EVIDENCE FOR ARYL PARTICIPATION IN MASS SPECTROMETRIC FRAGMENTATION PROCESSES

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Abstract—While heterolysis of oxonium ions generated upon electron-impact in the mass spectrometer is a well documented phenomenon in the fragmentation of aliphatic ethers, little analogy exists for structurally comparable immonium ions. Exceptions are ions of the latter class in which dissociation is facilitated by the presence of proper substituents in positions allowing stabilization of daughter ions. Two main types of substitution were explored providing (1) resonance stabilization of the product ions by aryl substituents in *benzylic* heterolysis, and (2) aryl neighboring group participation in *homobenzylic* heterolysis, possibly yielding phenonium ions (or isomeric ions via further rearrangement) as stable products in the gas phase. In the discussion emphasis will be placed on Case 2.

INTRODUCTION

THE EJECTION of stable neutral molecules in the course of *heterolytic dissociation* processes undoubtedly represents one of the most characteristic modes of fragmentation of oxonium ions formed in the gas phase from suitable precursors upon electron bombardment. Obviously, this behavior is a consequence of high product stabilities of small, oxygen-containing molecular entities commonly expelled and sufficient driving force is frequently mobilized even for the formation of primary carbonium ions lacking particular stabilization. The bonds suffering such cleavage are, of necessity, the bonds adjacent to the ionic center of the decomposing species, rendering the centers of electron deficiency and reactivity identical.¹

Well known examples for this mode of fragmentation are the following decompositions of even-electron species,* usually documented by the observation of pertinent metastable peaks:

$$\begin{array}{c} R--CH_{2}\overset{\frown}{\longrightarrow}^{+}OH_{2} \rightarrow R--CH_{2}^{+} + H_{2}O\\ R--CH_{2}\overset{\frown}{\longrightarrow}-CH_{2} \rightarrow R--CH_{2}^{+} + CH_{2} = O\\ R--CH_{2}\overset{\frown}{\longrightarrow}-CE=O^{+} \rightarrow R--CH_{2}^{+} + C \equiv O \end{array}$$

* Heterolysis of carbon-oxygen bonds does not seem to be limited to the non-radical type of cations with even numbers of electrons. For instance, the following reaction can be viewed as an analogous decomposition (see e.g. ref. 3) of odd-electron radical ions:

Such processes are likely to be complicated, however, by the interference of two centers of reactivity (ionic and radical site) and will therefore not be considered in this discussion.

In the first case, the decomposing fragment ions originate from a side-chain elimination associated with double hydrogen transfer, as exhibited by aliphatic ethers meeting certain minimum chain-length requirements.^{2,3} The ions in the other two cases arise from common α -cleavage of simple aliphatic ethers² and ketones,⁴ respectively.

Benzylic Heterolysis

In contrast to the quite general occurrence of heterolytic carbon-oxygen bond fission, evidence for comparable dissociation processes involving carbon-nitrogen bonds seems to be scarce. Thus, numerous examples in the literature reflect the absence or insignificance of such parallels, particularly if primary or secondary carbonium ions would result.⁵ This is, for example, documented by the spectrum of N-n-hexyl- β -phenylethylamine, (I) (Fig. 1). Abundant loss of benzylic radicals leads to aliphatic immonium ions of mass 114 which subsequently undergo an even-electron type McLafferty rearrangement* to ions of mass 44, rather than heterolytic loss of CH₂==NH to m/e 85 ions.

In this and similar cases the differences in ion stabilities between immonium and carbonium ions are apparently too large to be sufficiently offset by the stability of the corresponding imines or Schiff-bases that might be formed as neutral products. If, however, effective stabilization can be provided for the resulting daughter-ions, comparable heterolytic dissociation becomes feasible to the extent that its products sometimes dominate the spectral pattern. This is, for instance, true for resonance stabilization offered by aromatic systems,[†] particularly when properly substituted, as is borne out by the spectra of various benzyl- β -phenylethylamines such as II, III, and IV (Figs. 2 to 4).

The important feature of these spectra is the presence of two prominent fragment peaks, e.g. at m/e 120 and 91 in the case of II, due to favored benzylic cleavage (with charge retention on the nitrogen atom) and subsequent dissociation of the resulting immonium ions:



The observation of a metastable peak for the transition m/e 120 $\rightarrow m/e$ 91 indicate that at least a portion of the recorded m/e 91 ions is of secondary origin, i.e. derived from heterolysis. A substantial primary contribution from direct benzylic cleavage, with charge retention by the aromatic moiety, is not too likely, however, as can be concluded from related model compounds in which heterolytic alternatives are excluded. Usually, benzylic cleavage of such compounds affords product ions with predominant charge retention on the nitrogen-containing fragment, and to a much lesser degree by the corresponding benzylic moieties or their tropylium-equivalents. This remarkable preference for the formation of immonium vs. tropylium ions is also reflected in the

* The close analogy of the even-electron variety with the McLafferty rearrangement of oddelectron ions is emphasized by the demonstration of a comparably specific γ -hydrogen transfer.^{6,7}

