Reaction Mechanisms of Gaseous Organic Ions. Part 17.[1] Intramolecular Stereoselective Competition in Mass-spectral Homolytic Reactions of *NO*-Heterocyclic Molecular Ions

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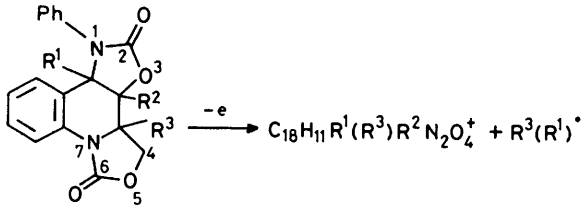
3a,11b-Dimethyl-1-phenyl-1,3a,3b,4,7,11b-hexahydroquinolino[2,1-*c*:4,3-*d*]dioxazolo-2,6-dione molecular ions eliminate methyl radicals in a selective manner. This effect increases when slow reacting ions are examined, showing that the ionized molecule at low energy states contains a similar population of the rotational levels as the precursor, the spatial disposition of the phenyl group being almost unchanged by rotation. The results, obtained by exact mass measurements, m.i.k.e. and combined scan analysis, deuterium labelling, and *X*-ray stereochemical studies, indicate that the high selectivity is due to stereochemical effects on the single-bond dissociation which is controlled by delocalization of the MO of the fragment ions; loss of the 3a-methyl produces greater stabilization of the corresponding fragment than 11b-methyl elimination.

UNIMOLECULAR, multi-bond cleavages of organic ions during mass spectrometry are dependent on conformational relationships.[2] The ordered transition state for rearrangement processes determines selection among formally similar groups and reveals an apparently subtle effect due to the initial thermal energy of the parent molecule.[3] On the other hand, single-bond ruptures may be less influenced by stereochemical differences because of the formation of a looser activated complex during dissociation even though specific elimination of a methyl group is observed when the precursor molecular ions are conformationally frozen.[4]

The gas-phase decompositions of the *NO*-heterocyclic molecular ions (1) (Scheme), containing two similar lactone–lactam functional groups,[5] allow the observation that the reactivity of ionic intermediates in the mass spectrometer is directly influenced by thermodynamic factors strictly related to stereochemical effects of a rotational nature and to the formation of the least endothermic reaction products. The fragmentation reactions of (1) have been investigated by exact mass



(1) $R^1 = R^3 = CH_3, R^2 = H$

(2) $R^1 = CD_3, R^2 = H, R^3 = CH_3$

SCHEME

measurements, m.i.k.e. analysis,[6] semi-automatic combined scan analysis [1,7] and deuterium labelling studies, using a Varian Mat CH5-DF–Spectro system SS-100 mass spectrometer–computer system under normal operating conditions.

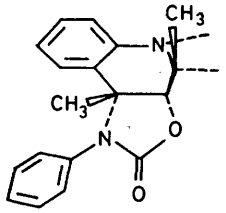
The molecular ion (1) decomposes in slow reactions through loss of Me•, CO_2, Me + CO_2, PhNCO, and PhNCO + Me•, with relative abundances, derived from the m.i.k.e. spectrum, of 74, 1, 4, 13, and 8%, respectively. Homolytic expulsion of the methyl radical is also a dominant process in fast reaction conditions, *i.e.* the stable ion, *m/e* 335, corresponds to 30% of the base peak ($M^{+\cdot}$) in the mass spectrum of (1). These results do not allow any distinction to be made between the two formally equivalent pentacyclic rings in their directing capabilities towards methyl elimination, both containing the leaving group α to nitrogen. The deuterium-labelled compound (2), synthesized by previously reported procedures,[5,8] permits the fragmentation path to be clarified, thus revealing a driving force for preferential expulsion of the methyl radical from one of the two positions, 3a and 11b. The 70 eV mass spectrum of (2) shows peaks at *m/e* 339 ($M^{+\cdot} - CH_3^{\cdot}$; 16.6, 15.7% corrected for isotope contribution) and 336 ($M^{+\cdot} - CD_3^{\cdot}$; 5.5, 4.6% corrected), while that at 13 eV gives corrected values of 2.5 and 0.6% for $CH_3^{\cdot}$ and $CD_3^{\cdot}$ loss. Combined scan analysis gives a relative abundance of 60 (loss of $CH_3^{\cdot}$) and 8% (loss of $CD_3^{\cdot}$) for metastable transitions in the first drift region of the reversed Nier–Johnson instrument. The m.i.k.e. spectrum of the molecular ion, *m/e* 354, indicates that labelled and unlabelled methyl elimination compete effectively when this process occurs in the second drift region, *i.e.* loss of $CH_3^{\cdot}$ bears 67% of the total ion current and loss of $CD_3^{\cdot}$ 3%. In both drift regions, intramolecular H–D exchange can be excluded.

The results show favourable homolytic cleavage of the methyl group adjacent to the nitrogen atom of the tetrahydroquinoline moiety which has a fused aromatic ring in the proper position for potential 3a-methyl loss. This process appears to increase in selectivity on going from highly energized reactive states of the radical cations, *i.e.* those dissociating in the ion source, to the lowest reactive states accessible in conventional instruments (reactions occurring in the second drift region). The internal energy dependence of this selective reaction is confirmed by the ratios of the two competing fragmentations from molecular ion (2); the ratio $CH_3^{\cdot} : CD_3^{\cdot}$ is 3.4 (70 eV), 4.2 (13 eV), 7.5, and 22.3 in the ion source and the first and second drift region, respectively.

