

Competitive Reduction of 1b and 3b with Tributyltin Hydride. Into a 5-mm NMR sample tube were placed 77 mg (0.462 mmol) of 1b, 99 mg (0.480 mmol) of 3b, 571 mg (1.962 mmol) of tributyltin hydride, and a catalytic amount of AIBN under a nitrogen atmosphere. Before the sample tube was sealed, 12 mg of benzotrifluoride and a capillary containing TFA were introduced to it as a reference for determination of the products and for NMR analysis, respectively. This mixture was heated and kept at 80 °C with occasional shaking, and ^{19}F NMR analyses were made every hour. The reduction occurred very cleanly, no byproducts such as a ring-opened compound being formed. The amounts of the reduction products 7c, 7d, and 9d were determined from their resonance peak areas due to the 7-fluorine atom relative to that due to benzotrifluoride in ^{19}F NMR spectra. The yields of the reduction products from 1b and 3b were 58.9% and 59.2% after 1 h, 76.8% and 76.9% after 2 h, 89.8% and 90.4% after 3 h, and 96.8% and 97.3% after 4 h, respectively. The complete

stereospecificity was observed throughout the reduction of 3b while the stereospecificity of the reduction of 1b was as follows: 84% after 1 h, 83% after 2 h, 84% after 3 h, 84% after 4 h.

Registry No. 1a, 78986-62-6; 1b, 79081-95-1; 2a, 56620-30-5; 2b, 56650-00-1; 3a, 78986-63-7; 3b, 79081-96-2; 4a, 78986-64-8; 4b, 79081-97-3; 5a, 56620-29-2; 5b, 56649-99-1; 6a, 16646-94-9; 6b, 16646-93-8; 7c, 78986-65-9; 7d, 79081-98-4; 8c, 56620-32-7; 8d, 56650-02-3; 9c, 78986-66-0; 9d, 79081-99-5; 10c, 78986-67-1; 10d, 79082-00-1; 11c, 56620-31-6; 11d, 56650-01-2; 12c, 16646-97-2; 12d, 16646-98-3; Bu_3SnH , 688-73-3; 1-methoxycyclohexene, 931-57-7; 1-(hydroxymethyl)cyclohexene, 4845-04-9; 1-(trimethylsilyl)cyclohexene, 17874-17-8; 1-methylcyclohexene, 591-49-1; 1-fluorocyclohexene, 694-51-9; *trans*-2-fluorocyclohexanol, 14365-32-3; *cis*-1-bromo-2-fluorocyclohexane, 51422-74-3; 1-[[[(2-tetrahydropyranyl)oxyl]methyl]-7-chloro-7-fluoronorcarane, 78986-68-2; 1-(hydroxymethyl)-7-chloro-7-fluoronorcarane, 78986-69-3; 7-chloro-7-fluoronorcarane-1-carboxylic acid, 78986-70-6.

Reaction Mechanisms of Gaseous Organic Cations. 20.¹ Reactivity of Ionized 3-Phenylisoxazol-5(4H)-one

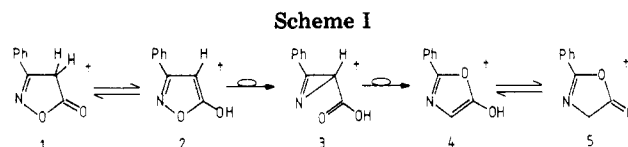
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The chemistry of ionized 3-phenylisoxazol-5(4H)-one, which is relatively slow reacting in the gas phase, has been investigated by analysis of the mass-analyzed ion kinetic energy spectrum (MIKES), kinetic energy release, appearance energy, exact mass measurements and D, ^{15}N , and ^{13}C labeling. Appropriate experiments show that the N,O-heterocyclic radical cations under study undergo unimolecular dissociations leading to the formation of benzoyl and formanilinium cations through pathways which involve phenyl migration. PhCO^+ fragment ion formation must occur through a reaction channel akin to a thermochemical process. This implies a deep skeletal reorganization similar to an electrophilic substitution onto the aromatic ring and excludes the occurrence of photochemical-like activation giving rise to isoxazole-oxazole ring isomerization. The decomposing ions possess, therefore, only a small excess energy, and have to follow only low-lying reaction channels.