† Related findings concerning the fragmentation of certain Amaryllidaceae alkaloids have been disclosed to the authors by Dr A. L. Burlingame, Space Sciences Laboratory, University of California, in a private communication.

spectrum of II (Fig. 2), even though the abundance of the immonium ions (m/e 120) is lowered in this case due to heterolysis. Nevertheless, the immonium ions still exceed their benzylic counterparts by more than a factor of ten as is apparent from the small peak at m/e 125.*

A comparison of the abundance ratios of the ions involved in heterolysis of compounds II to IV shows a strong influence of the functional groups on these reactions. From such data the structures of the product ions of benzylphenylethers⁸ have been deduced in a recent study. The present results appear, however, inconclusive with respect to the identity of the reaction products.

Homobenzylic Heterolysis

From the positive evidence of a pronounced heterolytic reactivity of benzylic systems in which strong product stabilization is provided by resonance, it seemed desirable to explore the scope and possible structural requirements of this behavior in more detail. Particularly the insertion of an additional methylene unit between the electron-donating aromatic system and the immonium nitrogen demanded interest, since model compounds incorporating this feature could be expected to furnish evidence *pro* or *contra* the operation of aryl participation in the gas phase.[†] The products of such neighboring group assistance in the heterolytic step of decomposition might be visualized as phenonium ions.[‡]



For the purpose of testing this possibility, several representatives of the following structural type were investigated:



* β -Phenylethylamine and benzylamine are similarly inefficient sources of tropylium ions: while the respective immonium fragments represent the base peaks in both spectra, the tropylium ions account for only 11% relative intensity for the former, and 17% for the latter.⁹

[†] Subsequent to submission of this manuscript, Professor R. H. Shapiro of the University of Colorado informed us of a study of the same phenomenon conducted in his laboratory, using a different approach. Receipt of his manuscript prior to publication is gratefully acknowledged.

[‡] While this work was in progress, a phenonium ion structure was proposed by Djerassi and co-workers to account for the decomposition of an oxonium ion formed from the TMS-ether of β -phenylethanol.¹⁰



FIG. 1. Mass spectrum of compound I.



FIG. 3. Mass spectrum of compound III, HCl.



FIG. 4. Mass spectrum of compound IV, HCl.



FIG. 5. Mass spectrum of compound V, HCl.



FIG. 6. Mass spectrum of compound VI, HCl.



FIG. 7. Mass spectrum of compound VII, HCl.



FIG. 8. Mass spectrum of compound VIII.





FIG. 9. Mass spectrum of compound IX.

The presence of two β -phenylethyl substituents provided for (1) favorable benzylic cleavage and consequently an abundant formation of immonium ions of type *a*, and (2) a two-carbon link between the reactive sites, which is required for β -aryl participation in the subsequent dissociation step. Representative examples of the compounds examined are the following:

| R ₃ | R_4 | |
|-------------------|--|--|
| Н | Н | |
| Cl | н | |
| CH ₃ O | CH₃O | |
| | R ₃ H Cl CH ₃ O | |

As can be seen from the spectra of these compounds (Figs. 5 to 7), provision (1) is met to such a degree that competing fragmentation is extensively suppressed. As a consequence of the same condition, of course, the intensities of the corresponding molecular ions are likewise reduced, amounting to less than 0.5% of the base peak and only slightly surpassed by [M + 1] and [M - 1] satellites.

The actual existence of a surprisingly prominent process compatible with the scheme outlined above (inasmuch as it reflects a net homobenzylic cleavage of primarily formed immonium ions) is borne out by the high-intensity peaks at m/e values expected for fragment ions of structure b. These peaks represent in all three cases the second most abundant fragments formed and are related to their precursor ions a (accounting for the base peaks of the spectra) by proper metastable peaks, thus leaving little doubt about their largely secondary origin. At lower ionizing voltages the process, together with fragmentation of less importance, is almost completely suppressed.

To rule out mechanistic alternatives possibly involving reciprocal double hydrogen transfers,* and consequently simulating the direct, anchimerically assisted heterolysis in the net result, compound VIII and the two deuterium-labeled analogs VIIIa and VIIIb were prepared and studied:

$$\langle \bigcirc -CR_2'-CR_2''-NH-CH(CH_3)-CH_2-\langle \bigcirc \rangle$$

(VIII): R', R" = H; (VIIIa): R' = D, R" = H; (VIIIb): R' = H, R" = D)

The spectra of these compounds are reproduced in Figs. 8, 8a and 8b.

