrisation of the Modified Neglect of Diatomic Differential Overlap
ppm	parts per million
Pr	*n*-propyl
PT	pyridinethione
ρ	Hammett parameter measuring the susceptibility of the reaction to electronic effects
R	gas constant
R	alkyl radical *or* substituted alkyl radical
RBF	round-bottomed flask
R_E	proportion of original concentration of label remaining in the oxygen of the same hybridisation in the product ester
Rf	chromatographic retardation factor
σ	standard deviation
σ_p^+	Hammett parameter describing the degree to which a *para* electron-donating group interacts with a developing positive charge in the transition state
SAR	sarcophagine
SGE	Scientific Glass Engineering (company)
SOMO	singly occupied molecular orbital
SSIP	solvent-separated ion pair

STO-3G	basis set consisting of Slater-type orbitals approximated by three primitive Gaussian functions
SVF	standard volumetric flask
T	temperature
t	time
t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBTH	tributyltin hydride
TCD	thermal conductivity detector
TFAA	trifluoroacetic anhydride
tfc	3-(trifluoromethylhydroxymethylene)camphorato
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl *or* tetramethylsilane
Tol	*p*-tolyl
Tos	*p*-toluenesulfonyl
triflic	trifluoromethanesulfonic
TS	transition state/structure
TTMSS	tris(trimethylsilyl)silane
U	uracil
UV	ultraviolet
Val	valine
vis	visible
VLC	vacuum liquid chromatography
w.r.t.	with respect to
WCOT	wall-coated open-tubular
[X]	concentration of substance X

Word Count

Chapter	Words
1	5263
2	15546
3	17761
4	15263
5	26896
6	6091
7	3272
Total	90092

Contents

Chapter 3: A labelled-oxygen study of the regiochemistry of the β-trifluoroacetoxyalkyl radical rearrangement 74

Chapter 4: An esr study of β-oxygenated alkyl radicals 133

Chapter 5: The mechanism of the catalysed rearrangement of *N*-alkoxy-2(1*H*)-pyridinethiones 192

Chapter 7: General experimental 306

Appendix D: The preparation, purification, purity determination and storage of tributyltin hydride 344

I had learned that all the greatest and most important problems of life are fundamentally insoluble. They must be so, for they express the necessary polarity in every self-regulating system. They can never be solved, but only outgrown....What a fool I was! How I tried to force everything to go the way I thought it ought to!

C. G. Jung

Commentary on 'The Secret of the Golden Flower', *Collected Works* 13 (1938).