Information about the chemistry of organic ions in a noninteracting environment can be acquired by investigating the behavior of a beam of positive ions reacting via unimolecular processes in a mass spectrometer. The chemical reactivity of the molecular ion of a given precursor has already been exploited to predict the primary products of photolysis or thermolysis of the same molecule^{2a} and to project synthetic approaches to complex natural products by the analysis of some retro mass spectral processes.^{2b} The relationship between chemical reactions occurring in a mass spectrometer and those taking place as a result of thermal and photochemical activations has been the subject of several recent investigations.^{2a,3a} Since the energy of the conventional colliding particle used during the ionization process is fairly spread out,⁴ some excitation energy is generally transferred to the reacting ions. This means that the excess energy available to the gaseous organic ions can reduce selectivity between the competing dissociation paths accessible to the reacting species. Thus, the major difference between the photochemical and thermochemical processes of neutrals in the condensed phase may be less evident in ionic dis-



sociation reactions in the gas phase, because at the energies available both the ground and excited electronic states can be populated, giving rise to a different electronically controlled reactivity of the ions. However, during a mass spectrometric experiment, isolated organic ions can either undergo unimolecular degradation closely similar to^{2,3a,b} or strictly analogous with⁵ that of thermochemical processes, or else they can follow competing fragmentation paths involving bond breaking and formation in conformity with a high-energy reaction channel. If the chemistry of ionic processes in different systems is to be correlated and used for the purpose mentioned above, it must be concerned with ionic reactions that can be thoroughly investigated as, for example, for those occurring when metastable ions are sampled.⁴

The chemical behavior of ionized 3-phenylisoxazol-5(4H)-one (1)^{5,7-9} and related systems¹⁰⁻¹² has attracted

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particular attention, since it is possible to postulate some analogies between the photolysis of substituted isoxazoles^{13,14} and the unimolecular degradation of 1 via its enolic formula 2 as shown in Scheme I. The reaction sequence from 1 to 5, which may give rise to the formation of product ions, i.e., benzoyl cations⁷ and those due to loss of CO plus OH and C₂H₂NO⁸, requires two ring isomerization steps. The first leads from the 5-hydroxy-3-phenylisoxazolic (2) to the 2-carboxy-3-phenylazirinic (3) radical cation and the second from the latter to the 5-hydroxy-2-phenyloxazolic radical cation (4).

It has already been experimentally ascertained that the first ring isomerization step of Scheme I does occur in neutral analogues of 2, i.e., 3-phenyl-5-methoxyisoxazole.^{15,16} The second isomerization step of Scheme I may proceed by a path similar to the photolytic ring opening and recycling of acylazirines.^{13,14,17} In fact, the latter ring reorganization step would not 2-carboxy-3-phenylazirinic under thermolytic conditions, since acylazirinic systems of type 3 are known to undergo a ring opening at the C-N single bond which leads to different reaction products through a nitrenic intermediate.^{18a} Later experiments on the unimolecular dissociation of 3,5-diphenylisoxazole indicate, by use of deuterium and ¹³C labeling, that all reactions proceed through the benzoylazirinic radical ion which specifically eliminates CO from its original position.^{18b} This can exclude any further need for rearrangements to isomeric forms of type 4 which would require some carbon scrambling, which was not observed during the elimination of CO.^{18b} Thus the derivative of type 3, once formed in its ground electronic state, appears to dissociate faster than any further isomerization process leading to some carbon equivalence. Therefore, should the whole rearrangement process from 1 to 5 occur, it would have to originate from the excited state of the molecular ion; that from the ground state of 1 to its isomeric form 3 would not give rise to the reacting structures 4 and 5 which may be responsible for the formation of benzoyl cations among the reaction products of the unimolecular degradation of the original isoxazolonic system. However, the reaction channel followed by the reacting ions 1 from their ground state could also be another one leading to the experimentally formed fragments *m/z* 105.

Previous experiments on the unimolecular chemistry of the same and of differently substituted ionized molecules have revealed that their lowest activation energy process is strictly correlated with the thermally allowed Beckmann rearrangement.⁵

An investigation of the rearrangement proposed in Scheme I could show that a photochemical-like allowed process, requiring selective activation by the electronic excitation of the precursor system, takes place from 1. This could in turn demonstrate the occurrence of competing reaction paths resulting from low- and high-energy channels, which both take place as metastable transitions. In this case, hierarchy discrimination favoring competing

reactions with similar activation energies¹⁹ would not operate.