An asymmetrical structure has been chosen for VIII to force primary α -cleavage

* The operation of hydrogen transfers seemed conceivable, since the system offers activated benzylic positions for hydride-ion abstraction in a possibly favorable five-membered transition state:



preferentially into one direction, namely the branched unlabeled substituent:



The predominantly formed immonium ions a_1 of mass 148 are shifted in both spectra of the labeled derivatives to m/e 150, and distinct shifts of two mass units to m/e 107 are observed for their daughter ions b_1 (m/e 105). This clearly demonstrates the retention of the α as well as β hydrogen atoms in the course of this process. In addition, the largely suppressed a_2 ions, also of mass 148 and therefore coinciding with the a_1 ions in the spectrum of VIII, are recorded at m/e 148 in the case of VIIIa, and at 150 for VIIIb. In all three cases ions of mass 119 are formed from a_2 via an analogous heterolytic decomposition and represent methyl-substituted homologs of the m/e 105 ions. The absence of label in these fragments is complementary evidence for the non-existence of reciprocal hydrogen transfers between the reactive sites.

If, as inferred above, the formation of a phenonium structure does in fact provide the decisive driving force for the observed heterolysis, a definite dependence of the rates of formation from the nature of the substituents attached to the aromatic nucleus should be expected. Donor substituents in *para* positions, for instance, like one of the methoxy groups in VII (Fig. 7), could be anticipated to enhance the rate of decomposition of the immonium ions,* while electron withdrawing groups might be expected to retard the process. From the data currently available, however, such effects seem to be minor as is apparent from the similar a/b intensity ratios in the

* Any expected rate enhancement could possibly be obscured, e.g. by the intervention of δ -aryl participation as a competing alternative. Such a process might stabilize precursor ions *via* formation of rings geometrically more favorable then in the case of phenonium structures, and might consequently lower the concentration of reactive (uncyclized species) to counteract faster decomposition:



Since under such circumstances differences between ρ -values (rather than the values themselves) would be observable in the over-all fragmentation, any dependence of dissociation on substitution might appear minor. Cyclization of analogous even-electron species involving aromatic systems has, for instance, been invoked in mass spectrometry to explain the fragmentation of benzoylmalonates,¹³ as well as in solution chemistry to explain the solvolytic behavior of 4-phenyl-1-butyl brosylates.¹⁴

spectra of V, VI, VII. This finding stands in some contrast to the observation of considerable substituent effects on the benzylic cleavage in compounds II to IV. A more detailed study of these effects, which were recently investigated for several other types of mass spectrometric fragmentation, $1^{1,12}$ is currently in progress.

In this context, of course, the question arises whether aryl participation in the special case of β -aryl substituents is particularly favorable, as compared to assistance of more distant aryl moieties. For this reason it was desirable to probe the fragmentation behavior of related γ -aryl homologs for analogous modes of fragmentation. One of the compounds selected for this purpose was IX (Fig. 9). Ions of mass 153 which would indicate the existence of comparable fragmentation processes for these compounds are, however, conspicuously absent,* while their lower benzylic or tropylium homologs (m/e 125) show surprising prominence. The origin of these latter ions is not established, particularly since pertinent metastable peaks could not be detected. Nevertheless, a direct formation from the molecular ion appears questionable, since it fails, as previously mentioned, to constitute a major source of such ions in the case of the α - and β -arylamines I to VIII. An alternative mode of assisted heterolytic decomposition might possibly be considered in this case:

$$\begin{array}{c} & & \\ & &$$

Such a process would resemble a solvolytic Grob-fragmentation¹⁵ inasmuch as an 'ethylogous' separation of the reactive sites could provide for a synchronous development of three energetically favorable products if sufficient orbital overlap can be achieved in the activated complex. A more detailed analysis of this system will, however, be required to establish a genuine heterolytic genesis for these ions.

EXPERIMENTAL

Compounds II and III,¹⁶ V and VII,¹⁷ and IV, VI, and IX,¹⁸ were prepared according to known procedures.[†] Compounds VIII, VIIIa and VIIIb were prepared by reacting 2-phenyl-1-methyl-ethylamine with the respective acid chlorides, followed by reduction of the resulting amides with LiAlH₄ (LiAlD₄ in the case of VIIIb). The starting material for VIIIa, α -d₂-phenylacetyl-chloride, was obtained *via* the following sequence: methyl phenylacetate was treated with CH₃OD and base to effect deuteration of the benzylic position. Saponification with D₂O and base, followed by SOCl₂ treatment, yielded the required acylchloride.

* A referee has pointed out that the absence of heterolysis in IX, as well as in I, might result from its suppression by a competing McLafferty rearrangement (leading to peaks at m/e 44) of much lower energy requirement. On the basis of this assumption, homobenzylic heterolysis in V to VIII would appear to be a simple consequence of the lack of γ -hydrogen atoms rather than the result of aryl participation. Such an interpretation can be rigidly excluded for V to VIII, if not also for I and IX, on grounds of the following arguments: (1) The prominent peaks observed in V to VIII would be of surprising intensity if due to unassisted heterolysis of immonium fragments to primary carbonium ions; (2) it seems unlikely that such unassisted heterolysis could compete favorably (as, in fact, it does) with the common olefin elimination from immonium ions, leading to m/e 30 fragments and substituted styrenes as neutral species in the present case; (3) data derived from CH₂=N⁺ (R)CH₂-CH₂Ar ions (R = n-butyl), where heterolysis and McLafferty rearrangement can compete, establish homobenzylic heterolysis as the decidedly dominating alternative.

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