Since the operation of a secondary deuterium isotope

effect cannot be invoked in the interpretation of such a large difference between labelled and unlabelled methyl loss at any internal energy of the reacting precursors, this striking preference can be explained in terms of conformational effects which control the two competitive reaction channels, *i.e.* simple, homolytic cleavage of C–C bonds α to formally similar nitrogens [see compound (1)]. The fact that elimination of 3a-methyl is favoured relative to that of 11b-methyl derives from stereochemical analysis of the parent molecule.[9] The less rigid part of the tetrahydroquinoline group of (1) adopts a half-chair conformation [as shown in (3)] which is distorted because of steric hindrance due to the aryl group at position 1 and to the pseudo-axial 3a- and 11b-methyls; thus the fused ring portion with the aromatic group conjugated to the nitrogen in the tetrahydroquinoline part of the molecule is almost planar, while the phenyl ring is at an angle of 59.7° with the plane of the lactone–lactam group.[9] Therefore, each of the two methyl groups in question, *i.e.* 3a- and 11b-CH_3, is part of two systems, each containing a nitrogen atom and a π-system. One of the two systems, *i.e.* that containing 3a-CH_3, is held almost flat by the fused ring of the immonium system left behind by loss of the 3a-methyl. On the other hand, the second nitrogen–π-system moiety is characterized by a phenyl ring which is partially forced to rotate away from the plane for stabilization. *X*-Ray data for the solid phase also suggest that this ring is normally out of the plane. Moreover, the fused aromatic ring, available to stabilize the developing radical site on C-3a, is twisted steeply away from the C-11b radical orbital in the transition state.

Since the minimum-energy reaction path for loss of methyl from the ionized compound (1) is defined by the



(3)

attainment of the lowest energy transition state, elimination of a radical from position 3a is assisted by the formation of a more delocalized MO for the product ion than in the case of loss of a radical from C-11b if there is conformational correspondence between the condensed and the gas phase. In fact, in the first case $sp^3 \longrightarrow sp^2$ rehybridization of C-3a to couple the unpaired electron on the adjacent nitrogen leads to full planarity of the system, while the torsional strain of the phenyl ring, in its original conformation, prevents delocalization and thus reduces the stabilization of the activated complex in the reaction process with loss of 11b-methyl. The high stereoselectivity of elimination at low internal energy of the reacting ions can be controlled by the rotational barrier of the phenyl ring which is overcome at higher energy states. This could justify the observed difference of activation energy for the two homolytic cleavages, *i.e.* ΔE_{CD_3} 57.2 ± 0.8 and ΔE_{CH_3} 40.4 ± 0.8 kcal mol^{-1} from I(M) and $A(X^+)$ ($\Delta\Delta E$ 16.8 kcal mol^{-1}).* This energy consideration explains why 11b-methyl elimination competes more effectively in the ion source than in the drift regions of the mass spectrometer and clearly confirms that the population of the rotational levels at high energy states must be quite different from those at low ones. It is thus possible to infer that rotational conformation around the bond between the nitrogen and the phenyl ring must be preserved in low energized reacting ions (the ratio $CH_3 : CD_3$ is 7.5 and 22.3 in the first and second drift region, respectively) and is lost to some degree in those ions which fragment with a larger excess of internal energy than those sampled in the drift regions. In fact, the observed ratios for the homolytic reactions associated with methyl and labelled methyl loss from (2) are 3.4 and 4.2 at 70 and 13 eV, respectively, as reported above.

The mass-spectrometric findings, discussed above, are intelligible in terms of quasi-equilibrium theory.[11] The elimination of 11b-methyl can be seen as a rearrangement reaction controlled by phenyl ring rotation. This aromatic group, bound to the nitrogen in position 1, must ' rearrange ' into a planar conformation in order to stabilize the immonium system resulting from the loss of 11b-methyl. This affects the frequency or the pre-exponential factor in the rate expression [11] for 11b-methyl loss. Moreover, this process is not compensated by a low competitive energy of activation, because even when the phenyl ring finally swings into the planar conformation, the delocalization is no better than that already set up for C-3a by the other fused aromatic ring.

In addition, the steric strain of bringing the rotating phenyl group to the planar position should also play an important but not a unique role. In fact, the two methyls in question are not identically bonded and this can give a satisfactory explanation of the energy barrier found (16.8 kcal mol^{-1}) from the rearrangement-like process thus observed.

Thus, for the experimental evidence reported here, the two methyl groups of (1) at C-3a and -11b are lost to different extents and this difference depends on the ion lifetime and therefore changes in the ion internal energy. Furthermore, the conclusion must be that the major part of gaseous ionic reactions of (1) in mass spectrometry takes place from molecular ions at the lowest electronic levels. The conformation of these ions is very similar to that of the molecule before ionisation and, in particular, the conformation around the Ph–N bond is not changed by rotation. Furthermore, the rotational levels of the molecular ions of (1) must also be similar to those of the original molecule and they are differently populated according to the internal energy

* I(M) and A(X) values were determined using argon as reference gas and the results were analysed using the ' semi-log plot ' method.[10]

content of the reactant ions. In conclusion, the most stable conformation of a complex molecule is that achieved in the diffused phase before packing into crystals [12] and this resembles, in plausibly close similarity, that assumed for the gas phase before and after ionisation, following the Franck–Condon principle.[3] Furthermore, the experiment discussed confirms the operation of conformational selectivity on single bond rupture and the applicability of mass spectrometry as a stereochemical probe.[13]

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