The choice of metastable transitions for the examination of the unimolecular reactions of 1 relies on a highly informative experiment which can be performed by using a mass spectrometer with the magnetic analyzer preceding the electrostatic one. By this means, it is possible to isolate the beam of ions to be studied by mass analysis and then to follow its unimolecular dissociations in the drift region between the two sections by varying the voltage of the electrostatic analyzer. The pure metastable spectrum recorded is defined as a mass-analyzed ion kinetic energy spectrum (MIKES).²⁰ The MIKES experiment thus obtained gives information on the reactions of ions which have little excess energy (between 0 and 20 kcal mol⁻¹)²⁰ above the transition state for unimolecular dissociation, due to the relatively long lifetime (ca. 10⁻⁵ s) after the formation of the reacting species. When isolated organic ions undergo metastable transitions, the nonfixed energy⁴ above the potential reaction barrier is present at such low levels (only 1–2 kcal mol⁻¹) as to be of the same order of magnitude as that resulting in thermal processes in solution. In fact, the primary isotope effects for some dissociations occurring 10⁸ vibrations after ionization are very large.²¹ Furthermore, the shapes of the metastable peaks allow the kinetic energy released during the unimolecular decomposition to be assigned to a specific type of reaction.^{4,21}

Therefore, the investigation of slow reacting ions 1 should discriminate against ionic isolated states and indicate that photolytic-like isomerizations, similar to that depicted in Scheme I, may well occur.

Results and Discussion

When 3-phenylisoxazol-5(4*H*)-one (1) is ionized, one of the metastable processes observed corresponds to the transition from M⁺ (*m/z* 161) to *m/z* 105.⁵ This carries 12% of the total ion current of the MIKES spectrum and 14% of that obtained by the combined scan procedure,²² referring to the unimolecular reactions occurring in the first drift region of the instrument. Since the neutral molecule 1 might undergo thermal isomerization, as has been experimentally shown for related systems at high temperature,^{15,16} the alteration of the M⁺/*m/z* 105 ratio in the "stable" ion spectrum has been tested by changing the probe temperature. It was found that the relative intensity ratio of M⁺/*m/z* 105 decreases from an initial value of 13.3 at 100 °C down to one of 1.8 at 250 °C. Therefore, careful attention was paid to the experimental conditions under which the samples were introduced into the ionization chamber which was always kept at a temperature of around 120 °C, which is much lower than that reported for isomerization of the neutrals^{15,16} under thermal excitation.

Exact mass measurements on the *m/z* 105 peak have given a composite with 25% of C₇H₅O and 75% of C₇H₇N,⁵ while those concerning the metastable peak originating in the second drift region have revealed a composition of 46% C₇H₅O and 54% C₇H₇N. Therefore, one of the dissociation pathways of 1 corresponds to the formation of benzoyl

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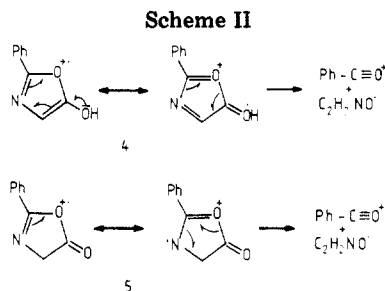
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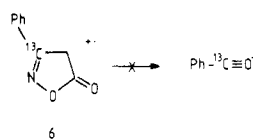
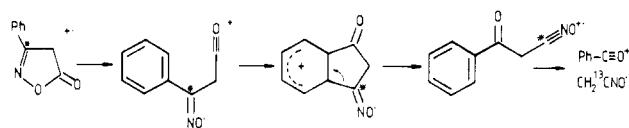


cations, both in the ion source and in the drift regions, as demonstrated by the successive elimination of CO from m/z 105 which originates from the ^{15}N -labeled analogues of 1 (see below). The other transition leading to m/z 105 is associated with the elimination of two carbon monoxide molecules from the molecular ion. Both reactions require a deep modification of the original structure 1, since the formation of the $\text{C}_7\text{H}_5\text{O}$ product ions must result from the phenyl group and a CO moiety which are not directly linked in the precursor 1, while that of $\text{C}_7\text{H}_7\text{N}$ results from the phenyl group attached to a CH_2N unit. In the latter case, the $\text{C}_7\text{H}_7\text{N}$ group must also be formed by an intramolecular isomerization of the reactant 1.

A possible way in which precursor 1 is isomerized may be that reported in Scheme I; throughout this reaction path benzoyl cations may be obtained from the phenyl ring bonded to the C-2 and the oxygen atom of the five-membered heterocyclic nuclei 4 and 5, via the possible mechanisms reported in Scheme II.

