

Center For Heterocyclic Compounds, Department of Chemistry, University of Florida
Gainesville, Florida 32611-2046, USA

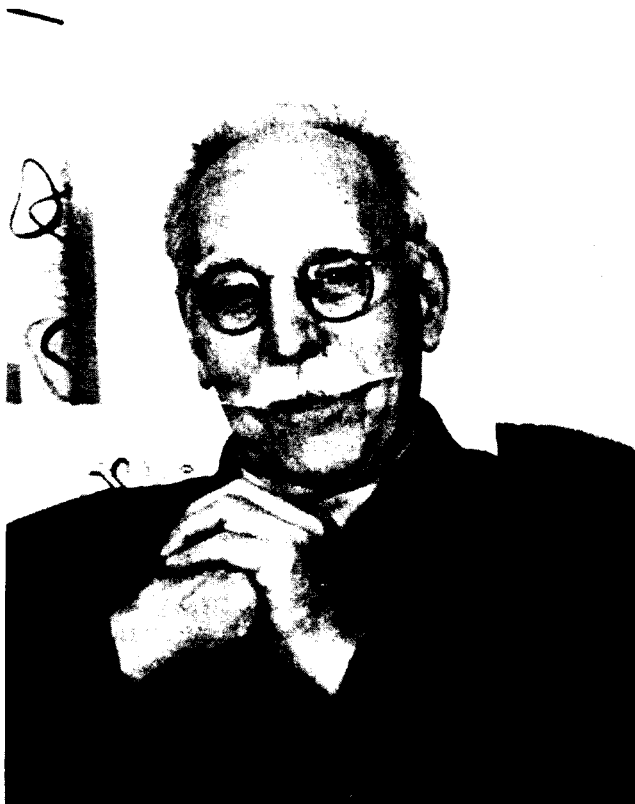
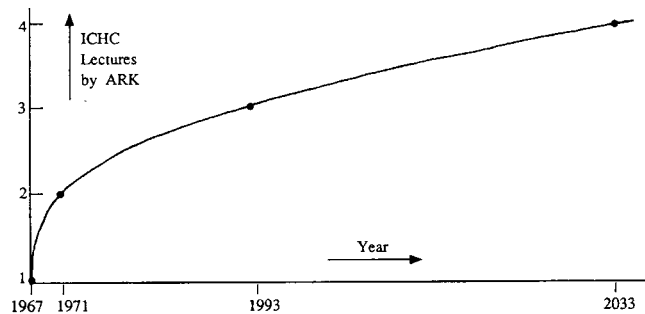
J. Heterocyclic Chem., **31**, 569 (1994).

I must start by thanking all who have made this lecture possible: our ISHC President, Jan Bergman, the Selection Committee for the Award, the Parke-Davis Division of Warner-Lambert, and the Conference President Professor Frank Aldeweirdt. I realize that this is a most important, and indeed a unique, opportunity. I have had the honor of delivering Plenary Lectures previously at two of these International Conferences of Heterocyclic Chemistry. In 1967, in 1971, and now in 1993. These points lie on a smooth curve (Scheme 1), and by extrapolation, I realize that the next time I shall receive this honor will be in 2033. Unfortunately, for various reasons, I feel it probable that many of you may not be in Lima to hear me. So I will try to do my best today.

Two major early influences were my father, Charles Katritzky (he was not a chemist even though several times people around the world have told me that they were familiar with some of my father's chemical publications), and Bill Fieldhouse, my first teacher of chemistry, who died this year at the age of 92 (Scheme 2). These were the good old days when the sticks were big and the carrots

Scheme 1. Highlights from 50 Years of Heterocyclic Chemistry

My heart felt thanks to	My realization of an important opportunity
President Professor Jan Bergman	1st ICHC 1967 Albuquerque, New Mexico
The Selection Committee for the Award	3rd ICHC 1971 Sendai, Japan
Parke Davis Division of Warner-Lambert	14th ICHC 1993 Antwerp, Belgium
Conf. President Professor Frank Aldeweirdt	34th ICHC 2033 Lima, Peru (unfortunately many of you will not be there to hear me)

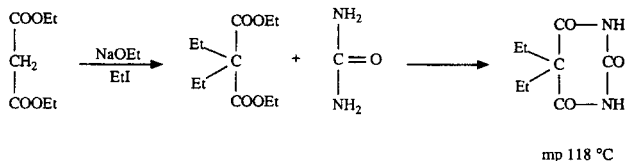


Scheme 2. F. Charles Katritzky and W. C. Fieldhouse

Scheme 3. Early Influences : Big Sticks and Little Carrots

F. Charles Katritzky
Father : 1928-75W. C. (Bill) Fieldhouse
Schoolmaster: 1941-2

August 18th, 1943 : Preparation of Veronal



were little. My first preparation of a heterocyclic compound took place on my 15th birthday, when I prepared the compound Veronal, as shown in Scheme 3. This was truly the stone age, as you see from the archaic rectangular structure used for barbiturate drugs at that time.

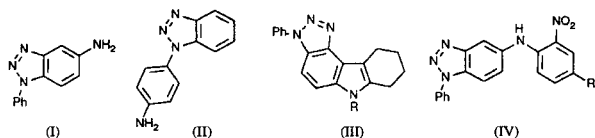
Scheme 4. 1948 - 1958 : Oxford Training

Freddie Brewer
Inorganic Tutor
+ Mayor of OxfordDicky Barrow
Physical Tutor
+ PhilosopherS. G. P. Plant
Organic Tutor
+ Taskmaster

Printed from the Journal of the Chemical Society, February 1953, (83), Pages 412 - 416

Experiments on the Preparation of Indolocarbazoles. Part
VI.* Compounds from Two of the Amino-1-phenylbenzotriazoles

By A. R. Katritzky and S. G. P. Plant



Substituted 5-Amino-1-phenylbenzotriazoles (IV). - After a mixture of 5-amino-1-phenylbenzotriazole, mp 158° (5 g, prepared by a method essentially the same as that of Beretta, *Gazzetta*, 1925, 55, 788), 1-chloro-2,4-dinitrobenzene (5.5 g), and anhydrous sodium acetate (5 g) had been heated on a steam-bath for 2 hours, the whole extracted with dilute hydrochloric acid, and the dried residue crystallised from acetic acid, 5-(2,4-dinitroanilino)-1-phenylbenzotriazole (6.2 g) was obtained in orange needles, mp 229-30° (found: C, 57.0; H, 3.6. calc. for C₁₈H₁₂O₄N₆: C, 57.4; H, 3.2%). The substance is evidently the same as that (mp 228°) prepared by Manjunath (*J. Indian Chem. Soc.*, 1927, 4, 271) and called "1-p-2'-4'-dinitroanilinophenylbenzotriazole." In early preparations 5-amino-1-phenylbenzotriazole was obtained in an unstable polymorphic form, mp 128°.

The period 1948 to 1958 I spent at Oxford, and had the pleasure and fortune to be instructed by three very different tutors (Scheme 4). Freddie Brewer did not know too much chemistry but he was the source of wisdom on many other topics. Sidney Plant, a no-nonsense organiker kept my nose to the grindstone. I have tried to emulate his techniques in my own dealings with my students because I know how much they will appreciate it later, if not

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OUR REF.

LETTER NO.

DATE

STAFF DEPARTMENT (R). 24808/T.

A.R. Katritzky, Esq.,
37 Pembroke Street,
Cowley Road,
OXFORD.

23rd May, 1952.

Dear Sir,

With reference to your meeting with our Selection Panel at Shell Lodge, this is to advise you that we have given careful consideration to your application and it is with regret we are writing to say we can find no opening in our organisation, either in this country or overseas, which we could offer you.

We should like to take this opportunity of thanking you very much for the trouble you have taken in pursuing your application and ask you to accept our best wishes for your future success.

We are returning herewith the photograph you so kindly sent us.

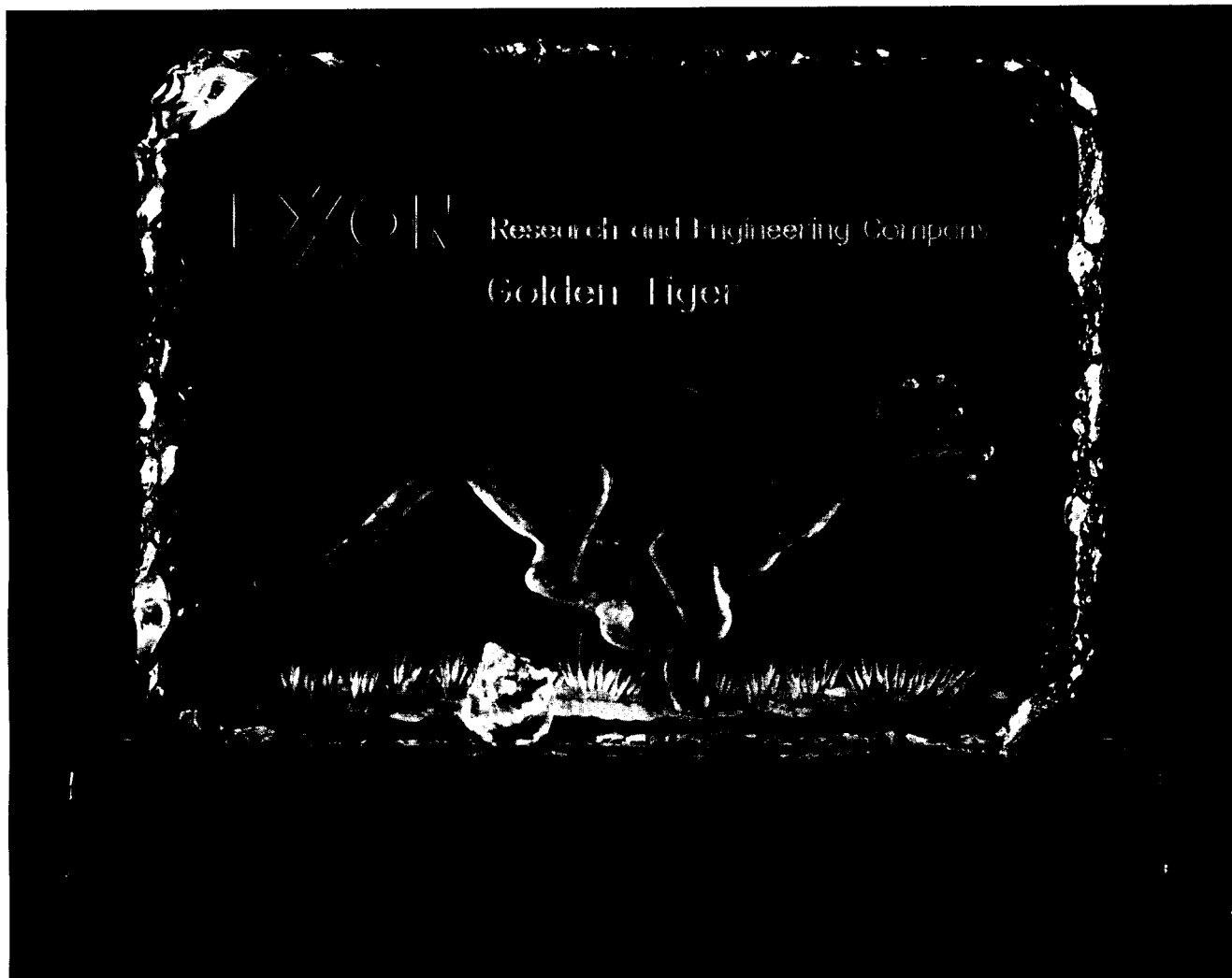
Yours truly,
For: THE SHELL PETROLEUM CO., LTD.

AFR/APN.

Scheme 5. Rejection by Shell

always at the time. Finally, Dicky Barrow, who I am pleased to say is still alive, was a grand tutor of Physics and Metaphysics as well as of Thermodynamics. For my part two thesis, the year of research that is carried out at Oxford, I worked with Sid Plant, and you will see that my first paper in benzotriazole chemistry was published more than 40 years ago in 1953. When people tell me I have been publishing too many papers dealing with benzotriazoles, I point out that the average is still less than three a year from the time I commenced.

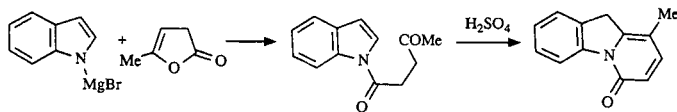
1952! There I was, degree in hand and ready to serve the world. I offered myself (Scheme 5) to your Dutch cousins (yes, cousins "familie heeft men, vrienden kiest men")—confident that they would recognize their opportunity. Alas, it was not to be! (See Scheme 5). How different life would have been -I would be here today with my personal jet rather than as a poor academic! Thirty years later, in partial compensation, I became senior chemical consultant to Exxon and you can see the tiger jumping over the shell in Scheme 6, but at the time I had to resign myself to futher study.



Scheme 6. Senior Chemical Consultant for Exxon 1981-present

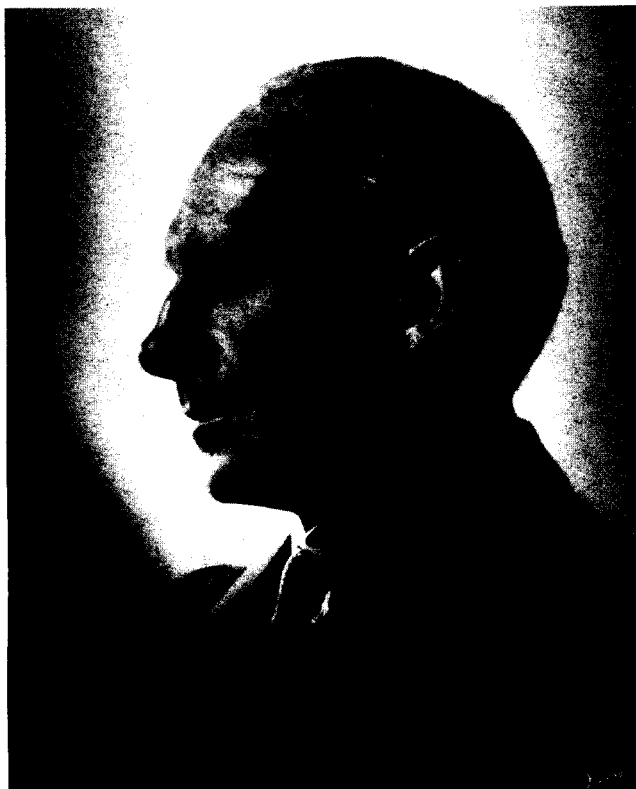
Scheme 7. Doctoral Training : D. Phil 1952 - 1954

Sir Robert Robinson, O.M., FRS
President of the Royal Society



Doctoral training was with Sir Robert Robinson (Scheme 7), who I was fortunate to see no less (or more!) than five times for discussion during the two years needed for my D. Phil. (Scheme 8). He believed in teaching people to swim by throwing them in at the deep end: if one survived, it was certainly a very effective method. However, it was only by my luck that I achieved my doc-

torate because I already had in press the first of what, unfortunately, was to be a series of highly untactful papers scattered throughout my career. This paper (Scheme 9) appeared in the Spring of 1955 and made fun of Professor Wilson Baker's representation of mesomeric betaines. I was able to show that a logical extension of Baker's reasoning would mean that we should draw a \pm inside a circle within all benzene rings! Wilson Baker was at the time a big-name professor at the University of Bristol. More importantly to me, he was my external examiner for the D. Phil. degree. I was encouraged to write and submit the paper by Sir Robert Robinson. When it had been accepted, I felt it would only be polite to send a copy to Professor Baker, but when I did this, he reacted most violently. (Sir Robert claimed that he had received the most vigorous letter of his career.) Professor Baker wanted me to withdraw the paper, but like the young fool that I then was (and some 50% of this phrase still applies), I persisted.



Scheme 8. Sir Robert Robinson, O. M., F.R.S., Waynflete Professor, Oxford & Doctor-vater

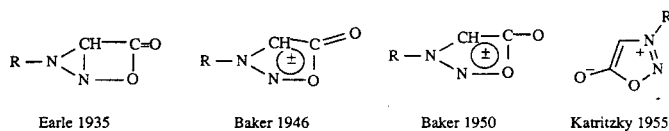
Scheme 9. Reprinted from Chemistry and Industry, 1955, pp. 521-522

THE REPRESENTATION OF THE SO-CALLED MESOIONIC COMPOUNDS

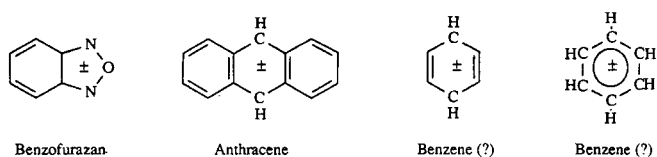
By A. R. Katritzky

The Dyson Perrins Laboratory, Oxford University

The purpose of this paper is to point out inconsistencies in the literature and future dangers in the use of \pm and the term "mesoionic".



It is not clear why syndones should be called mesoionic because they are fundamentally different from other organic compounds yet other compounds are called partially mesoionic.



Sir Robert Robinson: "You are doing a public service but please tone down your thanks to me".

It was not all work and study at Oxford and some other aspects of life there are shown in Schemes 10-12.

In 1955, Sir Robert was succeeded at Oxford by Sir Ewart Jones, and I continued my independent research



Scheme 10. Watching our next victims - summer nights, 6 bumps, 1949



Scheme 11. View of Oxford College



Scheme 12. Punting

Scheme 13. Heteroaromatic N-Oxides (66 Papers, 1956-1993)

- Review:** "The Chemistry of the Aromatic Heterocyclic N-Oxides", *Quar. Revs.*, **10**, 359 (1956).
- Monograph:** "Chemistry of the Heterocyclic N-Oxides", (with J. M. Lagowski), Academic Press, London and New York, 1971.
- Review:** "Heterocyclic N-Oxides and N-Imides", (with J. N. Lam), *Heterocycles*, **33**, 1011 (1992).

