PHYSICAL METHODS

IN

ORGANIC CHEMISTRY

by

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Papers have been set out essentially in chronological order within each section of the thesis. This constitutes a logical sequence for sections A and B. Subdivision of section C has not been undertaken, because of the difficulty of classifying papers on the basis of skeletal-rearrangement or normal fragmentation processes (many papers contain accounts of both types of fragmentation), and of further subdivision within a group (certain papers describe more than one type of rearrangement process).

(A) Structure-Elucidation of Natural Products

The great potential of mass spectrometry and N.M.R. spectroscopy for the determination of structure is exemplified by the following studies.

(i) Aphid Constituents

Papers 2-5 describe the elucidation of the structures of the dactynaphin and rhodoaphin pigments, while papers 1 and 6 are records of the chemistry of aphid constituents. Paper 7 gives an account of the mass spectra of known aphid derivatives, a knowledge of which was vital for the interpretation of the mass spectra of the dactynaphins and rhodoaphins.

The rhodoaphin and dactynaphin pigments are among the most complicated quinones yet isolated from natural sources. Only very small amounts of these compounds were available for study. High-resolution mass spectrometry and N.M.R. spectroscopy allowed complete
structural formulations for the pigments. On the basis of these formulations, chemical experiments were designed which would either support or negate such structures. Electron-impact induced ring cleavage of the dactynaphins split each molecule into two known species which were readily identified by their known breakdown patterns. Chemical confirmation of the dactynaphin structures was obtained by reductive and hydrolytic cleavage of the molecules to produce either known compounds, or compounds which were readily synthesised from compounds of known structure. The mass spectrum of rhodoaphin was very similar to a known aphin derivative, dihydroxyerythroaphin-β. This indicated that the only difference between the two compounds was stereochemical in nature. As the N.M.R. spectrum showed rhodoaphin to be symmetrical, only one structure was possible for the molecule. This structure was confirmed chemically by acid-catalysed epimerisation of rhodoaphin to dihydroxyerythroaphin-β.

(ii) Miscellaneous Natural Products

The aphin problem described a situation where physical methods were successfully applied in the initial stages of structure elucidation. In the determination of the structure of the alkaloid repanduline (paper 8) the converse was true. The chemical investigation of repanduline had continued over a period of two decades, and was virtually at a standstill. The elemental composition of the molecule was unknown, as were its more important structural features. The problem was solved by the successive application of high-resolution mass spectrometry followed by N.M.R. spectroscopy. A successful synthesis of a degradation product has since partially confirmed the structure.
Other examples of the application of physical techniques are the determination of the structures of the antibiotic ochromycinone (paper 9), maesopsin degradation products (10), and the alkaloid moschatoline (11). Mass spectrometry clearly indicated the presence of a 3-methyl-1-tetralone moiety in ochromycinone, and allowed the determination of the relative positions of hydroxyl and methoxyl groups in moschatoline, because of the highly characteristic losses of methyl radicals from the 1- and 3- but not 2-methoxyl groups of alkaloids of this type.

(B) Solvent-Effects in N.M.R. Spectroscopy

It is widely accepted that 'solvent-shifts' of proton resonances in N.M.R. spectra may be used to aid structure elucidation of organic compounds, particularly those containing methyl or methoxyl groups. The 'solvent shift' is the difference between the chemical shifts of proton resonances measured in a 'complexing' solvent (e.g. benzene) and a 'non-complexing' solvent (e.g. carbon tetrachloride or cyclohexane). It is assumed that benzene forms a complex with a positive-centre in the solute, thus altering the chemical shift with respect to that obtained using a 'non-complexing' solvent. Controversy exists concerning the nature of the complex, and there is even doubt whether a complex is formed at all. Nevertheless, this approach may be used empirically in certain cases to determine the positions of methyl or methoxyl groups in a molecule. This is demonstrated for quinones (paper 12), anisole derivatives (13 and 14), flavones (15) and
α-diketone derivatives (16). Paper 16 questions the nature of the 'complex' formed between benzene and the α-diketone system.

(C) Mass Spectrometry

The original aims of this research were threefold.

(i) To investigate the normal fragmentation modes of a variety of organic systems. Knowledge of this work is essential for the organic chemist to be able to interpret spectra of such systems.

(ii) To discover and investigate skeletal-rearrangement processes in mass spectra. As skeletal-rearrangement processes involve the migration of groups other than hydrogen, the presence of fragment ions resulting from such processes cannot be explained in terms of the structure of the intact molecule. The recognition of such processes and a knowledge of the structures of the rearrangement ions are not only of vital interest to the mass spectrometrist, but are also essential if the organic chemist is to use mass spectrometry to determine the structures of organic compounds. This field of research is one of the most actively pursued in organic mass spectrometry at the present time, and is likely to continue to be so until such processes can be predicted with certainty, and until the mechanisms of the rearrangement processes are fully understood. The relative non-predictability of rearrangement processes at the present time also severely limits the important application of computer-aided mass spectrometry to structure elucidation.
(iii) In cases where extensive rearrangement (cf. ii) occurs in positive-ion mass spectra, interpretation is difficult because of the presence of the rearrangement ions. Negative-ion mass spectrometry should provide a viable alternative under these conditions, even though little development of this technique has previously occurred.

Papers 17-65 go some way to fulfilling these aims, and present work is directed towards the mechanism of rearrangement processes, the structures of ions, and the development of negative-ion mass spectrometry.

Papers 17-33 are the result of research performed at Cambridge and may be roughly divided into normal fragmentations of organic molecules upon electron impact (19-23, 25, 29, 31 and 33) and skeletal-rearrangement processes (17, 18, 24, 26-28, 30 and 32). The latter group contain examples of some of the first rearrangement processes encountered in mass spectrometry.

The publications 34-65 of section C comprise my major contribution to organic chemistry. Publications 34-36, 39, 42, 44, 50, 54, 56, 57, 58 and 60 record the basic fragmentations of a variety of aliphatic, aromatic and heterocyclic systems upon electron impact. Deuterium-labelling and high-resolution studies were necessary for many of the projects. Papers 37, 38, 40, 41, 43, 45-49, 51-53, 55, 59, 61-64 describe a multitude of new and novel skeletal-rearrangement processes as well as normal fragmentations which occur upon electron impact. The most notable of the rearrangements are those which occur in the spectra of compounds containing the $^+$ group, organo-sulphur compounds, and heterocyclic systems containing diphenyl substituents. For example, specific but complex rearrangement of the molecular ions
of azoxybenzenes (43,45), nitrones (59,62) and N-oxides (47) are observed. All involve carbon-oxygen bond formation. Reorganisation of the molecular ion is also observed for sulphonylanilines (41), thio[18]annulenes (49), mercapto esters (46,51) and sulphonamides (52,53). Migrations to carbon-ion centres are apparent in the spectra of thioglycollates (64). Many examples of the general rearrangement ABC → AC + B have been discussed; e.g. azobenzenes (40), azoxybenzenes (43,45), nitrones (59,62), sulphonamides (52,53) and anils (61). A remarkable rearrangement which occurs in the spectra of diphenyl heterocyclic systems (55,61) has been studied with the aid of extensive deuterium labelling.

The potential of negative-ion mass spectrometry is clearly demonstrated in paper 65. The positive-ion spectra of compounds containing the −N=O− group are complicated by pronounced rearrangement fragments. The corresponding negative-ion spectra are simple, diagnostic, contain pronounced molecular anions, and are devoid of rearrangement peaks.
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(ii) Miscellaneous Natural Products


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Section C. MASS SPECTROMETRY