This rearrangement can be supported by an examination of the gas-phase chemistry of the isomeric precursor 5 carried out under experimental conditions similar to those used for 1. MIKES analysis of the unimolecular dissociation of molecular ions 5 shows five metastable transitions associated with the formation of product ions m/z 134, 133, 132, 117, and 105, whose relative intensities are 1.5%, 1.8%, 0.5%, 89.7% and 6.5%, respectively. Experimental results obtained by the slow dissociations of precursor 1 under MIKES conditions⁵ are reexamined so that they can be compared with those of 5. Four metastable transitions are observed in the MIKES spectrum of 1, yielding product ions m/z 133 (flat-topped), 105, 103, and 93, whose relative abundances are 13%, 12%, 15%, and 60%, respectively. Therefore, the two isomers 1 and 5 have only two transitions in common, i.e., formation of m/z 133 and 105, all the others being different. Moreover, these two common reactions, experimentally found in the MIKES spectra of 1 and 5, differ not only in relative intensity (m/z 133 is 14% from 1) but also in the kinetic energy they release during dissociation. In the case of 1, the expulsion of carbon monoxide shows a gaussian peak with a relatively large kinetic energy release (294 meV mol^{-1}), while in the case of 5, this is 90 meV mol^{-1} for the same process.

The chemical information obtained by comparing the fragmentation of long-lived ions 1 and 5 indicates that they could even give partial isomerization, at least in that part which could be responsible for the formation of benzoyl cations and for the elimination of CO from those more highly energized reactants which travel the metastable region, thus dissociating in a photolytic manner. In the latter case, the larger release of kinetic energy may be due to the excess energy present in the transition state during the elimination step after the rate-determining rearrangement leading from 1 to 5.²¹ If such a conclusion holds for the system under study, it must be confirmed by labeling experiments. In fact, the phenyl group at C-3 of 1 must retain its bond intact throughout the isomerization

Scheme III**Scheme IV**

process of Scheme I. When the labeled analogue 6 (Scheme III) of 1 with one ^{13}C at position 3 is ionized, the MIKES spectrum shows peaks at m/z 105 (7%) and 134 (14%) and no signal at m/z 106. These experimental results were confirmed by combined scan analysis, where m/z 105 and 134 were 16% and 3%, respectively, while m/z 106 was absent.

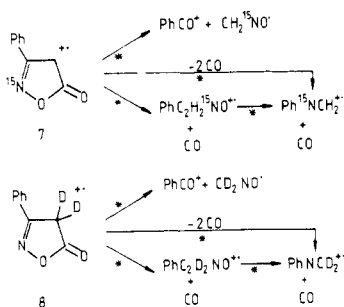
The data for 6 clearly demonstrate that the bond between the phenyl ring and the 3-carbon atom of the isoxazolone nucleus is not retained during the unimolecular process which leads to the formation of benzoyl cations, nor can any other plausible mechanism be suggested whereby precursor 1 could be transformed to its isomer 5, since the MIKES data clearly indicate that no such isomerization occurs. Further support for the conclusion cited is given by the results from the kinetic energy release discussed above. Therefore the photochemicallike path suggested in Scheme I cannot be operative. This conclusion is in agreement with the above-reported chemical data, which seems to suggest that a high-energy isomerization process takes place through the intermediate 5, while the reaction actually observed occurs in competition with others in the two drift regions and shows a relatively similar activation energy with the most abundant metastable reaction⁴ ($E_a \approx 23.1 \text{ kcal mol}^{-1}$ for the formation of PhNH_2^+ , and $E_a \approx 37.8 \text{ kcal mol}^{-1}$ for that of PhNCD_2^+ , measured from compound 8).

The experimental results are, therefore, consistent with a decomposition of 1 leading to benzoyl cation formation via a reaction path which resembles a thermolytic process. Since this dissociation implies breaking of the bond between the phenyl ring and C-3 as derived from the labeling results, an initial cleavage of the O-CO bond takes place which is similar to the reverse reaction of the formation of 1 in solution. This yields an isomeric open structure of 1 (see Scheme IV) which can undergo cyclization via an electrophilic substitution on to the aromatic group. The reversion of this process involving the bond between the aromatic group and the ^{13}C atom leads to the formation of radical cations which can eliminate the ^{13}C -labeled moiety. The interpretation of the unimolecular process discussed above is in good agreement with the energetics of the metastable reaction observed, because it is characterized by a relatively high-energy dissociation path compared with those occurring in the drift regions. This is in line with the fact that the O-CO bond, unlike the N-O one occurring in similar systems under different conditions,^{15,16,23} is not easily broken.