Coworkers in N-Oxide Field

Group Members: Initials and surnames listed alphabetically

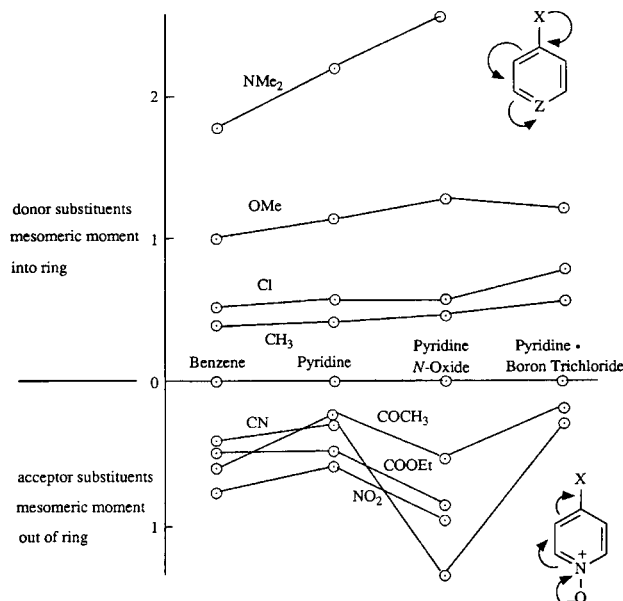
E. Anders	V. Feyselman	D. J. Short
P. Barczynski	M. Gordeev	P. Simmons
A. J. Boulton	C. D. Johnson	M. Szafran
M. P. Carmody	J.M. Lagowski	R. D. Tack
S. J. Cato	J. N. Lam	T. W. Toone
A. V. Chapman	P. Linda	J.-J. Vanden Eynde
M. J. Cook	G. Musumarra	H. Witek
N.L. Dassanayake	A. D. Page	Z. Zhang

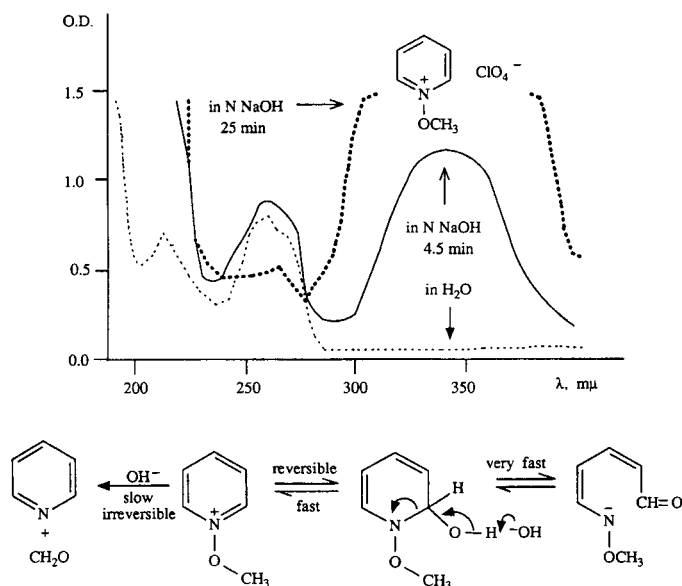
External Collaborators: Initials and surnames listed alphabetically

M. H. Abraham	G. M. Glover	D. Pisano
A.F.Danil de Namor	T. C. Ho	J. Reisse
L. Dumont	M. Hely Hutchinson	L. E. Sutton
C. Ebert	G. J. Palenik	J. G. Tropsch
		N. S. Zefirov

with my first chemical love, the pyridine *N*-oxides. The extent of our work in *N*-oxide chemistry is shown in Scheme 13. One of my first papers was to demonstrate by the concept of mesomeric moments that the *N*-oxide group could be either a source of electrons or an electron sink, depending on the electronic character of the substituent in the 4-position of the pyridine 1-oxide ring. The

Scheme 14. Mesomeric Moments of Pyridine N-Oxides and Related Compounds



Scheme 15. Action of Hydroxide Ion on *N*-Methoxyppyridinium Perchlorate

mesomeric moment of a conjugated compound is obtained by subtracting the expected components from the actual dipole moment measured. This difference represents the degree of interaction between the substituents and the ring heteroatom. As shown in Scheme 14, the interaction of electron donor groups in the 4-position increases from benzene to pyridine to pyridine *N*-oxide and is the greatest in the pyridine-boron trichloride complexes. However, for electron acceptor groups in the 4-position, the mesomeric moment out of the ring is much greater for pyridine *N*-oxides than for either pyridines or for pyridine-boron trichloride complexes, demonstrating that the *N*-oxide can be an electron-donor.

Another facet of *N*-oxide chemistry was discovered when the action of dilute sodium hydroxide solution on *N*-methoxyppyridinium perchlorate, a reaction well-known to yield pyridine and formaldehyde, was followed in the ultraviolet spectrum. Surprisingly, a transient intense band with a maximum near 340 millimicrons was uncovered. This was tracked down to be due to two successive reversible attacks on the pyridine ring by hydroxide groups resulting in the transient formation of an open chain conjugated species as shown in Scheme 15.

A second major research field that commenced in 1958 was the study of heteroaromatic tautomerism as documented in many papers and reviews (Scheme 16). An ongoing interest was the effect of substitution on tautomeric equilibria. This is illustrated for chlorine substitution at the top of Scheme 17, where the very different effects of chlorine atoms in different positions are shown: almost no change in K_T for 3,5-substitution but with a dramatic effect from 2,6-substitution. The rationalization

Scheme 16. Heteroaromatic Tautomerism (71 Papers, 1958-1993)

- Reviews: "Prototropic Tautomerism of Heteroaromatic Compounds: I. General Discussion and Methods of Study", (with J. M. Lagowski), *Adv. Heterocycl. Chem.*, **1**, 312 (1963).
 "Prototropic Tautomerism of Heteroaromatic Compounds: II. Six-Membered Rings", (with J. M. Lagowski), *Adv. Heterocycl. Chem.*, **1**, 341 (1963).
 "Prototropic Tautomerism of Heteroaromatic Compounds: III. Five-Membered Rings and One Hetero Atom", (with J. M. Lagowski), *Adv. Heterocycl. Chem.*, **2**, 1 (1963).
 "Prototropic Tautomerism of Heteroaromatic Compounds: IV. Five-Membered Rings with Two or More Hetero Atoms", (with J. M. Lagowski), *Adv. Heterocycl. Chem.*, **2**, 27 (1963).
 "Tautomeria Eteroaromatica", *La Ricerca Scientifica*, **53**, 36 (1968).
 "The Protropic Tautomerism of Heteroaromatic Compounds", *Chimia*, **24**, 134 (1970); Russian translation: *Uspekhi Khimii*, **41**, 700 (1972).
 "The Aromaticity of Heterocycles and Tautomeric Equilibria", *J. Heterocyclic Chem.*, **IX**, S-39 (1972).
 "Aromatic Property and Tautomeric Equilibria of Heterocycles", *Khim. Geterotsikl Soedin.*, **8**, 1011 (1972).
 "Prototropic Tautomerism of Heteroaromatic Compounds", (with M. Karelson and P. A. Harris), *Heterocycles*, **32**, 329 (1991).

Coworkers in Heteroaromatic Tautomerism

Group Members: Initials and surnames listed alphabetically

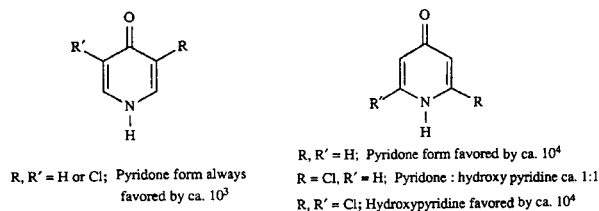
A. S. Afridi	T. M. Dand	A. A. Gordon	J. R. Lea	J. D. Rowe
G. Baykut	S. El-Abbadly	R. A. Jones	P. Linda	S. K. Roy
G. P. Bean	J. Elguero	M. Karelson	R. Murugan	T. D. Singh
A. J. Boulton	J. Ellison	H. Z. Kucharska	S. Nadji	J. Stevens
K. C. Caster	I. J. Fletcher	W. Kuzmierkiewicz	A. D. Page	M. Szafran
S. O. Chua	J. Frank	J. M. Lagowski	F. D. Popp	R. Tack
M. J. Cook	S. Golding	A. R. Lapucha	S. Rachwal	B. Ternai
			M. Ramaiah	A. J. Waring

External Collaborators: Initials and surnames listed alphabetically

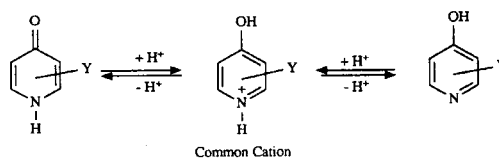
J. Arriau	R. Flamang	T. Matsui	G. Pfister-Guillouzo	C. B. Theissling
A. Dargelos	C. Guimon	Z. Meszaros	M. Taagepera	Y. van Haverbeke
C. de Meyer	L. G. Hepler	H. Mispereuve	R. W. Taft	M. C. Zerner
J. Eyley	A. Maquestiau	N.M.M. Nibbering	J. Teyssieyre	

is given at the bottom of Scheme 17, in terms of the common cation that is formed by the protonation of each tautomer: the tautomeric equilibrium can thus be deduced from the relative acidities of the two hydrogen atoms that can be lost from this cation. The position today is really

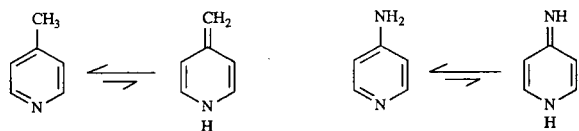
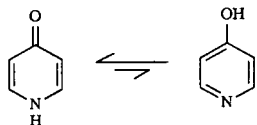
Scheme 17. Pyridone Tautomerism: Effect of Chlorine Substitution

(all K_T values refer to aqueous solution)

Effect of Additional C-Substituents on Tautomeric Pyridines

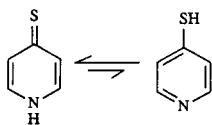
Loss of H from N: pK (substituted pyridine) = 5.25 - 5.90 σ_1 Loss of H from O: pK (substituted pyridone) = 10.00 - 2.11 σ_1 - 2.11 σ_2 (Where σ_1 refers to a substituent constant and σ_2 to a heterogroup constant)

Scheme 18. Summary of Heteroaromatic Tautomerism

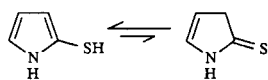
-CH₃ almost always exist as such-NH₂ almost always exist as such-OH frequently exist in C=O form when α or γ to a pyridine-like ring nitrogen

This tendency strongly decreased by:

- nonpolar media
- diminished basicity of pyridine nitrogen
- possibility for OH to hydrogen-bond



-SH resemble OH in six-membered rings

-SH resemble NH₂ in five-membered rings

quite simple: the generalizations given in Scheme 18 account for the correct tautomeric predominance of the vast majority of heterocyclic compounds, with potentially tautomerisable CH₃, NH₂, OH and SH substituents, although significant exceptions do exist.

Scheme 19. Call a Spade a Spade

Chemistry and Industry, 1965, pp. 331-335

H. L. Yale "Sulphur Compounds" in Erwin Klingsberg (Volume Editor) "Pyridines Part IV" in Weisberger (Series Editor) "Chemistry of Heterocyclic Compounds"



"Although the evidence favours the thione form, in this chapter they are represented in the thiol form to follow Chemical Abstracts" (the blind leading the blind).

Consequences of the blunder:

- p 353: acidity of SH discussed -- there is no SH group
- p 354: mechanism of oxidation given -- with wrong structures
- p 354: stated that pyridine thiols have the normal reactions of thiols -- quite incorrectly

I have always felt that a compound should be depicted by the formula that most accurately represents its structure, but this simple principle has frequently been neglected by chemists, at times quite willfully. My article "Call a Spade a Spade" was written in 1965 on the pretext of reviewing a book in one of the most famous reference series in heterocyclic chemistry. I pointed out that, because of the author's blunder, much of his ensuing dis-

Scheme 20. Extracts from subsequent correspondence: *Chemistry and Industry*, 1965, pp 335-812:

Dr. L. C. Cross (Editor, Chem. Soc.): difficulty arises because Dr. Ulbricht's "logically correct" name is wrong. The word "tool" is preferable to "4-pronged potato-fork".

Dr. S. C. Jolly (Pharm Soc. of G.B.): Dr. Cross's evasive action tool could be "beech-handled stainless-steel garden fork".

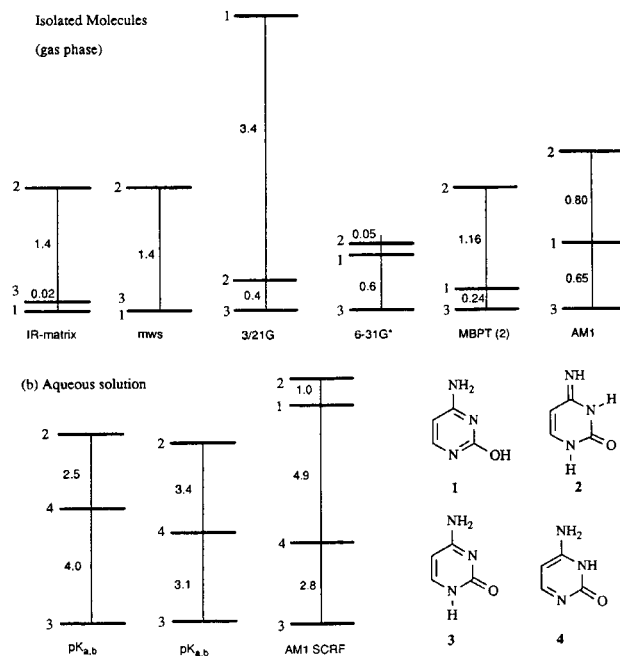
Dr. T. L. V. Ulbricht : question of which description is "right" has no bearing on the issue.

Dr. E. Klingsberg (Volume Editor): uniformity of nomenclature has overriding importance decision was taken before publication of much recent work.

Dr. F. R. Wetsel (Chem. Abstracts Service): CA does not change an author's name.

"To Call a Spade a Spade"

Udall (1542) translated Erasmus' rendering of Plutarch: "the Macedonians wer feloes of no fyne witte in their termes, but altogether grosse, clubbyshe, and rusticall, as they whiche had not the witte to call a spade by any other name then a spade."

Scheme 21
Experimental and Theoretical Estimations of the Relative Cytosine Tautomer Energies (kcal/mol)

cussion is completely incorrect (Scheme 19). The forthright critical tone of this article had some interesting consequences, some of which are mentioned in Scheme 20. In more recent years, we have been able, using semi-empirical molecular orbital methods, and in particular AM1 corrected for solvent interactions, to get good agreement with theory for tautomeric equilibria, both as isolated molecules and as aqueous solutions. Such work is illustrated for cytosine in Scheme 21, where the AM1

deduced K_T values are shown to be in good agreement with the published experimental data, some of which had been provided by our group 30 years earlier.

Scheme 22. Infrared Spectroscopy-Intramolecular Interactions (95 Papers, 1958-1990)

Reviews: "The Infrared Spectra of Heteroaromatic Compounds", *Quart. Revs.*, **13**, 353 (1959).

"Characteristic Infrared Absorption of Heterocyclic Compounds", *Adv. in Molec. Spectros.*, **834** (1962).

"Infrared Spectra", (with A. P. Ambler), **2**, 161 (1963).

"Distortions of the π -Electron System in Substituted Benzenes", (with R. D. Topsom), *Angew. Chem. (Eng. Ed.)*, **9**, 87 (1970). *Angew. Chem. (German Ed.)*, **82**, 106 (1970).

"The Infrared Spectroscopy of Heterocycles", (with P. J. Taylor), *Physical Methods in Heterocyclic Chemistry*, vol IV, Academic Press, New York, p.265 (1971).

"Infrared Intensities: A Guide to Intramolecular Interactions in Conjugated Systems", (with R. D. Topsom), *Chem. Rev.*, **77**, 639 (1977).

"Some Applications of Infrared Intensities to the Study of Intramolecular Interactions in Organic Chemistry", (with R. D. Topsom), *Vibrational Intensities in Infrared and Raman Spectroscopy*, Elsevier Scientific Publishing Company, New York, p.337 (1982).

Coworkers in the Field of Infrared Spectroscopy - Intramolecular Interactions

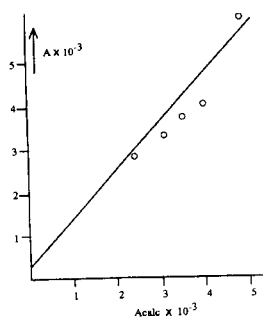
Group Members: Initials and surnames listed alphabetically

A. P. Ambler	N. A. Coats	A. R. Hands	A. F. Pozharsky	A. J. Sparrow
J. M. Angelelli	N. C. Cutress	K. F. Johnson	R. E. Reavill	F. J. Swinbourne
N. Bacon	M. Davis	R. A. Jones	B. J. Ridgewell	M. Szafran
P. Barczynski	Z. Dega-Szafran	H. J. Keogh	J. D. Rowe	C. Thirkettle
J. A. T. Beard	P. J. Q. English	J. M. Lagowski	R. G. Shepherd	T. T. Tidwell
A. J. Boulton	G. P. Ford	S. Oksne	M. Shome	R. D. Topsom
R.T.C. Brownlee	J. N. Gardner	C. R. Palmer	P. Simmons	A. J. Waring
B. Brycki	T. B. Grindley	R. F. Pinzelli	M. V. Sinnott	L. Yakhontov

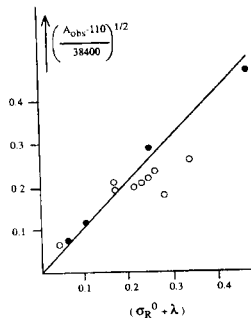
External Collaborators: Initials and surnames listed alphabetically

W. Armarego	E. Dulewicz	M. I. Kabachnik	B. Nogaj	G.P. Schiemenz
T. J. Broxton	C. Eaborn	P. Koziol	S. Ohlenrott	R. A. Shanks
G. Butt	H. Götz	K. Lempert	Y. T. Pang	P. J. Taylor
D.G. Cameron	S. Gronowitz	A. Liu	C. Paulmier	L. H. Teo
M. Chaillet	E. Heilbronner	R. Liu	C. Pouchan	E. N. Tsvetkov
G. Cheeseman	A. Hrynio	I. G. Malakhov	J. Puskas	D.R.M. Walton
A. Dargelos	R.E.J. Hutchinson	J. Morel		
L. W. Deady	H. Kaack	J.A. Munday		

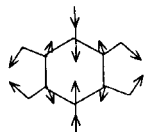
Scheme 23. Integrated Infrared Intensities as a Measure of Intramolecular Interaction



Plot of observed (A) vs calculated (A_{calcd}) intensities for the combined ν_8 vibrations of monosubstituted benzenes (line of best fit is $A = 1.16A_{\text{calcd}} + 48$; correlation coefficient, 0.989; standard deviation, 300)



Plot of $[(A_{\text{obsd}} - 110)/38400]^{1/2}$ against $[\sigma_R^0 + \lambda]$ for ν_{15} for 2-substituted furans: (●) donor substituents; (○) π -acceptors



normal coordinate for 1600 cm^{-1} band

$$A = \frac{\pi N_0}{3000C^2 \times 2.303} \left(\frac{\delta \mu}{\delta Q} \right)^2$$

Eq. Proportional to square of rate of change of dipole moment with the normal coordinate

The third major topic of research that I started while still at Oxford was that of infrared spectroscopy (Scheme 22) which developed later into the study of infrared inten-



Scheme 24. Oxford: Magdalen College Tower

shown in Scheme 23.

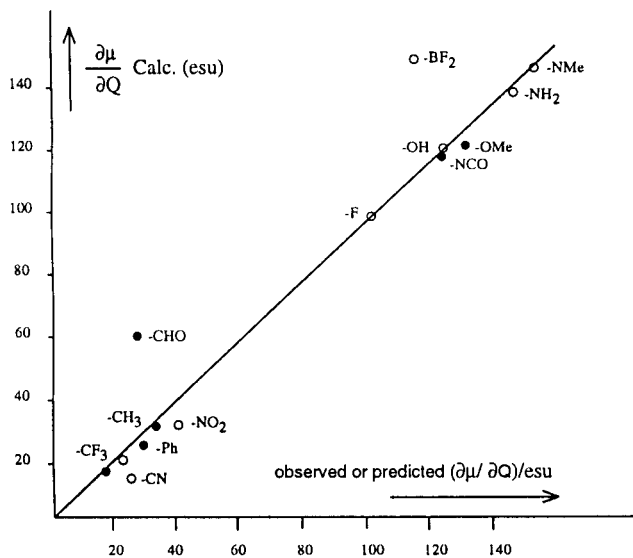
We demonstrated that it was quite possible to calculate infrared intensities for some of the aromatic ring stretching modes from first principles by considering the change

sities used particularly as a measure of intramolecular interactions. The application of some of this work to monosubstituted benzenes and to substituted furans is

Scheme 25. Molecular Orbital Calculation of IR Intensities

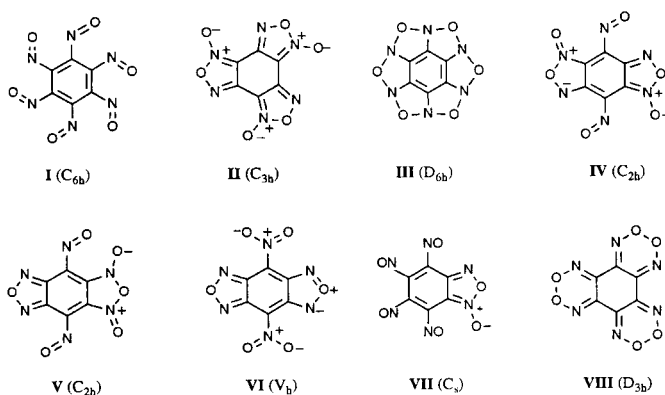
$$A = \frac{\pi N_0}{3000C^2} \left(\frac{d\mu}{dQ} \right)^2 = 0.702 \left(\frac{d\mu}{dQ} \right)^2$$

Calculation of $d\mu / dQ$: utilise variation of β with CC length and known normal coordinates; bond orders are given in units of β .



plot of calculated $d\mu / \partial Q$ value (in esu) for monosubstituted ethylene against observed (●) or predicted (○) values

Scheme 26. Structures for Hexanitrosobenzene



Hexanitrosobenzene				
Structure	Point group	IR	Ra	Coincidence
I	C _{6h}	7	13	0
III	C _{6h}	7	11	0
IV	C _{2h}	24	24	0
VI	D _{2h} (V _h)	13	16	0
II	C _{3h}	16	27	11
VIII	D _{3h}	13	22	11
V	C _{2v}	40	48	40
VII	C _s	48	48	48
Spectrum measured		15	15	8

Structure II later proved by X-ray analysis



Scheme 27. Cambridge: Trinity Hall

Scheme 28. Cambridge Interlude 1958 - 1963 : Oxbridge Colleges

Lord Todd, OM, FRS
Lord God of Chemistry

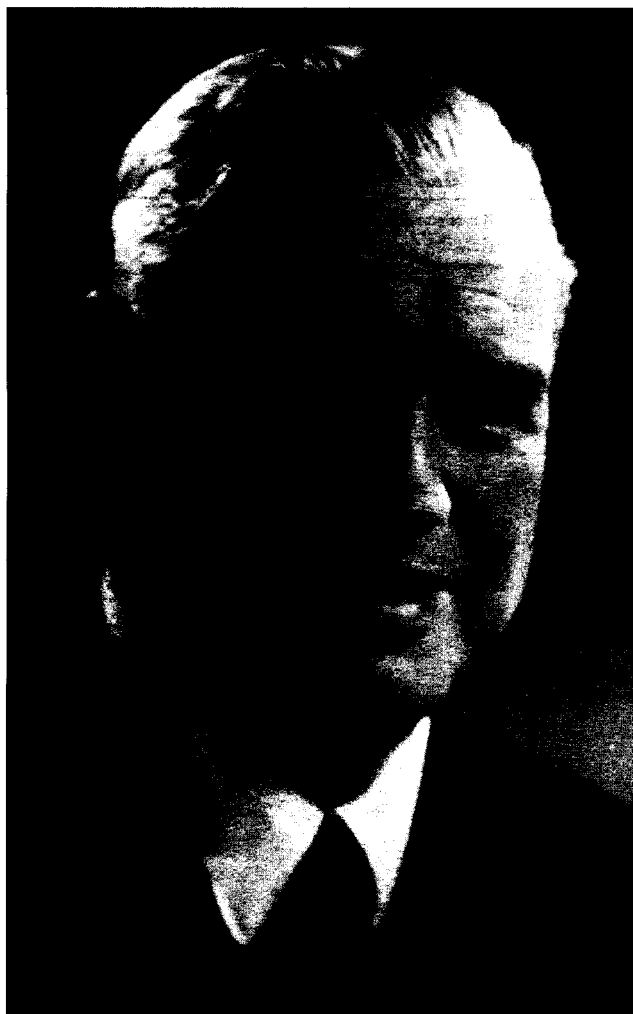
Sir John Cockcroft, OM, FRS
Founder Master of Churchill

Oxford		Cambridge	
St. Catherines - Commoner	1948	Trinity Hall - Senior Member	1958
Magdalen - Senior Demy	1956	Churchill - Founder Fellow	1959
Penbrook - College Lecturer	1957		

in the dipole moment of a molecule with the deformation along the normal coordinate of the particular vibrational mode. This is illustrated in Scheme 25. An application of infrared spectroscopy to heterocyclic chemistry was an examination of so-called hexanitrosobenzene for which the 8 structures at the top of Scheme 26 had all been considered. The point group of each of these alternative struc-

tures determines the number of infrared and Rahman bands that should be active, and the number of coincidences. It was thus clearly shown that the only two structures possible were II and VII, with II more probable. Shortly afterwards, II was indeed proved by X-ray analysis.

At the end of 1957, I left Oxford. Luckily, Professor Sir Ewart Jones was so extremely anxious that I should leave Oxford to gain good experience elsewhere, that he wrote an uncommonly glowing letter of recommendation to Lord Todd. And so I arrived in Cambridge. Of course, college affiliation at Oxbridge is very important. Also in this respect, I shifted around a little, as shown on Scheme 28. I was particularly lucky in Cambridge to become a Founder Fellow of the then-new Churchill College (Scheme 30), of which Sir John Cockcroft was the first Master. Sir John was not only a Nobel Prize winning physicist, he also was the most skilled person I have ever



Scheme 29. Lord Todd of Trumpington & Cambridge Chemistry, Sir John Cockcroft, Founder Master of Churchill College



Scheme 30. Sir Winston Churchill at official opening of Churchill College

Scheme 31. Conformational Analysis (107 Papers, 1961-1989)

Reviews: "Conformation of Piperidine and of Derivatives with Additional Ring Heteroatoms", (with I. D. Blackburne and Y. Takeuchi), *Acc. Chem. Res.*, **8**, 300 (1975).

"The Conformational Analysis of Saturated Heterocycles", Published by Polish Academy of Science, 1975.

"N-Methyl Inversions Barriers in Six-Membered Rings", (with R. C. Patel and F. G. Riddell), *Angew. Chem. Int. Ed. Engl.*, **20**, 521 (1981).

"Conformational Equilibria in Nitrogen-Containing Saturated Six-Membered Rings", (with T. A. Crabb), *Adv. Heterocycl. Chem.*, **36**, 1 (1984).

Coworkers in Conformational Analysis

Group Members: Initials and surnames listed alphabetically

E. Anders	G. Desimoni	R. A. Kolinski	D. L. Ostercamp	B. B. Shapiro
K. K. Andersen	D. Dineen	P. G. Lehman	C. R. Palmer	M. Snarey
L. Angiolini	H. Dorn	H. H. Luce	R. C. Patel	F. Soti
V. J. Baker	R. P. Duke	J. P. Majoral	S. Rahimi-Rastgoo	A. J. Sparrow
R. W. Baldock	I. J. Ferguson	D. G. Markees	D. M. Read	J. M. Sullivan
I. D. Blackburne	G. Fodor	A. R. Martin	R. E. Reavill	F. J. Swinbourne
R. Bodalski	P. J. Halls	P. G. Mente	K.A.F. Record	Y. Takeuchi
P. J. Brignell	B. J. Hutchinson	A. M. Monro	A. C. Richards	D. L. Trepanier
F.M.S. Brito-Palma	J. -L. Imbach	M. Moreno-Manas	P. L. Russell	A. J. Waring
K. Brown	L. G. Jacks	R. Murugan	S. Saba	R. J. Wyatt
M. D. Brown	C. D. Johnson	M. Nesbit	R. Scattergood	
M. J. Cook	R.A.Y. Jones	D. L. Nicol	M. J. Sewell	

External Collaborators: Initials and surnames listed alphabetically

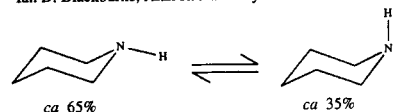
F. A. L. Anet	T. A. Crabb	T.M. Moynihan	U. Shmueli	M. S. Tute
W.L.F. Armarego	W. Fedeli	S. F. Nelson	K. Shofield	A. Vaciago
R. J. Bishop	R. B. Finzel	K. Ogawa	S. H. Simonsen	S. Weinman
R. W. Broadbent	B. Fuchs	G. Pfister-Guillouzo	R. Spagna	R. J. Wells
M. Camalli	B. Gadsby	K. Pietrusiewicz	L. E. Sutton	I. Yavari
J. R. Carruthers	C. Guimon	G. W. H. Potter	E. S. Turner	S. Yoshimura
P. J. Chivers	R. L. Harlow	F. G. Riddell		
J. J. Cook	F. Mazza	M. J. T. Robinson		

known in imposing his will on a fractious body of Fellows in a seemingly most mild manner. Political maneuvering at Oxbridge colleges is an excellent training and it stood me in good stead later at East Anglia.

Scheme 32. [ACCOUNTS OF CHEMICAL RESEARCH, 1975, 8, 300]

Conformation of Piperidine and of Derivatives with Additional Ring Heteroatoms

Ian D. Blackburne, Alan R. Katritzky and Yoshito Takeuchi



The Orientation of NH in Piperidine

Early Erroneous Conclusions in Favor of NH-Axial

1956	Barton and Cookson	Analogy with carbanions	ax
1958	Aroney and Le Fevre	Kerr constants	ax
1964	Claxton	Calculations	ax

Apparant Victory for the NH-Equatorial

1964	Katritzky and Sutton	Dipole moments	eq
1965	Allinger	Dipole moments	eq
1965	Allinger	Calculations	eq

The NH-Axial Counter-attack and Rivalry Battles

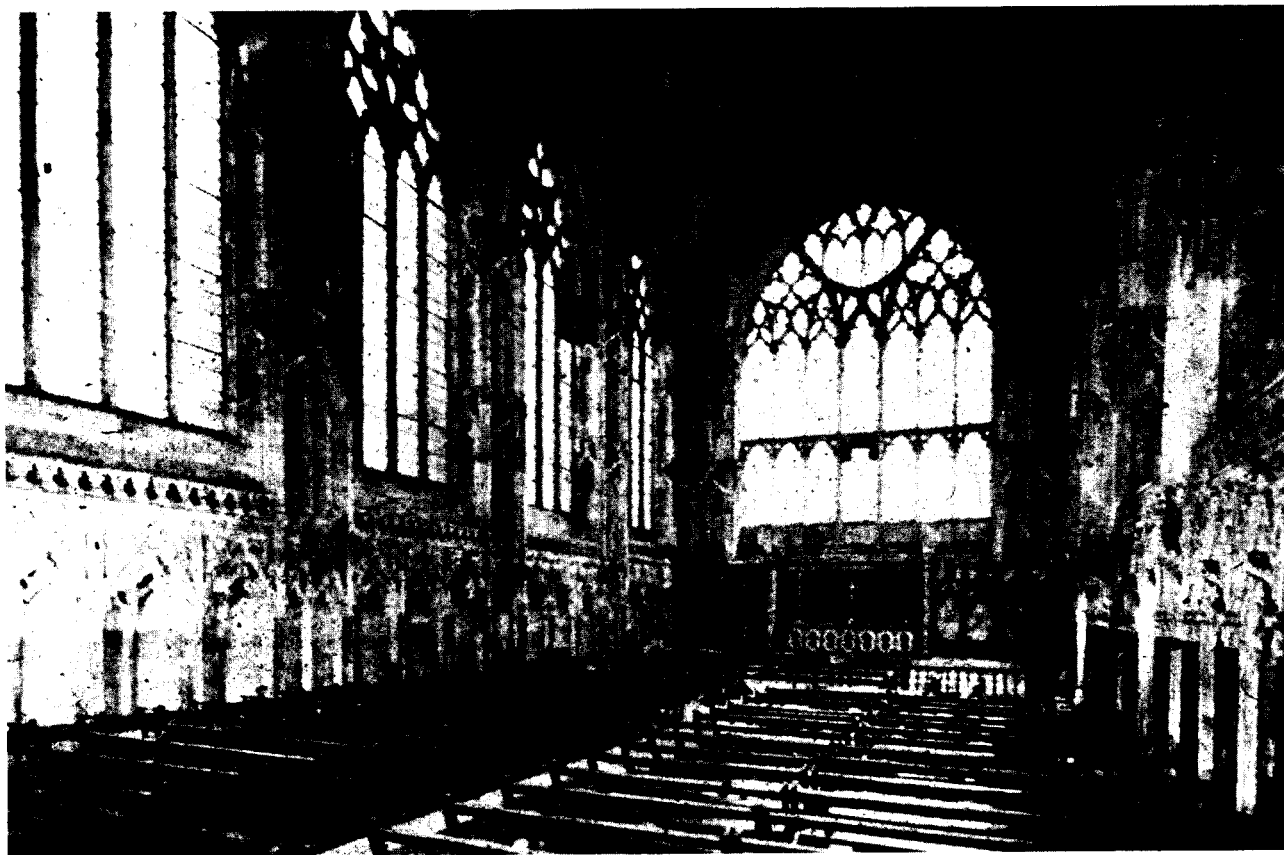
1966-67	Lambert	NMR shifts	ax
1967	Allinger	Calculations	ax
1967	Costain	Micro wave	ax
1968	Robinson	NMR shifts	eq
1968	Tsuda	Bohlmann bands	eq
1968	Katritzky	Quantitative IR	eq
1969-72	Lambert	NMR shifts	ax
1970	Costain	Micro waves	eq
1970-71	Yonezawa + Morishima	NMR shift reagents	ax

Final Prevailing of NH-Equatorial Viewpoint

1971	Scott	Thermodynamic	eq
1971	Scott	X-ray crystallography	eq
1972	Booth	Kinetic protonation	eq
1973	van Binst	NMR J. value	eq
1974	Katritzky	NMR shift reagents	eq

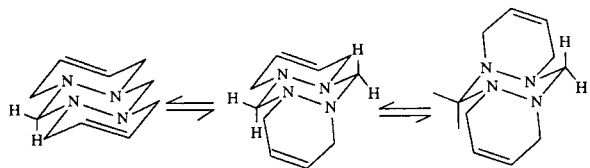
A major research topic which commenced in 1961 was the conformational analysis of heterocycles (Scheme 31). This has been another highly contentious topic. Thus, opinions regarding the dominant conformation of piperidine has been through many stages (Scheme 32) with first the NH-axial form said to be favored, then the NH-equatorial, followed by intense controversy before it was finally generally accepted that the NH-equatorial is indeed favored to a rather small extent. All this was documented in "Accounts of Chemical Research" in 1975. This account is perhaps worth recalling for the fact that the referees reports (there were five of them) amounted to about double the 15 or so pages of the scientific manuscript.

One rather spectacular result is shown for the tricyclic tetrazine in Scheme 34. This compound exists as three conformers, and the low-temperature proton and C-13 spectra show the individual signals for each of these three forms. However, on heating, these complex spectra coalesce because, at high temperatures, the conformational equilibrium is fast on the nmr time scale. The high temperature proton spectrum has just two bands. In the C-13



Scheme 33. Ely Cathedral, Lady Chapel

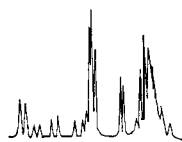
Scheme 34. Variable Temperature NMR Spectra of Tricyclic Tetrazine



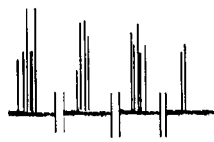
5 types of proton
3 types of carbon

16 types of proton
10 types of carbon

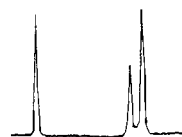
5 types of proton
3 types of carbon



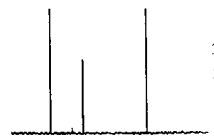
^1H NMR at $-30\text{ }^\circ\text{C}$
very complex spectrum



^{13}C NMR at $-30\text{ }^\circ\text{C}$
sixteen lines



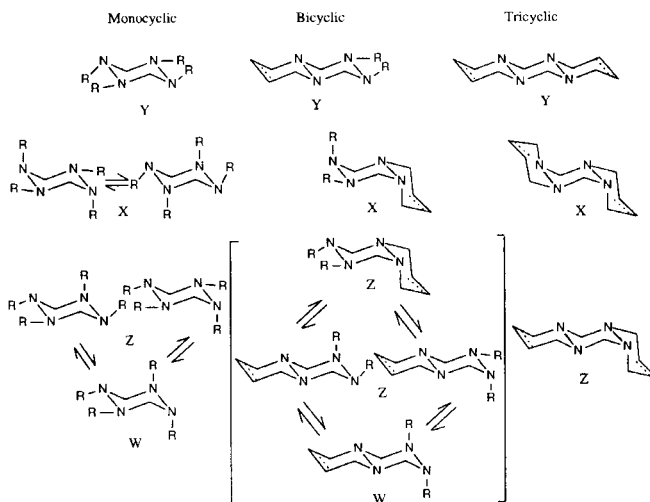
^1H NMR at $+80\text{ }^\circ\text{C}$



3 types of proton
3 types of carbon

spectrum, just three peaks remain. The conformational behavior of these tetrazines has been completely rationalized in terms of different types of barriers (Scheme 35).

Scheme 35. Rationalization of Conformational Behaviour of Tetrazine



barriers : (a) ring inversion, (b) passing R/R, (c) non-passing R/R



Scheme 36. The family, 1965

The distinction is clear between inversions of six-membered rings and inversion at a nitrogen atom. However, of vital importance is that a nitrogen inversion is greatly influenced as to whether the inverting substituent has to pass by another substituent on a neighboring atom. Thus, the terms "passing" and "nonpassing" nitrogen inversions

were introduced.