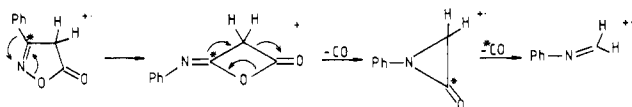
Another metastable dissociation has been shown to take place from 1 to yield the cation PhNCH_2^+ (m/z 105). This appears to be due to the consecutive elimination of two

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Scheme V



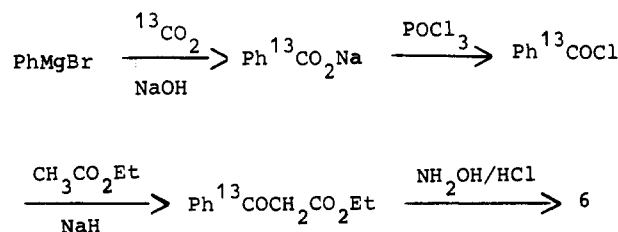
Scheme VI



CO molecules. In fact, when the ^{15}N -labeled analogue 7 of isoxazolone 1 (see Scheme V) is made to react in the second drift region, the three peaks of interest observed are those at m/z 134 (15%) and at m/z 106 and 105 (totaling 11% since they are not perfectly resolved). By use of the combined scan mode,²² three transitions can be clearly distinguished at the same values for apparent masses: at m/z 134 (3%; this peak is broad in the MIKES spectrum and therefore suffers from energy discrimination under the experimental conditions used), at m/z 106 (6%), and at m/z 105 (5%). This situation corresponds to a preliminary CO elimination occurring in the drift regions at a fast rate followed by a second expulsion of CO during 3×10^{-6} s which is spent by the precursor metastable ions m/z 162 and m/z 134.²⁴ Since the time required for the two fragmentations is shorter than that of residence in the two drift regions, both metastable peaks are observed. Moreover, combined scan analysis on the m/z 134 precursor from 7 gives a peak for the transition leading to m/z 106 with only CO loss. Similar results have been found in the case of compounds 6 and 8 (see Scheme V). Metastable ions m/z 134 from 6 lead to m/z 106 only. Moreover, fragment ions m/z 105 (elemental composition $\text{C}_7\text{H}_5\text{O}$) eliminate CO under metastable conditions, thus showing the chemistry of benzoyl cations as reported above. During the MIKES experiment, the molecular ion 8 decomposes to m/z 135 (14%) and 107 (11%) and in the first drift region to the same product ions with 4% and 7% relative abundances, respectively. Also in this case the combined scan analysis gives the signal relating m/z 135 to 107 and precludes the transition to m/z 105 from the same precursor.

All the data for the labeled analogues discussed above indicate that the PhNCH_2 group must be formed by a process which involves the migration of phenyl from its initial position. In fact, 6 does not generate the $\text{PhN}^{13}\text{CH}_2$ (m/z 106) group either directly or stepwise. The derivative 8 shows that there is no intervention of H/D migration before the formation of PhNCH_2 , and, therefore, the methylene group at position 4 of the ring could be directly

Scheme VII



involved in the formation of the isobaric nitrogen containing m/z 105. Thus it must be concluded that the two CO molecule losses are in competition with the elimination of C_3O_2 which is also preceded by a phenyl migration from carbon to nitrogen. The reaction path reported in Scheme VI can explain the way in which the anilinium radical cations are formed through a first step in common with that leading to the aniline molecular ions⁵ and then a second one which might involve an aziridone structure which is known to easily undergo mass spectrometric elimination of CO.²⁵ This isomerization of 1 with initial N-O bond cleavage is in competition with the previous one which must take place via O-CO breaking.

In conclusion, the most important feature of the unimolecular gas-phase chemistry of ionized 3-phenylisoxazol-5(4H)-one, reacting at relatively slow rate, is that all the experiments can be interpreted in terms of their thermal-like behavior even in the case of low-abundance transitions which can occur from the ground state of the molecular ions where the energy difference between the ground and first excited states is sufficiently high to be above the excess energy accessible during the metastable dissociations, thus forcing it to select between the photochemical-like and thermal-like processes.²⁶

Experimental Section

Mass spectra were recorded on a Varian MAT CH5-DF mass spectrometer with an electron beam energy of 70 eV and at a constant acceleration potential of 3 kV. $I(M)$ and $A(X)$ values were determined by using argon as a reference gas, and the results were analyzed by using the "semi-log plot" method.²⁷ Exact mass measurements at a minimum resolution of 10 000 were obtained from a Spectro-System SS 100 computer. Samples were introduced through the direct inlet system at a source temperature of 120 °C, the sample probe being at room temperature. Metastable transitions were determined by using the DADI technique²⁰ and the combined scan method.²²

Unlabeled compounds were synthesized by unexceptional methods. Isotopically labeled compounds 7 and 8 were obtained as previously described,⁵ and 6 was prepared as outlined in Scheme VII.

Acknowledgment. Financial support from the CNR (Rome, Grant 79.01417.03) is gratefully appreciated.

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