A second major research field that was entered during the Cambridge years was the study of heterocyclic rearrangements (Scheme 37). What is sometimes denoted

Scheme 37. The Boulton and Related Rearrangements (18 Papers, 1961-1993)

Reviews: "Heterocyclic Synthesis by Rearrangement", (with A. J. Boulton), *Advances in Pesticide Science*, (Proceedings of the Fourth International Congress of Pesticide Chemistry, Zurich, Switzerland, 24-28, 1978). Part 2. ed. H. Geissbuhler, Pergamon, Oxford & New York, pp. 58 (1979).

"Heterocyclic Rearrangements of Benzofuroxans and Related Compounds", (with M. F. Gordeev), *Heterocycles*, 1993, in press

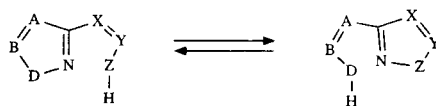
Coworkers in Field of Rearrangements

Group Members: Initials and surnames listed alphabetically

A. S. Afridi	G. de Ville	A. C. Gripper-Gray	R. C. Patel
S. Bayyuk	I. J. Fletcher	A. Majid-Hamid	C. A. Ramsden
A. J. Boulton	P. B. Ghosh		

External Collaborator: R. Harlow

Scheme 38. Boulton's Monocyclic Rearrangement - Scope

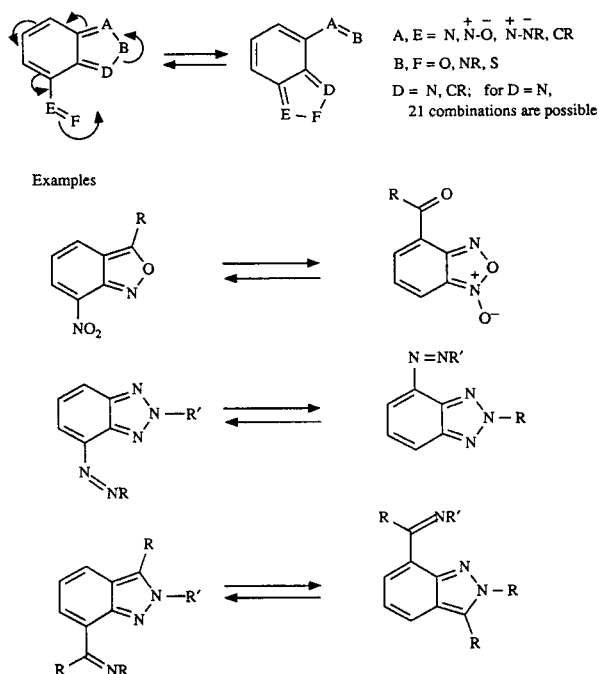


Starting Material		Product	
ABD ^a	Ring	XYZ ^a	Ring
C=C-O	isoxazole	C-C=C	pyrrole ^b
C=C-O	isoxazole	C-C=N	pyrazole ^b
C=N-O	1,2,4-oxadiazole	C-N=C	imidazole ^b
N=C-O	1,3,4-oxadiazole	NH-C=C	imidazole ^b
C=N-N	1,2,4-triazole	C=C-O	isoxazole
N=C-N	1,2,4-triazole	O=C=C	oxazole
N=N-N	tetrazole	C=N-N	1,2,3-triazole

^aH atoms are not shown; ^bInitial products undergo isomerization to a stable tautomer.

"Boulton's Monocyclic Rearrangement" is shown in Scheme 38. A few early examples had been reported but

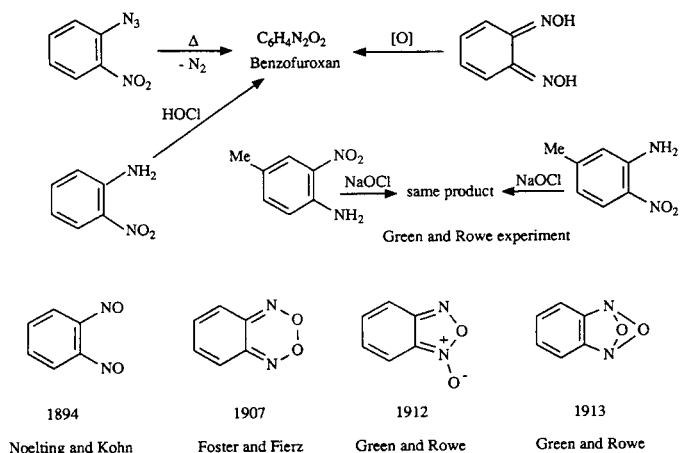
Scheme 39. The Bicyclic Boulton Rearrangements



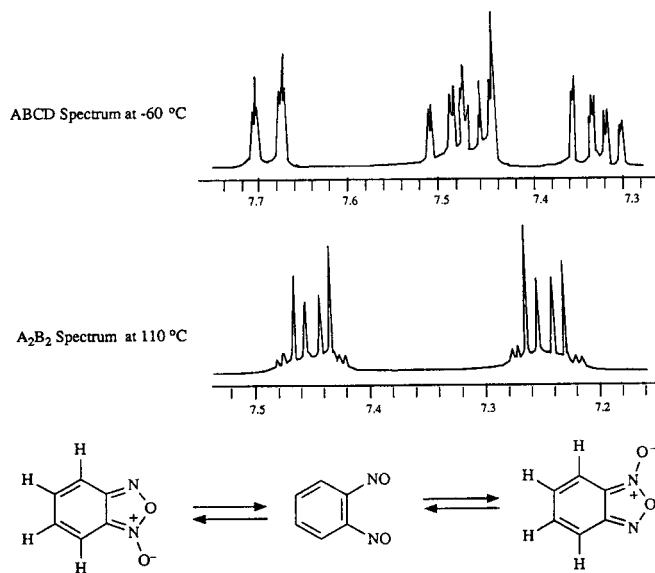
we were able to demonstrate the generality of this rearrangement. Boulton's "Bicyclic Rearrangement" is shown in Scheme 39. Although again there was an example in the literature, it had not been recognized as such. We demonstrated as exemplified in the bottom of Scheme 39 that this is indeed a general rearrangement.

You may be interested to learn how John Boulton learned to bicycle. At that time, we were interested in the chemistry of benzofuroxan, a fascinating compound

Scheme 40. Preparations and Suggested Structures for Benzofuroxan

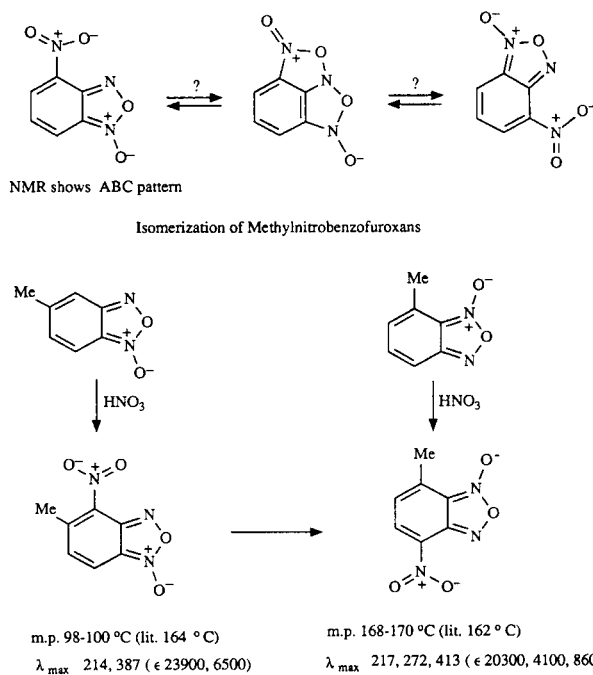


Scheme 41. High and Low Temperature NMR Spectra of Benzofuroxan



Rowe in 1912 proposed the correct structure. But unfortunately, as happens to many of us, they did one experiment too many. As shown at the bottom in Scheme 40, they got the same compound from the sodium hypochlorite oxidation of two isomeric *ortho*-nitroanilines. This led them to believe that benzofuroxan had two-fold symmetry and thence to their incorrect 1913 structure. The correct expla-

Scheme 42. How John Boulton Learnt to Bicycle



which had been prepared by a number of different routes (Scheme 40). After two erroneous suggestions, Green and

nation for all this was suggested some years later, i.e. that the two forms of benzofuroxan interconvert via the nitroso compound. We proved this hypothesis conclusively by the examination of variable temperature proton spectra (Scheme 41) which give an ABCD spectrum at -60°C , coalescing to an A_2B_2 spectrum at 110°C .

Scheme 43. FIRST CONSULTANCIES AND RESEARCH SUPPORT FROM INDUSTRY

International Synthetic Rubber Company, Hythe, UK

The following advertisement appeared in 1961 in "Chemistry and Industry":

A newly-founded research-oriented company seeks consultants in chemistry, physics, polymer sciences, rubber technology and related disciplines. All those interested should apply with CV and publications list to Box No. 4714.

There were 678 applicants; 49 were interviewed, and twelve consultants were appointed to start work in 1962. By 1964 eleven of them had quit or had been fired - I continued to consult until the company merged in 1978.

Pfizer, UK, Ltd.

Consulting from 1963-1981
Numerous joint research projects
Short courses
Industry based MSc and PhD

Ex-group members working for Pfizer UK

Dr. Alastair Monro
Dr. Mike Sewell
Dr. Michael Snarey
Dr. John Arrowsmith

Back to John Boulton's bicycling lessons, at the top of Scheme 42, we see a potential interaction between the nitro group in the benzofuroxan 4-position and the 3-position nitrogen atom which could lead to a tricyclic structure. The nmr spectrum of 4-nitrobenzofuroxan clearly

Scheme 44.

3M: Minnesota Mining and Manufacturing : Ex-Katritzky Group Members Employed by 3M

Dr. Paolo Beretta, Ferrania, R & D Mgr., Organic Synthesis
Dr. Enrico Coraluppi, Ferrania, Sr. Research Specialist
Dr. Alan Cutler, Rochester, Res. Specialist, Printing and Publishing
Dr. Terry Davis, St. Paul, Sr. Chemist, Encapsulated Tech
Dr. Ivano Delprato, Ferrania, Sr. Research Specialist
Dr. Brad Duell, St. Paul, Sr. Chemist, Encapsulated Tech
Dr. Wei-Qiang Fan, St. Paul, Sr. Research Chemist, Specialty Chemicals
Dr. Alan Ferguson, Austin, Technical Director, Elec. Special.
Dr. Ian Ferguson, Ferrania, Technical Director, 3M Italia Ricerche
Dr. Mario Gandino, Ferrania, Lab Manager, Photo Tech. & Sh. Res.
Dr. Nicholas Grzeskowiak, Harlow, Sr. Research Specialist
Dr. Kam-Wah Law, St. Paul, Senior Chemist, Data Storage Products
Dr. George Millet, St. Paul, Technical Mgr. Spec. Fluoropolymers
Dr. Bruno Minasso, Ferrania, Manager Analytical
Dr. Ramaiah Muthyalu, St. Paul, Sr. Research Specialist, Dry Silver
Dr. Steve Newman, Harlow, Sr. Research Specialist
Dr. Ranjan Patel, Harlow, Staff Scientist
Dr. David Read, St. Paul, Sr. Research Specialist, Infection Control
Dr. Ken Reynolds, Harlow (retired), Staff Scientist
Dr. Gebran Sabongi, St. Paul, Project Manager, Encapsulated Prod.
Dr. Kumars Sakizadeh, St. Paul, Research Specialist, Dry Silver Tech.
Dr. John Stevens, St. Paul, Staff Scientist, Technical Computations
Dr. Douglas Weiss, St. Paul, Senior Specialist, CRP/TL, Grp Leader for Radiation Process
Dr. Dong-Wei Zhu, St. Paul, Senior Research Chemist, Fluorochem. Tech. Cr.

Consultant since 1963 at Harlow, U.K. Since 1964 at St. Paul, MN. Since 1965 at Ferrania, Italy.

Since 1989 at Austin, TX. Since 1993 at Antwerp, Belgium.

showed an ABC pattern, and thus the symmetrical structure could not be the ground state. However, such a structure could be an intermediate in the conversion of one nitrobenzofuroxan isomer into another. Experiments showed that the nmr spectrum did not coalesce up to 150°

Scheme 45. JOYS AND REWARDS OF CONSULTING

Question: Professor Katritzky, just one question for you today: how would you stick two blocks of concrete together?

Answer: Well what have you tried? - ah yes, phenol formaldehyde resin that soon failed well, did you consider if buffering actions was needed - do I understand the theory of buffering? Well,

Extract from letter after another consulting visit:

We thank you very much for participating in our round-table discussion of the role of the phase rule in purification methods for zinc oxide ... we all feel most stimulated ... on reflection it is not quite evident just what you contributed to the discussion ... but we were delighted to have you with us.

and thus any such rearrangement must have an activation energy above 20 kilocalories. This implies that the individual isomers should be isolable. Then to the literature:

Scheme 46. Electrophilic Substitution of Heterocycles (63 Papers, 1962-1993)

Reviews: "Electrophilic Substitution of Heteroaromatic Compounds with Six-Membered Rings". (with C.D. Johnson, G. P. Bean, P. J. Brignell, B. J. Ridgewell, N. Shakir, H. O. Tarhan, M. Viney and A. M. White), *Angew. Chem.*, 79, 629 (1967); *Angew. Chem. Internat. Edn.*, 6, 608 (1967).

"Cinetica E. Meccanismo di Sostituzione Elettrofila di Composti Eteroaromatici", *La Ricerca Scientifica*, 53, 7 (1968).

"Quantitative Aspects of the Electrophilic Substitution of Heteroaromatic Compounds", *Estratto da Cronache di Chimica*, 53 (1977)

"Mechanism and Rates of the Electrophilic Substitution Reactions of Heterocycles", (with W.-Q. Fan), *Heterocycles*, 34, 2179 (1992).

Monograph: "Electrophilic Substitution of Heterocycles. Quantitative Aspects", (with R. Taylor), *Adv. in Heterocycl. Chem. vol 47*, Academic Press, (1990)

Coworkers in Electrophilic Substitution

Group Members: Initials and surnames listed alphabetically

J. Banger	A. El-Anani	M. Kingsland	E. V. Scriven
G. P. Bean	H.M. Faid-Allah	M. Konya	N. Shakir
P. Bellingham	H. Faid-Allah	J. R. Lea	S. A. Shapiro
G. Bianchi	W.-Q. Fan	H. Luce	S. Tarhan
U. Bressel	G. P. Ford	A. Marzec	O. H. Tarhan
P. J. Brignell	P. P. Forsythe	G. Millett	O. S. Tee
K. Brown	R. D. Frampton	R. Muragan	B. Terem
A. G. Burton	P. J. Halls	B. R. O'Neill	M. Viney
S. Clementi	C. D. Johnson	C. Ogretir	A. M. White
M. Derehi	P. E. Jones	I. Pojarlieff	L. N. Yakhontov
R. P. Duke	R. A. Y. Jones	B.J. Ridgewell	

External Collaborators: Initials and surnames listed alphabetically

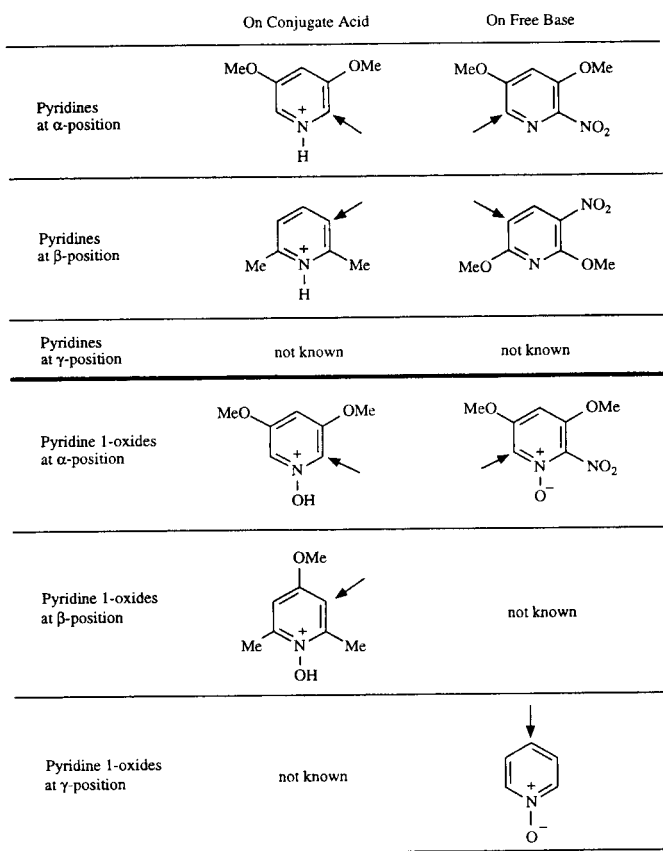
L. M. Alekseeva	J. V. Metzger	Y. N. Sheinker	K. F. Turchin
P. D. Bolton	E. E. Mikhlina	R. Taylor	A. D. Yanina
H. M. Dou	G. V. Sebastiani		

we found that, as is not infrequently the case, it had all been done "by the old Germanen in the old Annalen". As shown at the bottom of Scheme 42, the nitrations of 5-methylbenzofuroxan in the 4-position and of 4-methylbenzofuroxan in the 7-position were reported to give compounds with a suspiciously close melting point. Indeed, they are the same. But by working carefully, John Boulton was able to isolate the intermediate 4-nitro-5-methylbenzofuroxan, which on gentle heating, rearranges into the 4-methyl-7-nitro isomer.

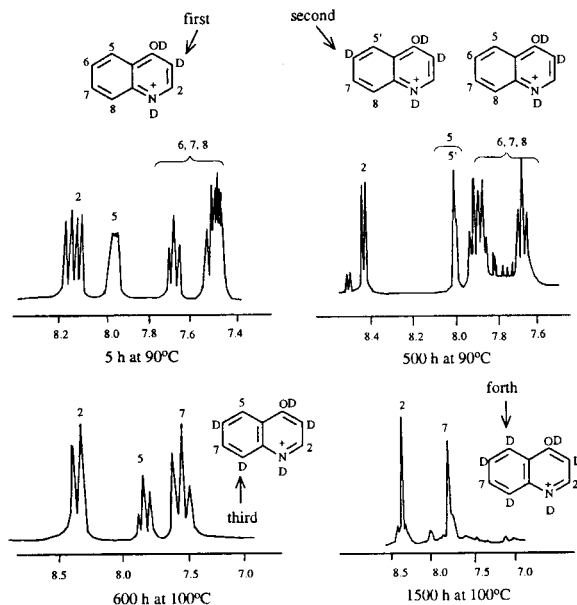
Support was now urgently needed for the growing research group and a series of lasting connections with industry were starting to be forged. The first of them was achieved by replying to an advertisement! (Scheme 43) from the International Synthetic Rubber Company. A little later I entered into an 18 year relationship with Pfizer and what is now a 30 year period of continuous consulting with 3M (Scheme 44). These and several other consulting relationships have provided material support and encouragement and other joys, some of which are mentioned in Scheme 45.

The reactivity and mechanism of the electrophilic substitution of heterocycles has long been a topic of great interest within our research group, as shown on Scheme

Scheme 47. Species and Orientations for Nitration of Pyridines and Pyridine 1-Oxides



Scheme 48. ^1H NMR of Hydrogen Exchange of 4-Quinolone at $\text{H}_\alpha = -9.2$



46. A series of investigations demonstrated that the species and orientations of nitrations in pyridines and pyridine 1-oxides are truly varied, as shown in Scheme 47. Depending on their structure, pyridines can undergo nitration at either the α - or the β -position, both as conjugate acids and as free bases. Pyridine 1-oxides, on the other hand, undergo substitution as conjugate acids in the α -position or β -position; as free bases in the α -position or at the γ -position. Extensive work has also been carried out on the hydrogen exchange of heterocycles. This is very conveniently monitored by proton nmr spectroscopy. In this way, successive hydrogen exchange at different positions can be followed in the same molecule. Some of our results for the hydrogen exchange of 4-quinolones are shown in Scheme 48.

In 1962, I was pre-appointed as the Foundation Professor of Chemistry at the then-new University of East

Scheme 49. Career Culmination (?) UEA 1963 - 1980: Promotion from Demonstrator to Dean

Main Players		
Sir Christopher Ingold, FRS (wanted his way)	Frank Thistlethwait (Vice Chancellor)	Prof. Bennet-Clark, FRS (socialist Dean of Biology)

The Academic Advisory Board Plans for East Anglia

- Seven schools - including
- Mathematics and Physics
 - Biological and Chemical Sciences

Chemistry: a minor appendage to biology

Building program: 7 buildings simultaneously: Arts, Social Science, Library, Senate House, University House, Biology, Chemistry



Scheme 50. Sir Christopher Ingold, Vice Chancellor Frank Thistlethwaite, Professor Thomas Bennett'-Clark

Anglia in Norwich. This University was then at the planning stage. The Academic Advisory Board in its wisdom had laid down plans for seven Schools, which included on the science side: (i) Mathematics and Physics grouped together and (ii) the Biological Sciences with chemistry as a kind of minor appendage (Scheme 49). At least this was the view of Professor Bennet-Clark, FRS, the socialist Dean of biology who was then almost as old as I am now (at the time, I drafted an article suggesting that above the ranks of assistant, associate, and full professors, another should be created: the "Burst Professor"; I still have this draft, but somehow the desire to finish it has diminished). Other major players were Sir Christopher Ingold of the Academic Planning Board and Vice-Chancellor Frank Thistlethwaite (Scheme 50). Fresh from the schooling of college mafia politics in Cambridge, I was well-prepared. While still a demonstrator at Cambridge, I maneuvered my promotion from Professor to Dean at U.E.A. I have a copy of the letter I wrote to Vice-Chancellor Thistlethwaite in which I asked him "who did he think should determine the syllabus for chemistry: the new Professor in whom he should have every confidence, or Sir Christopher Ingold?" Surprisingly, the answer was remarkably favorable. The building program initially planned for seven buildings

constructed simultaneously. But it turned out that only one building could be built at a time, and a game of Russian roulette ensued between the Deans, of whom I was by far the most junior. I am happy to inform you that the survivor was the chemistry building, and indeed it was

Scheme 51. The History of Chemistry at UEA (1962 - 1993)

	Professors	Total faculty	Grad Students	U. Grads	Published papers
1962	0	0	0	0	0
1963	1	3	18	0	10
1964	3	10	48	41	54
1965	3	14	62	98	63
1966	3	20	84	153	79
1967	4	26	84	194	101
1970	4	26	92	206	135
1980	5	27	102	169	73
1984	3	26	81	135	82
1989	4	26	90	183	116
1993	4	28	110	206	131

1989 rated in 2nd group of British Universities (out of five groups)

1993 again rated in 2nd group

Scheme 52. 3-Oxidopyridinium Betaines (65 Papers, 1971-1992)

Reviews: "Heteroaromatic Betaines as 1,3-Dipoles: The Reaction of Analogues of Anhydro-3-hydroxy-1-methylpyridinium Hydroxide with Dipolarophiles", (with Y. Takeuchi N. Dennis and I. Taulov), *Proceedings of the Third International Congress of Heterocyclic Chemistry*, Sendai, Japan, August 23-27, 1971

"Synthetic Applications of Heteroaromatic Betaines with Six-Membered Rings", (with N. Dennis and Y. Takeuchi), *New Synthetic Methods*, Verlag, Weinheim, 4, 241 (1979); [A revised version of *Angew. Chem. Internat. Edn.*, 15, 1 (1976)].

"Recent Progress in the Cycloaddition Reactions of 3-Oxidopyridinium Betaines and Analogous Compounds", (with N. Dennis), A Chapter in *New Trends in Heterocyclic Chemistry*, Elsevier, Amsterdam, pp 290 (1979).

"Cycloaddition Reactions of Heteroaromatic Six-Membered Rings", (with N. Dennis), *Chem. Rev.*, 89, 827 (1989).

"Cycloadditions of Six-Membered Heteroaromatic Betaines", (with M. Karelson and G. J. Hitchings). *Revs. Heteroatom Chem.*, 5, 43 (1991).

Coworkers in Dipolar Cyclo-Additions

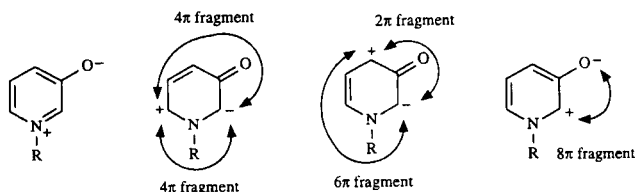
Group Members: Initials and surnames listed alphabetically

M. Abdallah	H.A. Dowlatshahi	G.J. Hitchings	C. Ogretir	H.J. Salgado Zamora
J. Banerji	B. El-Osta	B. Ibrahim	S. K. Parton	Y. Takahashi
S. I. Bayyuk	J. Ellison	M. Karelson	S. Rahimi-Rastgoo	Y. Takeuchi
A. M. A. Bolouri	H. Faid-Allah	C. Laurence	M. Ramaiah	I. G. Taulov
A. Boonyarakvanich	I. J. Fletcher	E. Lunt	R. Rittner	L. Turker
B. A. Boyce	J. Frank	T. Matsuo	S. Q. A. Rizvi	H. Wilde
A. T. Culter	N. E. Grzeskowiak	M. Michalska	G. J. Sabongi	E. U. Wurthwein
N. Dennis	G. Guiheneuf	G. Musumarra		

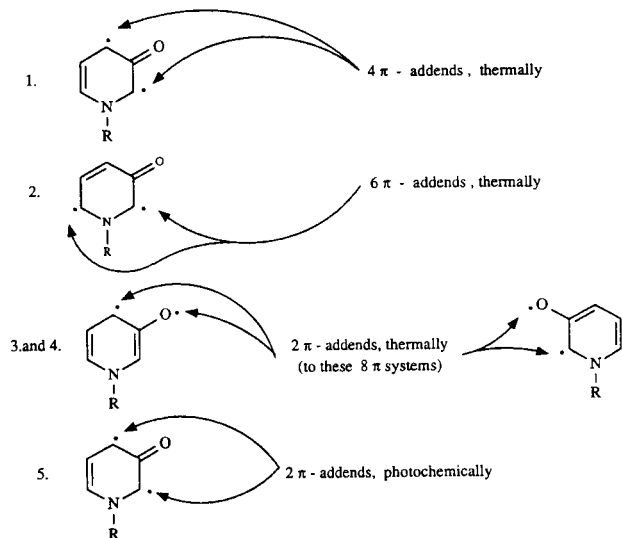
External Collaborators: Initials and surnames listed alphabetically

M. Chaillet	G. W. Fischer	R. L. Harlow	C. Larrieu	M. Parvez
M. El Mouhadi	K. J. Fischer	C. Y. Ishag	E. Laurence	S. H. Simonsen
G. Ferguson	E. Gavuzzo	G. M. Iskander	Y. Nomura	A. Vaciago

Scheme 53. 3-Oxidopyridinium Betaine Cycloadditions



Predictions of Allowed Reactions



Scheme 54.

Her Majesty the Queen opening the School of Chemical Sciences

the first constructed. The history of chemistry at East Anglia is briefly summarized in Scheme 51; hopefully, success in leadership can be measured by making oneself dispensable.

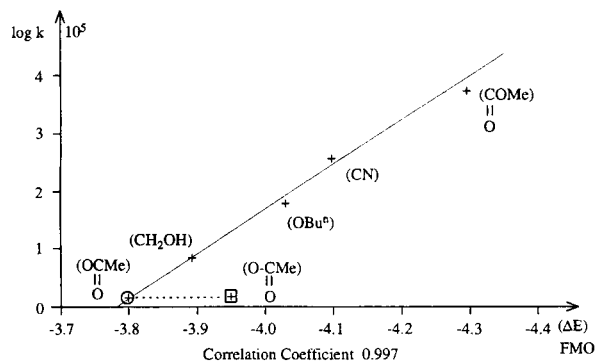
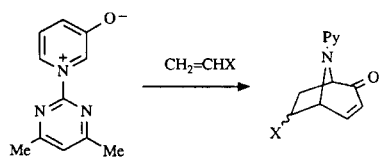
3-Oxidopyridinium betaine chemistry (Scheme 52) proved a rich lode. Cycloaddition reactions, were predicted to be possible across (i) the 2- and 6-positions, (ii) the 2- and 4-positions, (iii) the 2-position and oxygen and (iv) the 4-position and oxygen. In fact, examples of each of these addition modes were uncovered experimentally (Scheme 53). The achievement of these reactions depends vitally on the choice of the substituent at the pyridinium nitrogen atom.

This led to a general consideration of the ways in which

Scheme 55. The Seven Levels of Organic Chemistry -----Or How to Choose Your Substituents

LEVEL	METHOD	PREREQUISITE
1	Search the laboratory shelves	The gift of sight
2	Look at the literature	Ability to read
3	Apply the good old theories of yester-year	Can you draw a curly arrow?
4	Attempt that which is allowed and eschew the forbidden	Need to be able to count
5	Go into molecular orbit	Ability to think
----- Limit of Present Writer's Competence -----		
6	Apply inherited genius	Dexterity in choosing one's parents
7	Receive divine inspiration	State of grace

Scheme 56. Correlation of FMO Energies [$\Delta E_{\text{int.}}$] with Rate Constants of Addition to 1-(4,6-Dimethylpyrimidin-2-yl)-3-oxidopyridinium



Scheme 58. Polymer Chemistry (33 Papers, 1972 - 1992)

Reviews: "Nuclear Magnetic Resonance in Polymer Analysis and Design", (with E. W. Duck and A. Smith), *Polymer Age*, 3, 303 (1972).

"Polymer Microstructures and ¹³C NMR", (with D. E. Weiss), *Chem. in Brit.*, 12(2), 45 (1976).

Coworkers in Polymer Chemistry Field

Group Members: Initials and surnames listed alphabetically

M. K. Bernard	K. Sakizadeh	J. Swinson	D. E. Weiss
S. J. Cato	A. Smith	R. D. Tarr	D.-W. Zhu
B. Ibrahim			

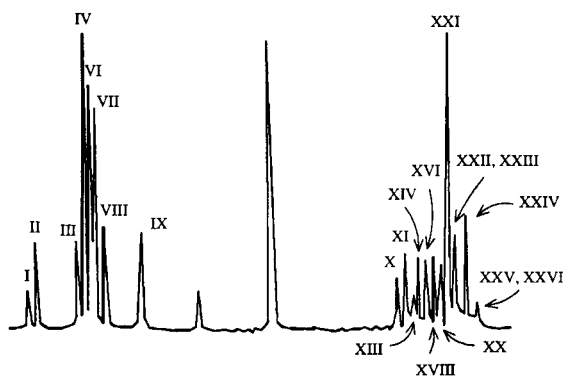
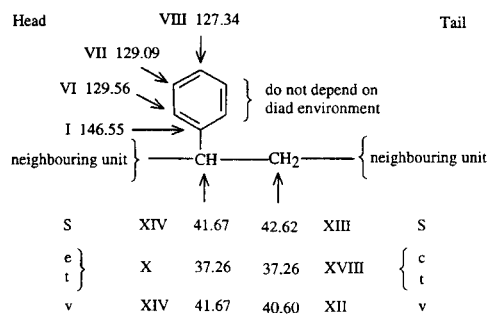
External Collaborators: Initials and surnames listed alphabetically

S. M. Heilmann	D. M. Moren	J. K. Rasmussen	E. W. Duck
L. R. Krepski	S. V. Pathre	H. K. Smith II	

substituents are chosen by experimentalists, indeed, it seems possible to divide organic chemists into seven levels, as shown in Scheme 55, the lower five according as to whether the chemist can see, read, draw, count, or think. Two higher levels are also postulated, but these are

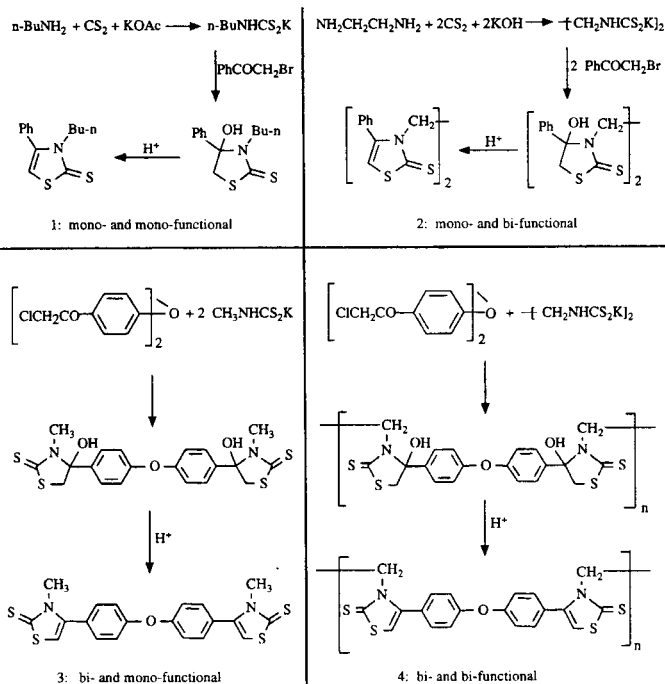


Scheme 57. 396 Unthank Road, Norwich, Scene of many group parties

Scheme 59. ¹³C-NMR for Polymer Sequencing

beyond my competence. We were able to apply simple molecular orbital theory to rationalize these cycloaddi-

Scheme 60. The Preparation of Heterocyclic Polymers



tions as shown in Scheme 56.

During the Norwich years, we entered the field of polymer chemistry (Scheme 58). We were able to apply ¹³C-nmr for polymer sequencing, as shown in Scheme 59 for styrene-butadiene rubbers, where the “blockiness” can be deduced from the detailed nmr spectrum. Many heterocyclic polymers have been prepared: an example of such a preparation by condensation methods is given in Scheme 60, to prepare a polymer molecular of type A-B-A-B..., we examined successively two monofunctional components to give AB, and then each combination of mono- and di-functional components to give ABA and BAB, before undertaking the polymerisation.

Scheme 61. Pyrylium/Pyridinium Chemistry and Heterocycles in Organic Synthesis (181 Papers, 1976-1993)

Reviews: “Conversions of Primary Amino Groups into Other Functionality Mediated by Pyrylium Cations”, *Tetrahedron*, **36**, 679 (1980).

“Pyrylium Mediated Transformations of Primary Amino Groups into Other Functional Groups”, (with C. M. Marson), *Angew. Chem. Int. Ed. Engl.*, **23**, 420 (1984).

Coworkers in Pyrylium/Pyridinium Chemistry

Group Members: Initials and surnames listed alphabetically

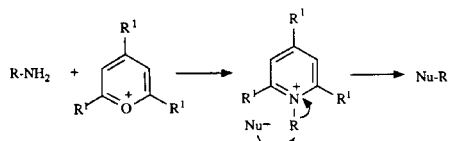
M.F. Abdel-Megeed	R.T.C. Browlee	A.M. El-Mowafy	D.H. Kenny	P. Molina-Buendia	H. Schultz
B. J. Agba	B. E. Brycki	B. S. El-Osta	A. Krutskova	N. Mongelli	O. A. Schwarz
M. Alajarin-Ceron	J. Z. Breznaki	S. M. M. El-Shafie	G. L'Hommet	M. Moreno-Manas	S. Sengupta
F. Al-Omran	K. Burgess	J. Eliason	J. N. Lam	R. Murgan	M. Shana
J. Alvarez-Builla	J. C. Cas	E. M. Eliaeeou	R.T. Langthorne	G. Musumara	H. Steikh
A. Anani	S. J. Cato	J. Epezzajn	N. Laif	P. L. Nie	T. Siddiqui
E. Anders	A.V. Chapman	N. F. Eweiss	D. E. Leahy	H. H. M. Noor	M. Subbaranadevi
J.M. Aureocochea	J. L. Chen	H. Faïd-Allah	B. P. Laddy	B. Nowak-Wytra	J.N. Singh
R. Awartani	A. Chemprapai	W.-Q. Fan	J. Lewis	Y. X. Ou	M. Szajda
P. Ballesteros	S. Clementi	V.M. Feygelman	Q.-L. Li	I. R. Parker	A. Tarraga-Tomas
A. Banerji	R.M. Ciaramunt-Elguero	A. Gonzalez-Gazulla	G. Liso	R. C. Patel	S. S. Thind
J. B. Bapat	M. J. Cozens	B. Gabrielson	J. M. Lloyd	B. Plau	L. Urogdi
G. Baskirides	R. Cruz-Almanza	B. J. Graphakos	U. Grunz	M.L. Lopez-Rodriguez	A. Prout
W. H. Basinski	N. Dabbas	U. Grunz	E. Lunt	C. A. Ramsden	J. J. Vanden Eynde
H. A. Beltrami	Z. Dega-Szafran	N.E. Grzeskowiak	R. H. Manzo	O. Rubio	M. M. Vukovic
Z. bin Babari	M. de Rosa	K. Horvath	D. G. Markes	D. Rasala	D.-K. Wittmann
R. J. Blide	G. de Ville	A. A. Iksizler	J. Marquet	K. Reynolds	F. Yates
A. J. Boulton	K. Dill	P. G. Jones	C. M. Marson	A. Saha	W. K. Yeung
S. Bravo-Borja	A. Dinulescu	B. Jovanovic	L. Marzotati	F. Saczowski	T. I. Yousaf
S. B. Brown	M. Drewiak-Deyrup	M. A. Kasimiri	G. H. Milet	K. Sakizadeh	Z. Zakaria
	J. G. Keay		C. Sana-Ullah	A. Zia	

External Collaborators: Initials and surnames listed alphabetically

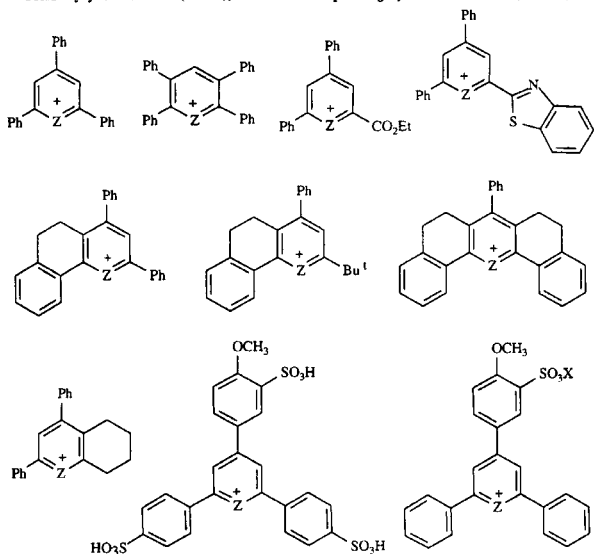
A.E. Abdel Rahman	J. J. Cerdá	M. Gawron	S.P. McManus	M. Prat	J. G. Tropisch
J. Adamson	F. Chiralou	R. L. Harlow	D. Lamba	R. Provo	Y. R. Tymanyanski
S. Alunni	G. Cirna	L. R. Hearing	A. Maza	K. Quian	A. Vaccaro
F. M. Assad	R. Crupi	S. Hu	N. Misirsky	S.H. Simonsen	M. J. Vilaplana
A. T. Balaban	T. Crutcher	O. Kennard	S. Muratore	R. Spagna	C. H. Wasth
F.P. Ballistreri	A. Dondoni	D. N. Kevill	R.W. Naumann	B. R. Stevens	S. Wild
J. H. Bieri	E. A. Elsherbini	R. W. King	P. Pacheco	J. J. Stezowski	E. R. Woodward
M. Bruno	J. R. Eyler	M.I. Knyazhanskii	G. J. Palenik	D. Tassi	S. E. Zoutart
R. D. Carter	A. Fernandez	A. E. Koziol	M.L. Podmore	K. L. Tate	

In the mid-70's, we commenced our work (Scheme 61) in pyrylium/pyridinium chemistry. As shown in Scheme 62, this is based on the reaction of primary amines with pyrylium cations to give the corresponding pyridinium cations in which the primary amine residue can now be transferred away from the nitrogen, to be replaced by a large variety of groups. Many different pyrylium cations were developed for various purposes as exemplified in Scheme 62. Scheme 41 shows some transformations of lysine and glycyl-glycine carried out in aqueous solution under mild conditions without the need for any protection.

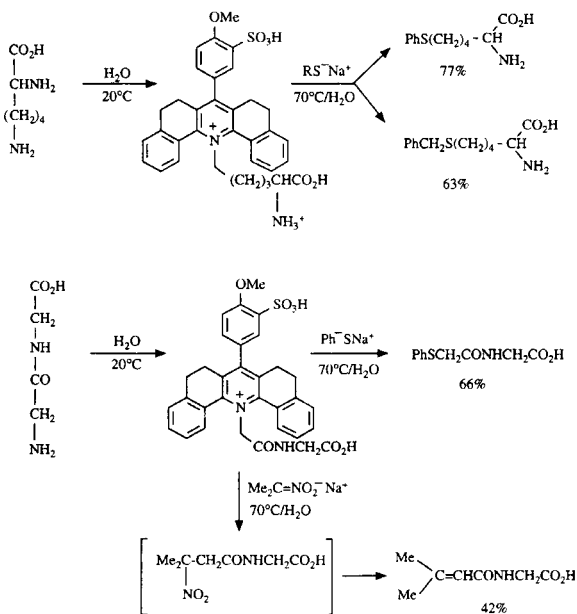
Scheme 62. Pyrylium Mediated Conversion of Amino into Other Functionality



Useful Pyrylium Cations (Z = O), and the Corresponding Pyridinium Cations (Z = NR)



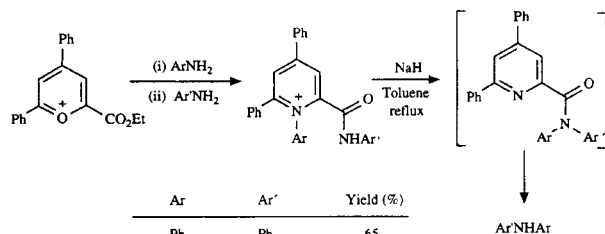
Scheme 63. Transformations of Lysine and Glycylglycine



For the corresponding transformations of arylamines and heteroarylamines, geometrical considerations make it necessary to use intramolecular displacement. Examples of such reactions are shown in Scheme 64. The concept of deamination as compared with dehydration is expounded in Scheme 65.

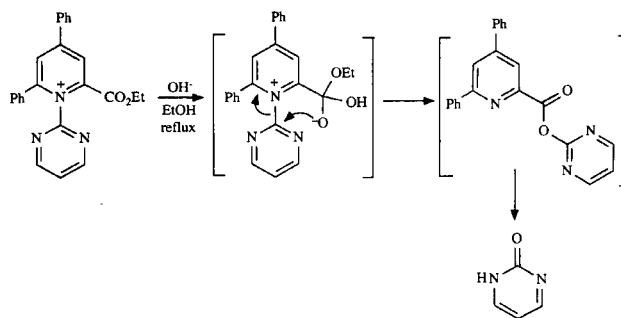
The Norwich years were also years of writing and

Scheme 64. Preparation of Diarylamines



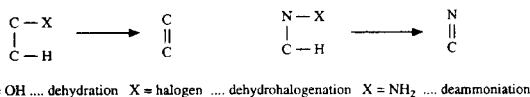
Ar	Ar'	Yield (%)
Ph	Ph	65
4-MeC ₆ H ₄	4-MeC ₆ H ₄	65
4-MeC ₆ H ₄	4-PhC ₆ H ₄	62
4-MeC ₆ H ₄	4-MeOC ₆ H ₄	55
4-MeC ₆ H ₄	4-ClC ₆ H ₄	58
Ph	4-MeC ₆ H ₄	63

Conversion of 2-Aminopyrimidine into 2-Pyrimidinone

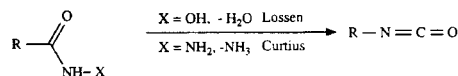


spreading the Gospel, which was translated into different languages (Scheme 67). I lectured widely in Europe, North Africa, Asia, Australia, and the Americas (Schemes 68-72).

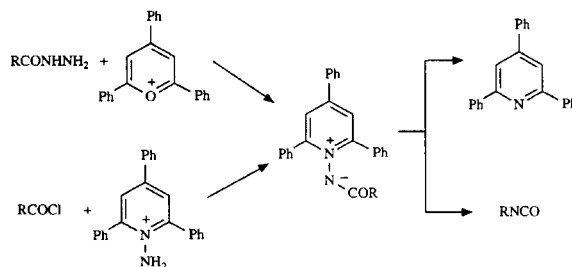
Scheme 65. The Concept of "Deamination"



Examples of related rearrangements:



Preparation of Isocyanates (RNCO) by Thermolysis of Acylimides



Then in 1980, the long awaited award of FRS (Scheme 73) came, and I retired to Florida. The "Golden Years" of



Scheme 66. Norwich Cathedral

my life, full of recreation and pleasure. Only somehow, it did not turn out that way. I found the United States, in some major ways, to be the land of the heathen.

Scheme 67. Writing and Spreading the Gospel

Textbooks: "Heterocyclic Chemistry", (with J. M. Lagowski), Methuen & Co. Ltd., London, 1960; John Wiley and Sons Inc., New York, 1960.

"The Principles of Heterocyclic Chemistry", (with J. M. Lagowski), Methuen & Co. Ltd., London, 1967; Chapman and Hall Ltd. London, 1971.

Translations: "Khimia Geterociklitcheskikh Soedineni", Moscow, 1963.

"Chemia Związków Heterocyklicznych", Państwowe Wydawnictwo Naukowe, Warszawa, 1966.

"Chemie der Heterocyclen", Springer-Verlag, Berlin, 1968.

"Principes de la Chimie des Composés Hétérocycliques", Gauthier-Villars, Paris, 1968.

"Química Fundamental de Heterociclos", Editorial Alhambra, S. A., Madrid, 1968.

"Principi di Chimica Eterociclica", Casa Editrice Ambrosiana, Milano, 1968.

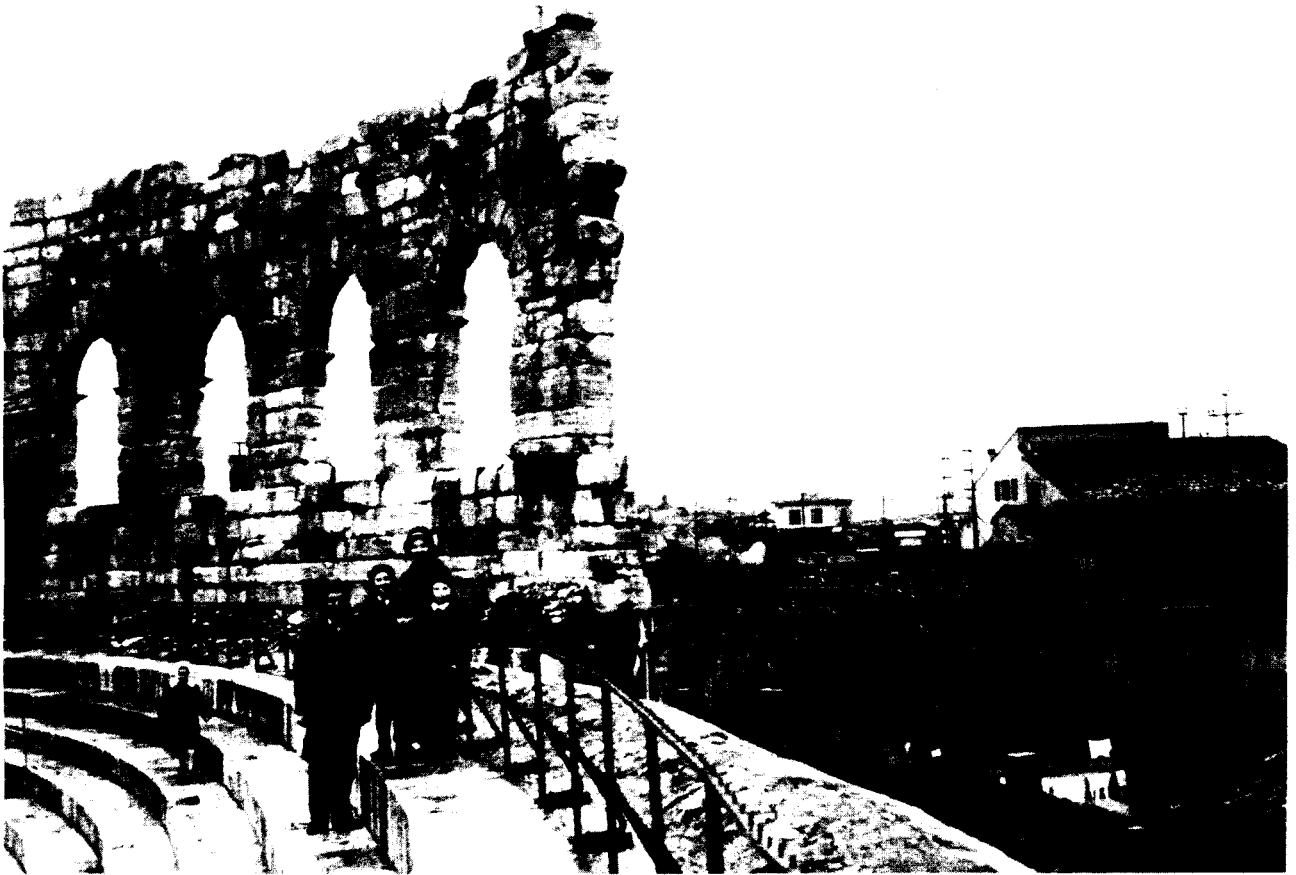
"The Principles of Heterocyclic Chemistry", Japanese edition, Tokyo, Japan, 1968.



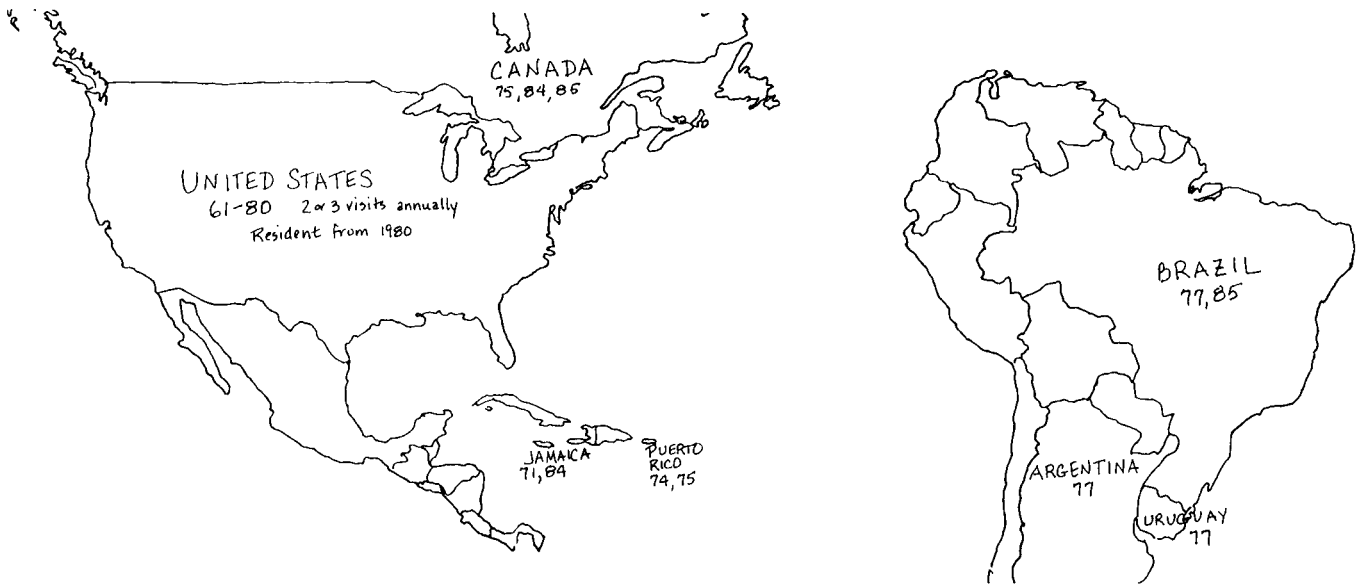
Scheme 68. Lectures in Europe/North Africa

Heterocyclic chemistry was (and is) not considered a serious academic pursuit. These aspects are contrasted in Scheme 74. But America is also the Land of Opportunity.

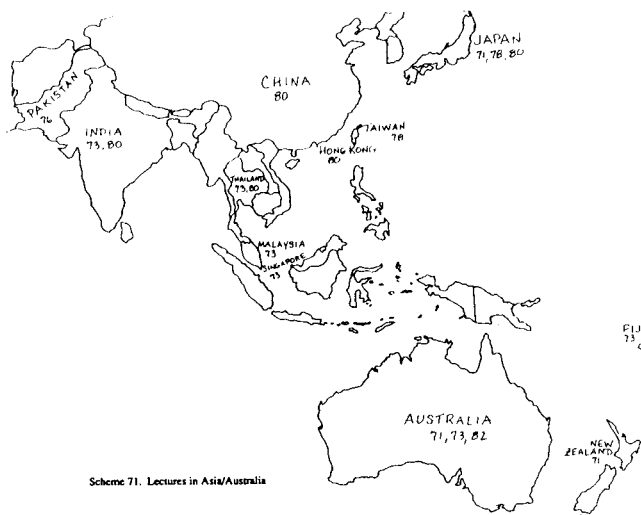
If heterocyclic chemistry is under-represented in American academia, the dollar signs it represents are certainly recognized in all their due importance by indus-



Scheme 69. Time off at the Colosseum



Scheme 70. Lectures in Americas



Scheme 71. Lectures in Asia/Australia

Scheme 74. The Golden Years -- Retirement [?] to Florida 1980 for Windsurfing and Partying

The Land of the Heathen !

"There is an interesting psychology associated with heterocyclic chemistry which persists to this day. It is commonly accepted that a majority of the published work in organic chemistry involves at least one heterocyclic ring. Moreover, in providing us with a wealth of fascinating molecular arrays over half of which possess heterocyclic constitution, nature presents a most cogent argument for developing an appreciation for this area. And yet, while numerous synthetic practitioners devote their entire careers to the laboratory-based construction of heterocycle-containing natural products, rarely does one^{*} consider himself^{*}, LET ALONE ADMIT TO BEING, A HETEROCYCLIC CHEMIST. This state of mind endures, made more inveterate by the constant short shift which undergraduate textbooks notoriously afford this topic. Even invited lecturers, e.g., at Gordon Conferences on this area, are oftentimes quick to amusingly comment when a particular target or intermediate constitutes a "real" heterocycle".

Quoted from *Chem. Rev.*, 1986, 86, 795.

* lots of us are evidently non-persons! * hopefully women are less prejudiced?

try. Albeit with intense competition, we have been able to harness this to some good effect (Scheme 75).

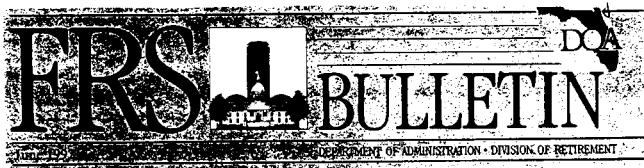
A major new topic of research was heterocyclic carbanion chemistry: protection and activation (Scheme 76). A



Scheme 72. Sidon, Lebanon 1974 in peaceful times

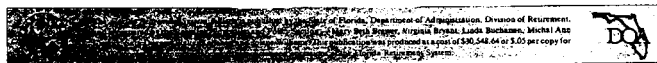
Scheme 73. 1980 - F.R.S. AT LAST!

What does FRS stand for?: no forty round the seat!



The actuarial firm of Milliken and Robertson Inc. had the following to say about the financial condition of the FRS:

"the 1991 actuarial valuation produced evidence that stabilization is occurring ... The following illustrates the liability of the FRS: \$15.9 billion unfunded actuarial accrued liability calculated as the difference between liabilities and assets"



Scheme 75. The Land of Opportunity

Companies which have contributed substantially to
The Center for Heterocyclic Compounds at UF

Connecticut	New Jersey
Boehringer-Ingelheim	Exxon Corporation, Linden
Bristol-Meyers Squibb	Exxon Corporation, Clinton
	Merck, Rahway
Illinois	North Carolina
Monsanto, NutraSweet Division, Chicago	Sandoz, Charlotte
Abbott Laboratories, Chicago	
	Ohio
Indiana	Monsanto Rubber Division, Akron
Dow-Elenco	
Reilly Industries, Indianapolis	Texas
	3M Corporation, Austin
Louisiana	UK
Exxon Corporation, Baton Rouge	3M Corporation, Harlow
	Exxon Corporation, Abingdon
Michigan	Glaxo Company, London
Parke Davis, Ann Arbor	
Upjohn Corporation, Kalamazoo	Italy
	3M Corporation, Ferrania
Minnesota	Japan
3M Corporation, St. Paul	SDS Corporation
Missouri	
Monsanto Ag. Division, St. Louis	
	New York
	Oxychem, Grand Island

Scheme 76. Heterocyclic Carbanion: Protection and Activation (52 Papers, 1980-1993)

Reviews: "Some New Strategies for Protection, Activation and Direction in Lithiation Chemistry", (with G. W. Rewcastle, J. N. Lam and S. Sengupta), *Prog. Heterocycl. Chem.*, **1**, 1 (1989).

"Generation and Reactions of sp^3 Carbanionic Centers in the Vicinity of Heterocyclic Nitrogen Atoms", (with G. W. Rewcastle), *Adv. Heterocycl. Chem.*, **56**, 155 (1993).

Coworkers in Heterocyclic Carbanion Chemistry

Group Members: Initials and surnames listed alphabetically

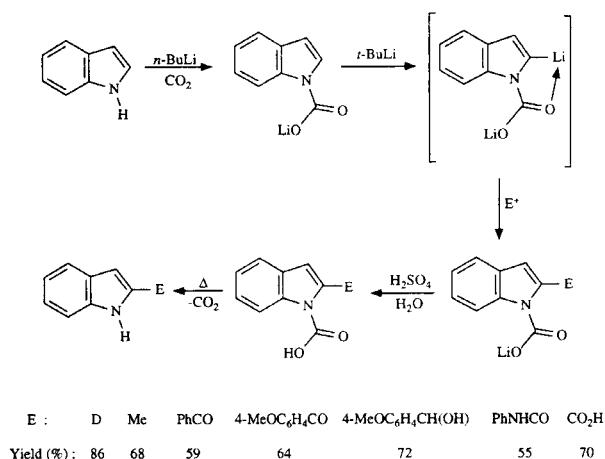
A. E. Abdel-Rahman	G. P. Ford	N. Malhotra	O. A. Schwarz
K. Akutagawa	N. E. Grzeskowiak	C. M. Marson	S. Sengupta
J. Arrowsmith	C. Jayaram	R. Murugan	T. Siddiqui
J. M. Aurrecoechea	R. A. Jones	S. Perumal	J. J. Slawinski
Z. bin Bahari	W. Kuzmierkiewicz	N. K. Ponske	L.M. Vasquez de Miguel
M. Black	J. N. Lam	S. Rahimi-Rastgoo	S. N. Vassilatos
F. Brunner	K. Laurenzo	W. H. Ramer	J. Wang
Y.-X. Chen	D. E. Leahy	G. W. Rewcastle	D. Windwood
B. C. Chen	H. Luce	F. Saczewski	K. Yannakopoulou
A. Chemprapai	P. Lue	H. J. Salgado	

External Collaborators: Initials and surnames listed alphabetically

W. S. Brey	A. E. Koziol	D. I. Relyea	M. C. Zerner
S. Gorun	G. J. Palenik		

new method for indole 2-substitution was devised (Scheme 77) utilizing carbon dioxide as the protecting group. Fundamental is that the whole process can be car-

Scheme 77. New Method for Indole 2-Substitution



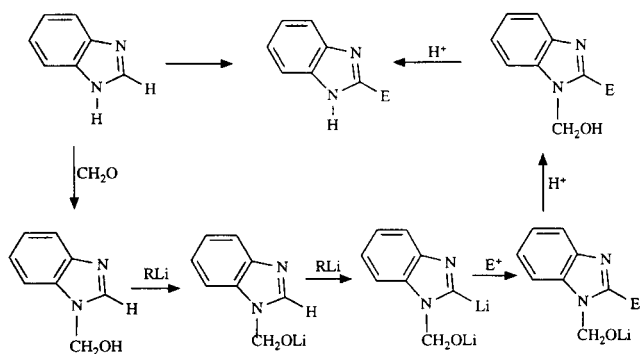
ried out in one pot by successive additions of butyllithium, carbon dioxide, more butyllithium, the electrophile, and dilute acid.

The carbon dioxide method has been applied in many cases, but fails in others such as benzimidazole. We therefore developed the formaldehyde method for 2-substitution of benzimidazoles, again as a completely one pot

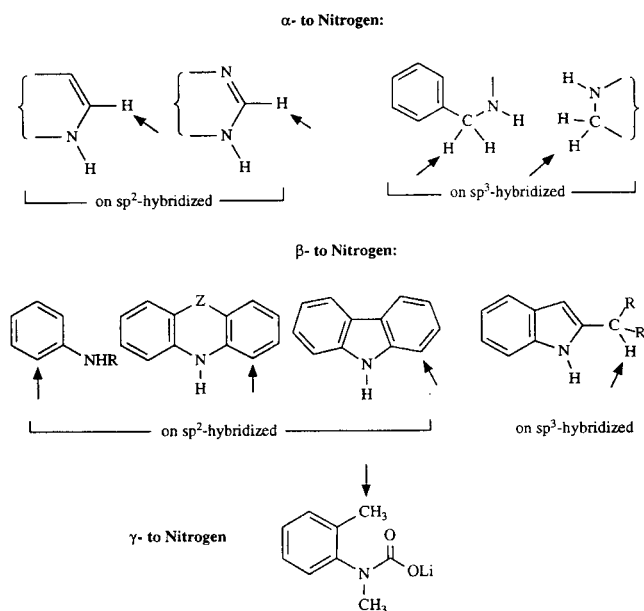


Scheme 78. Windsurfing

Scheme 79. One-Pot Method for 2-Substitution of N-H Benzimidazole



E	yield (%)	E	yield (%)
PhCH(OH)	72	Ph ₂ C(OH)	46
4-MeC ₆ H ₄ CH(OH)	50	9-hydroxyfluorenyl	45
4-ClC ₆ H ₄ CH(OH)	55	1-hydroxycyclohexyl	50
3,4-(MeO) ₂ -C ₆ H ₃ CH(OH)	59	MeS	58
c-C ₄ H ₃ OCH(OH)	54	PhCH ₂ S	53

Scheme 80. Substitutions α -, β - and γ - to Nitrogen

Scheme 81. University of Florida campus, historic 60 year old buildings

sequence, as shown in Scheme 79. In these activation and protection approaches, we were able to find methods for

substitution α -, β -, and γ - to nitrogen atoms as is recorded in Scheme 80.

Scheme 82. Mechanisms of Heterocyclic Ring Closures (6 Papers, 1986-1987)

Review: "The Mechanism of Heterocyclic Ring Closures", (with D. L. Ostercamp and T. I. Yousaf), *Tetrahedron*, 43, 5171 (1987).

Coworkers in Heterocyclic Ring Closures

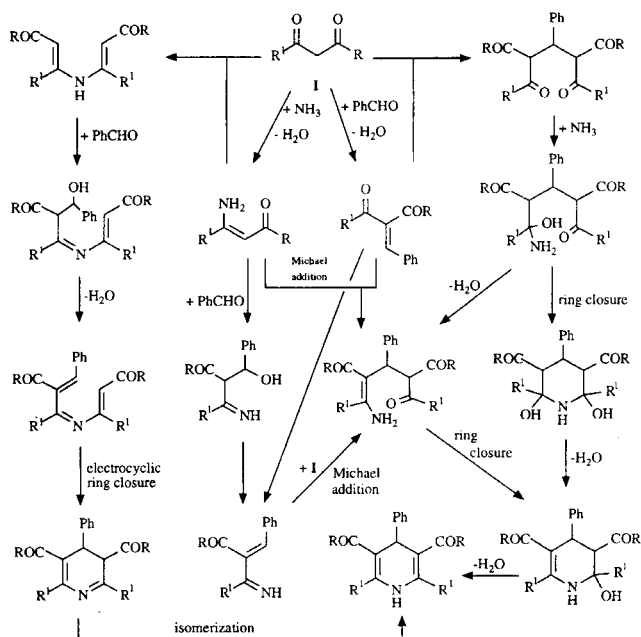
Group Members: Initials and surnames listed alphabetically

P. Barczynski B. C. Chen D. L. Ostercamp T. I. Yousaf G.-Z. Zeng

We also worked on the mechanisms of heterocyclic ring closures (Scheme 82). This is illustrated by the reaction pathways for the Hantzsch synthesis of pyridines, which was proven to proceed as shown in Scheme 83.

Another highly contentious topic which we have investigated extensively has been the mechanism of aliphatic nucleophilic substitution (Scheme 85). In particular, we were able to demonstrate that S_N1 and S_N2 reactions can take place simultaneously and quite distinctly, at the same time, on the same substrate. The key to a proper understanding of these reactions is the use of charged substrates with a neutral leaving group, such as a pyridine. The kinetic data recorded in Scheme 86 leave no doubt that

Scheme 83. Reaction Pathways for the Hantzsch Synthesis of Pyridines



Scheme 84. Where our chemistry is done at University of Florida

Scheme 85. Kinetics and Mechanism of Aliphatic Nucleophilic Substitution (40 Papers, 1980-1990)

Reviews: "New Insights into Aliphatic Nucleophilic Substitution Reactions from the Use of Pyridines As Leaving Groups", (with G. Musumara), *Chem. Soc. Rev.*, **13**, 47 (1984).

"Kinetics and Mechanism of Nucleophilic Displacements at sp^3 Hybridized Carbon Atoms with Heterocyclic Leaving Groups", (with K. Sakizadeh and G. Musumara), *Heterocycles*, **23**, 1765 (1985).

"Nucleophilic Substitution at Saturated Carbon Atoms. Mechanisms and Mechanistic Borderlines: Evidence from Studies with Neutral Leaving Groups", (with B. E. Brycki), *J. Phys. Org. Chem.*, **1**, 1 (1988).

"The Mechanisms of Nucleophilic Substitution in Aliphatic Compounds", (with B. E. Brycki), *Chem. Soc. Rev.*, **19**, 83 (1990).

Coworkers in Kinetics and Mechanism of Nucleophilic Substitution

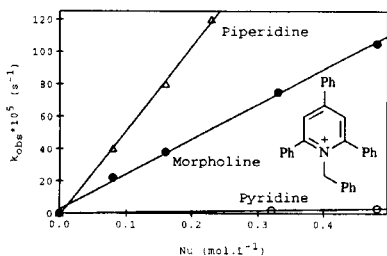
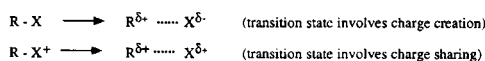
Group Members: Initials and surnames listed alphabetically

W. H. Basinski	Z. Dega-Szafran	B. Jovanovic	M. Misić-Vuković	F. Sączewski
B. E. Brycki	S. M. M. El-Shafie	J. G. Keay	M. Moreno-Manas	K. Sakizadeh
J. Z. Brzezinski	A. M. El-Mowafy	J. M. Lloyd	G. Musumara	C. Sana-Ullah
J. L. Chen	E. M. Elisseou	M. L. Lopez-Rodriguez	Y. X. Ou	H. Schultz
S. Clementi	J. Ellison	J. Marquet	R. C. Patel	M. Szafran
A. J. Cozens	B. Gabrielsen	C. M. Marson	A. Saba	S. S. Thind
				W. K. Yeung

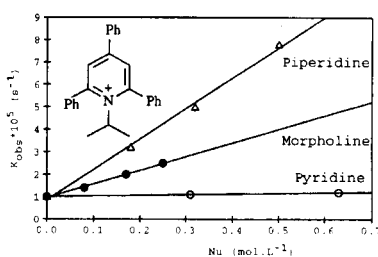
External Collaborators: Initials and surnames listed alphabetically

J. Adamson	G. Cirna	R. W. King	P. Pacheco	K. L. Tate
S. Alunni	R. Crupi	D. Lamba	M. Prat	A. Vacicgo
F. P. Ballistreri	T. Crutcher	S. P. McManus	R. Prewo	S. Wold
J. H. Bieri	J. R. Eyler	S. Muratore	R. Spagna	S. E. Zutaut
M. Bruno	D. N. Kevill	R. W. Naumann	J. J. Stezowski	

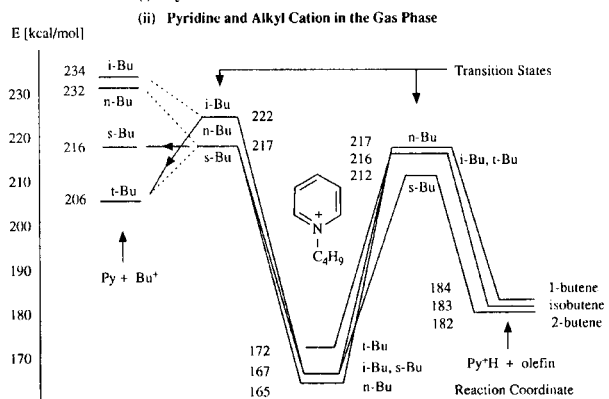
the S_N1 and S_N2 reactions are distinct, and there is no "merging" of mechanisms. But even though I broke into JACS with this heresy, the American gang of mechanistic referees still prevented me from publishing a simple report in *J. Chem. Ed!* More recently, we have extended this work into the gas phase. In Scheme 87, we can now

Scheme 86. Simultaneous S_N1 and S_N2 Reaction


Nucleophilic substitution by S_N2 ($A_N D_N$) reaction only: k_{obs} for 1-(benzyl-2,4,6-triphenylpyridinium) cation (1.6×10^{-3} M) plotted vs. nucleophilic concentration (chlorobenzene solution, 100°)



Nucleophilic substitution by simultaneous S_N1 ($D_N + A_N$) and S_N2 ($A_N D_N$) reactions: k_{obs} for 1-isopropyl-2,4,6-triphenylpyridinium cation (1.6×10^{-3} M) plotted vs. nucleophilic concentration (chlorobenzene solution, 100°)

Scheme 87. Collisionally Activated Dissociation of N-Alkylpyridinium Cations to (i) Pyridinium Cation and Olefins

Scheme 88. High Temperature Aqueous Chemistry (26 Papers, 1990-1993)

Review: "Reactivity of Organic Compounds in Hot Water: Geochemical and Technological Implications", (with M. Siskin), *Science*, **254**, 231 (1991).

Coworkers in Aqueous Chemistry

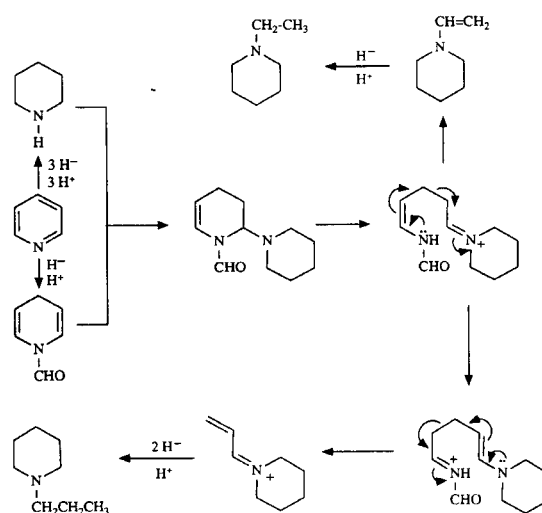
Group Members: Initials and surnames listed alphabetically

M. Balasubramanian	A. R. Lapucha	R. Murugan
J. V. Greenhill	F. J. Luxem	

External Collaborators: Initials and surnames listed alphabetically

G. Brons	D. R. Neskora	M. Siskin
C. C. Culross	S. D. Reynolds	S. N. Vaughn

give a rather complete picture of the gaseous S_N1 and $E1$ reactions of various *N*-alkylpyridinium cations. This work shows conclusively that, for example, the gas-phase rearrangement of isobutyl cation into tertiary butyl cation takes place in an ion-molecule complex.

Scheme 89. Reaction of Pyridine with Formic Acid




Scheme 90. One of Florida's 10,000 lakes with friendly alligators

Scheme 91. Aromaticity and QSAR/QSPR (25 Papers, 1960-1993)

Aromaticity Reviews: "Aromaticity of Heterocycles". (with M. J. Cook and P. Linda), *Adv. Heterocycl. Chem.*, **17**, 255 (1974).

"Heterocyclic Aromaticity", (with M. Karelson and N. Malhotra), *Heterocycles*, **32**, 127 (1991).

QSAR Review: "New Opportunities for the Organic Chemist in the Computer Age". (with S. J. Cato), *Computational Advances in Organic Chemistry: Molecular Structure and Reactivity*, eds. C. Ogretir and I. G. Csizmadia, Kluwer Academic Publishers, Netherlands, p. 355 (1991).

Coworkers in Aromaticity/QSAR field

Group Members: Initials and surnames listed alphabetically

E. Anders	M. J. Cook	P. Linda	R. D. Taek
P. Barczynski	N. L. Dassanayake	A. D. Page	T. W. Toone
A. J. Boulton	V. Feygelman	V. V. Shcherbukhin	J.-J. Vanden Eynde
M. P. Carmody	E. V. Gordeeva	D. J. Short	H. Witek
S. J. Cato	C. D. Johnson	P. Simmons	Z. Zhang
A. V. Chapman	G. Musumarra	M. Szafran	

External Collaborators: Initials and surnames listed alphabetically

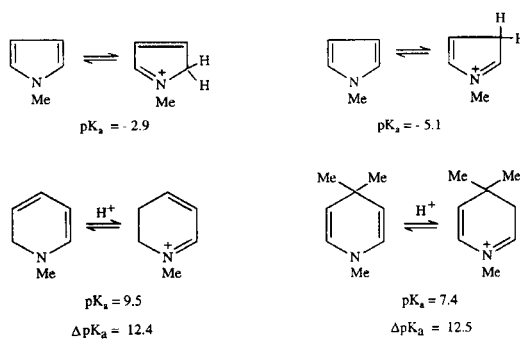
M. H. Abraham	G. M. Glover	G. J. Palenik	L. E. Sutton
A. F. Danil de Namor	M. Hely Hutchinson	D. Pisano	J. G. Tropsch
L. Dumont	T. C. Ho	J. Reisse	N. S. Zefirov
C. Ebert			

In an exciting joint project with Exxon, we have over the last 8 years explored high temperature aqueous chemistry (Scheme 88). The overall reaction pathways for a variety of 3-substituted pyridines are shown in Scheme 89. These include some interesting equilibria. Much more revolutionary were the findings shown in Scheme 90, which derived from the heating of pyridine with formic acid and the detection of significant amounts of 1-ethyl- and 1-*n*-propyl-pyridine among the products: a retrovinyl-ogous-diaza-Aldol reaction is implicated.

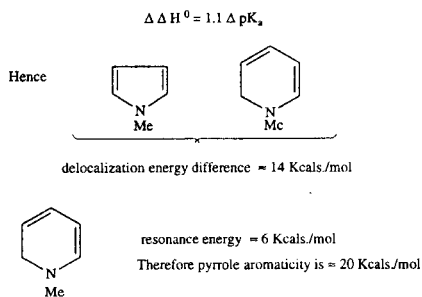
Aromaticity in general, and heteroaromaticity in particular, has always held particular fascination (Scheme 91), and this was increased when our studies of aromaticity led us into QSAR/QSPR statistical work. We estimated quantitatively the aromaticity of pyrrole from its basicity by comparison with the basicity of model compounds in which aromaticity was not lost on protonation (Scheme 92).

Many different measures of aromaticity have been proposed. However, it is quite evident that there is no single scale of aromaticities. Thus a plot, for example, of Bird aromaticity parameters against molar susceptibilities gives a scatter diagram (Scheme 94). In this situation, we

Scheme 92. Basicity of Pyrrole and Aromaticity of Pyrrole

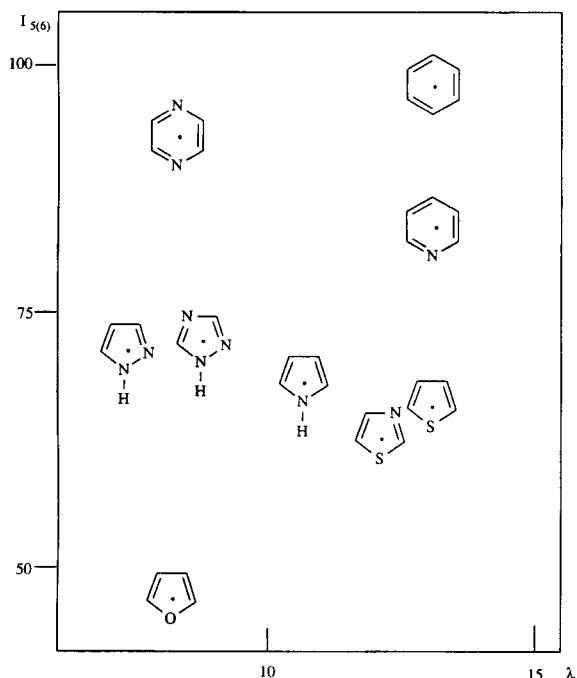


This difference in the basicities of pyrrole and model compounds can be used to calculate the aromatic stabilization energy of pyrrole.



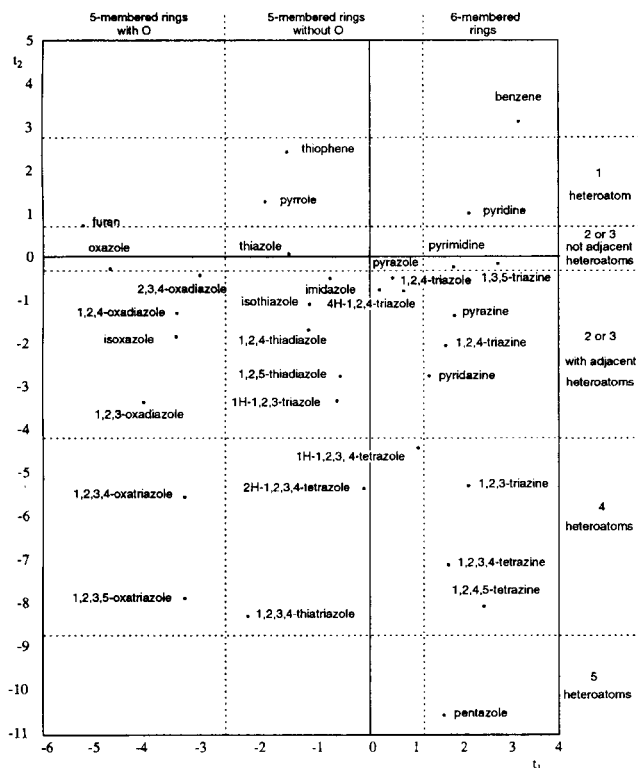
Scheme 93. Beach in Florida - nobody should work more than 100 hrs/week

Scheme 94. Plot of Bird Aromaticity Parameters $I_{5(6)}$ Against Molar Susceptibility Exaltation, λ

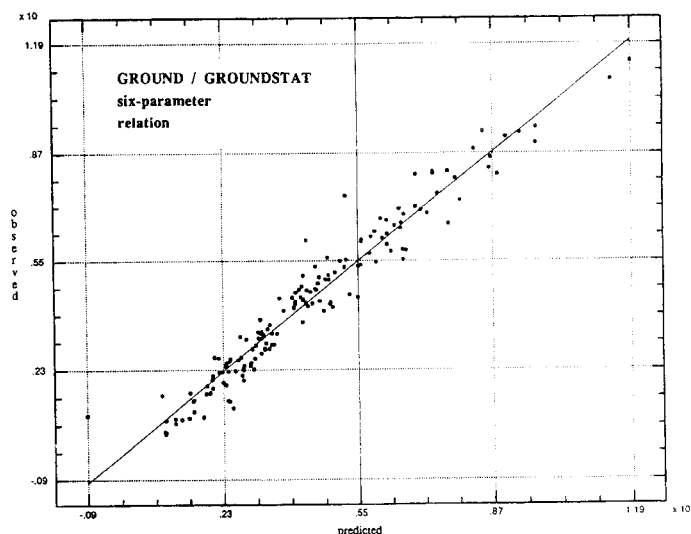


applied a statistical treatment and were able to show that one can obtain a satisfactory quantitative measure of aromaticity using two parameters. One of these we call "classical aromaticity" and it is this that determines geometries. Classical aromaticity depends on the nature of the heteroatoms (much reduced by oxygen) and on ring size (less for five than for six), and much less on the number of heteroatoms. The other, which we call "magnetic aromaticity" depends mainly on the number rather the nature of the heteroatoms (Scheme 95).

Scheme 95. Scores for the Total Set of Monocyclic Heteroaromatics



Scheme 96 Forecast of GC Retention Times



ical aromaticity" and it is this that determines geometries. Classical aromaticity depends on the nature of the heteroatoms (much reduced by oxygen) and on ring size (less for five than for six), and much less on the number of heteroatoms. The other, which we call "magnetic aromaticity" depends mainly on the number rather the nature of the heteroatoms (Scheme 95).

The molecular structure of a compound uniquely defines all its physical, chemical, and biological properties. QSAR is an attempt to decode this information and

Scheme 97. Miscellaneous Research Topics (50 Papers, 1959-1992)

Coworkers in Miscellaneous Research Topics

Group Members: Initials and surnames listed alphabetically

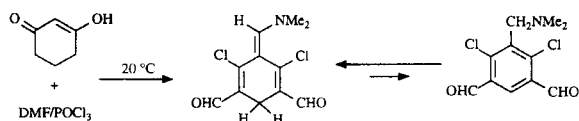
A. S. Afridi	W.-Q. Fan	D. E. Leahy	D. Rasala	M. Szajda
J. P. Baker	V. M. Feygelman	Q.-H. Long	M. N. Rudd	J. Thomson
S. Bayyuk	S. Golding	N. Malhotra	F. Saczewski	R. D. Topsom
J.A.T. Beard	J. V. Greenhill	C. M. Marson	K. Sakizadeh	M. J. Tucker
A. Bieniek	N. E. Greskowiak	A. M. Monro	M. Sammes	L. Urogdj
J. Borowiecka	P. A. Harris	B. Nowak-Wydra	G. P. Savage	Z. Wang
J. C. Cass	G. J. Hitchings	A. V. Ochkin	C. G. Schwarz	D. Winwood
K. C. Caster	R. A. Y. Jones	R. J. Offerman	M. J. Sewell	J. Wu
C. W. Conroy	G. R. Kham	B. Pilarski	T. P. Smith	K. Yannakopoulou
Z. Doga-Szafran	M. Kingsland	S. Rachwal	P. J. Steel	F. Yates
J. Elguero	A. Kotali	C. A. Ramsden	J. Stevens	X. Zhao
B. S. El-Osta	H. Z. Kucharska	M. S. C. Rao	J. Swinson	D.-W. Zhu
H. M. Faid-Allah				

External Collaborators: Initials and surnames listed alphabetically

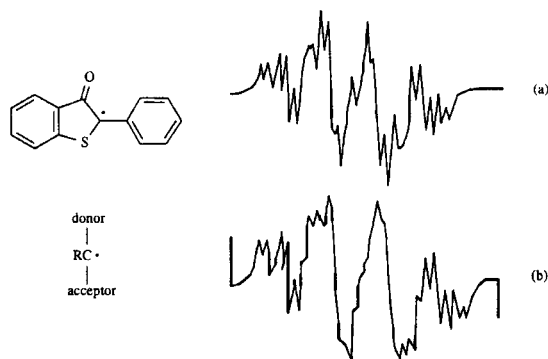
H. Aghabozorg	K. L. Busch	J. W. Johnson	T. M. Moynehan	K. S. Schanze
R. M. Alexander	L. Chiang	A. E. Koziol	G. J. Palenik	S. H. Simonsen
J. Augetein	R. G. Cooks	L. R. Krepski	S. V. Pathe	H. Vedage
A. Bar-Illan	M. A. Francisco	A. Kurs	G.W.H. Potter	J. K. Walker
S. S. Bhatnagar	S. M. Groen	D. W. Macomber	T.A. Ramanarayanan	K. V. Wood
J. F. Brody	R. L. Harlow	T. H. Maren	J. K. Rasmussen	H. M. Wuest
S. M. Heilmann	B. H. Hsu			

we are heavily involved in this area with novel QSAR programs. An example of the application of GROUND to the correlation and prediction of gas chromatographic response factors is shown in Scheme 96: this uses a six-parameter equation to relate R_f to molecular structure and is of great utility in the quantitative analysis of complex mixtures.

Scheme 98. Vilsmeier Chemistry



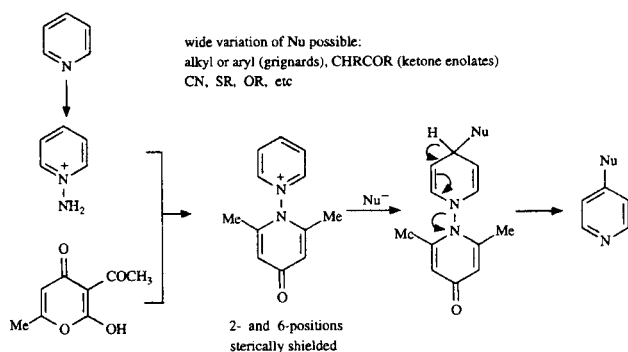
Scheme 99. Mero-Stabilization of Free Radicals



(a) ESR Spectrum; (b) Computer Simulation

In this lecture, I have not sufficient time to detail all the research topics that we have engaged in over the years. So the miscellaneous topics are lumped together and overviewed in Scheme 97. I pick three as illustrations. The first concerns Vilsmeier chemistry: as shown in Scheme 98, we were able to demonstrate that some potential benzenoid compounds prefer to exist in an alternative

Scheme 100. Regio Specific Nucleophilic Attack at 4-Position of the Pyridines



Scheme 101. Secondary Literature of Heterocyclic Chemistry

Advances in Heterocyclic Chemistry, [vol 1 (1964) - vol 58 (1994)]

Physical Methods in Heterocyclic Chemistry, [vol 1 (1964) - vol 6 (1974)]

Best Synthetic Methods (14 volumes), Co-edited with Otto Meth-Cohn and Charles Rees

Topics in Applied Chemistry (7 volumes), Co-edited with Gebran Sabongi

Comprehensive Heterocyclic Chemistry (8 volume), Co-Editor-in-Chief: Charles Rees

Volume Editors: Clive Bird, A. J. Boulton, Gordon Cheeseman, Colin Drayton, Walter Lwowski, Otto Meth-Cohn, Alexander McKillop, Kevin Potts

Scheme 102. Forthcoming Comprehensive Works

Organic Functional Group Transformations

(7 Volumes) Expected Publication 1995

Co-Editors-in-Chief: Otto Meth-Cohn, Charles Rees

Volume Editors: Tom Gilchrist, Gordon Kirby, Steven Ley, Chris Moody
Gerald Pattenden, Stanley Roberts

Comprehensive Heterocyclic Chemistry: 2nd Edition (CHEC-2)

(10 Volumes), Expected Publication 1996

Co-Editors-in-Chief: Eric Scriven, Charles Rees

Volume Editors: Albert Padwa, Alexander McKillop, John Boulton, Clive Bird
Otto Meth-Cohn, Dick Storr, George Newkome, Ichiro Shinkai

non-aromatic tautomeric form. Secondly, we proposed in 1974 the term "merostabilization" for free radicals stabi-

Scheme 103. Benzotriazole Chemistry (115 Papers, 1987-1993)

Reviews: "Benzotriazole as a Synthetic Auxillary", *Il Farmaco*, **43**, 1175 (1988)."Benzotriazole: A Novel Synthetic Auxillary", (with S. Rachwal and G. J. Hitchings), *Tetrahedron*, **4**, 2683 (1991)."N-Substituted Benzotriazoles: Properties, Reactivities and Synthetic Uility", *Bull. Soc. Chim. Belg.*, **101**, 409 (1992).

Coworkers in Benzotriazole Chemistry

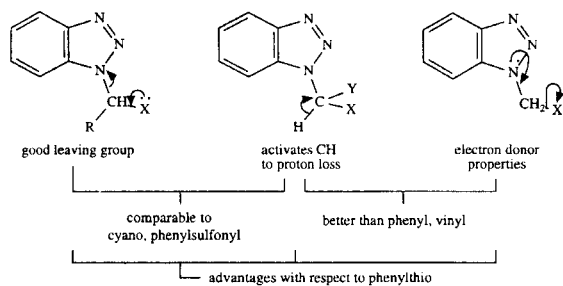
Group Members: Initials and surnames listed alphabetically

A. S. Afridi	M. Drewniak-Deyrup	X. Lan	J. Pernak	M. Szafran
K. Akutagawa	W.-Q. Fan	M. Latif	B. Pilarski	I. Takahashi
E. Anders	J. K. Gallos	K. W. Law	B. Rachwal	J. Thomson
J.M. Aurrecochea	B. Galuszka	J. Li	S. Rachwal	L. Urogd
S. I. Bayyuk	M. F. Gordeev	Q.-H. Long	M. S. C. Rao	J.-J. Vanden Eynde
P. Beretta	J. V. Greenhill	P. Lue	D. Rasala	Z. Wang
M. Black	P. A. Harris	F. Manhi	O. Rubio	L. Wrobel
J. Borowiecka	G. J. Hitchings	N. Malhotra	F. Saczewski	J. Wu
J. Z. Brezinski	C. V. Hughes	A. Mayence	G. P. Savage	L. Xie
F. Brunner	F.-B. Ji	V. Y. Mortikov	I. Shcherbakova	A. K. Yagoub
P. Cabildo	J. Jiang	Z. Najzarek	N. Shobana	Z. Yang
K. C. Caster	A. Jozwiak	G. Noble	M. Soleiman	K. Yannakopoulou
Y.-X. Chen	M. Kareison	R. J. Offerman	J. Stevens	Y. Zhang
T. Davis	W. Kuzmierkiewicz	M.H. Paluchowska	M. Sutharchanadevi	X. Zhao
Z. Dega-Szafran	J. N. Lam			

External Collaborators: Initials and surnames listed alphabetically

M. Bertoldi	M. A. Francisco	R. W. King	G. J. Palenik	P. J. Steel
D. Beugnies	J. W. Frankenfield	A. E. Koziol	R. Skarjune	M. Szczesniak
R. Flammang	C. Fu	A. Maquestiau		

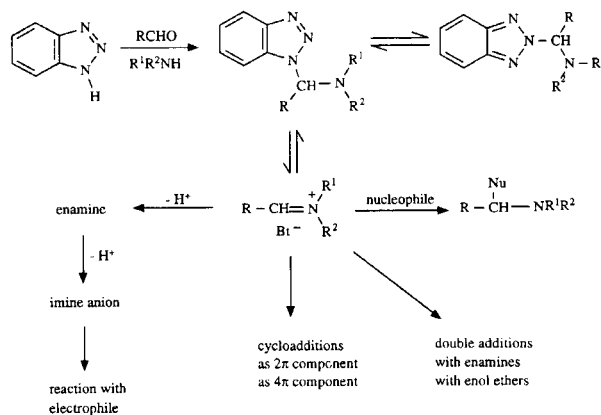
Scheme 104. Comparison of Benzotriazole with Other Activating Groups



lized by both an electron-donor and an electron-acceptor substituent. We were able to prepare the radical shown in Scheme 99 and measure its ESR spectrum. Third, regio-specific nucleophilic attack at the 4-position of the pyridine ring was achieved by using the 2,6-dimethyl-4-pyridon-1-yl substituent which shields the 2,6-position, thus directing regio-specific attack, and finally acts as a leaving group, as shown in Scheme 100.

The secondary literature of heterocyclic chemistry has

Scheme 105. Overview of Immonium/Imine Chemistry



Scheme 106. The Benzotriazole Code of Ethics

- | | |
|--|---|
| 1. Readily available and inexpensive | - Be there when your friends need you |
| 2. Bt ring both an electron donor and acceptor | - Remember it is blessed to give as well as receive |
| 3. Bt group endows desirable reactivity patterns | - Motivate the community to do better |
| 4. Bt residue easily cleaved | - Do not outstay your welcome |
| 5. Easily separated and recovered for repeated use | - Forgive, and come back when you are needed again |



Scheme 107. Group party at 1221 SW 21 Ave. (1985)

also been addressed. Projects completed or ongoing are shown in Scheme 101. Additionally, two major new projects are underway: the Second Edition of "Comprehensive Heterocyclic Chemistry", which will update the first work, and Organic Functional Group Transformations (Scheme 102).

Finally, I return to benzotriazole, which has occupied much of our attention over the last five years (Scheme 103). Benzotriazole can activate substituents attached to one to its nitrogen atoms in three quite different ways: (i) acting as a leaving group, (ii) promoting proton loss, (iii) as an electron-donor. The only other common group which has all three capabilities is phenylthio, but because of its great polarizability, benzotriazole does a better job in each of these modes of activation. The benzotriazole

bisylid equivalents depicted in Scheme 105.

But benzotriazole can do more than just help us with our synthetic organic chemistry. Its behavior is ideal as the basis for a code of ethics. Scheme 106 presents to you the attributes that we can all learn from this so-well-behaved molecule. I wish to close with thanks not only to all those excellent collaborators over years whose names have been mentioned in the slides, but also to my wife Linde who has helped me in so many ways. By a happy coincidence, today is our wedding anniversary and I would like to couple my thanks to you all for your kind patience and attention during the past hour in which you have been listening to this lecture with my gratitude to her for having done the same for the past 41 years. You see her with the Group of 1985 and again in the Group photograph of 1993



Scheme 108. The Group 1993

adducts (Scheme 104) undergo reversible ionization to immonium-benzotriazolite ion pairs, which show a great variety of reactions. Recently, we have coupled benzotriazole and phosphorus chemistry to give the two versatile

(Schemes 107, 108) as the true thread of continuity.

(Note: A systematic overview of work carried out in the Katritzky group 1953 -1993 is published in *Heterocycles*, 1994, ..., pp ..., including a complete reference list.)