MASS SPECTRAL FRAGMENTATION OF 1,5-DISUBSTITUTED TETRAZOLES AND REARRANGEMENT OF THE RESULTING NITRENES

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UDC 547.796.1:543.51

In agreement with the thermolysis characteristics of 1,5-disubstituted tetrazoles, the fragmentation pattern of 1-(o-, m-, and p-tolyl)-5-phenyltetrazoles has been shown to consist of a sequence of reactions, namely, initial tautomeric conversion to an azide structure, followed by elimination of a molecule of nitrogen, and rearrangement of the resulting nitrene intermediate to a cation-radical derivative of a methyl-substituted 2-phenylbenzimidazole compound. In the case of 1-(o-tolyl)-5-phenyltetrazole an alternative pathway is observed, involving cyclization of the nitrene intermediate at the methyl group (an insertion reaction into a C–H bond) to form dihydroquinazoline derivatives. An analogous cyclization process has been noted for the thermolysis process as well.

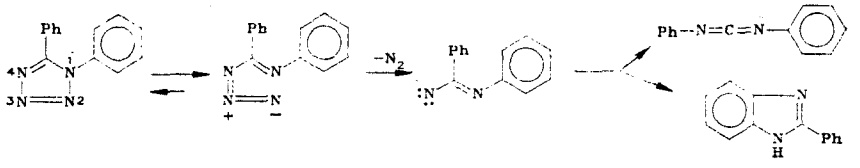
The recognition of an analogy between mass spectroscopic fragmentation processes and high chemistry [1-4] has stimulated a wide series of investigations, in which mass spectrometry is exploited as a source of information concerning the reactivity of organic compounds under extreme temperature, photolysis, or radiolysis conditions. As examples of these types of investigations, we cite that the revelation of the thermal rearrangement of N-alkyl-N-allylhydrazones to homoallylic azo compounds [5], which had been detected earlier in dissociative ionization processes [6]; the prediction, based on mass spectral data, of the composition and structure of the chemical decomposition products of diazoketones [7]; and mass spectrometry exploited for retrosynthesis [8].

In this regard, a question arises concerning whether the success of these cited studies can be utilized in the "reverse" direction, i.e., if the character of mass spectrometric fragmentation patterns can be estimated based on known chemical reactions, without resorting to empirical "structure–mass spectral" correlation experiments. This question centers on the possibility of using the theoretical framework of organic chemistry to resolve problems concerning the structures of ions and the mechanisms of reactions in mass spectrometry. The validity of this type of approach is supported by the observation that reactions of cation radicals, which comprise the reactive forms of molecules in positive ion mass spectrometry, are able to participate in organic chemical reactivity as well.

The subject of the present paper is an analysis of these questions or problems, using the dissociative ionization of isomeric 1-(o-, m-, and p-tolyl)-5-phenyltetrazoles as an example.

Based on currently accepted theory (see reviews [9, 10]), the thermolysis of 1,5-diaryltetrazoles can be expressed as a sequence of reactions, the first of which involves tautomeric conversion of the cyclic structure into an azide structure, which is followed in turn by elimination of a molecule of nitrogen and rearrangement of the intermediate nitrene to a carbodiimide and benzimidazole.

Scheme 1



K. A. Timiryazev Moscow Academy of Agriculture, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 925-930, July, 1988. Original article submitted December 12, 1986; revision submitted May 4, 1987.

 0009-3122/88/2407-0760$12.50

There is reason to believe that this scheme is valid for the mass spectrometric reactions (of 1,5-diphenyltetrazoles) as well. The similarity in the mass spectra of 1,5-disubstituted tetrazoles and organic azides supports the hypothesis that the initial stage in the dissociative ionization pathway involves tautomeric conversion; in both cases elimination of N_2 and N_3 species is observed [cf. studies [11] and [12, 13]). This hypothesis is also not contradicted by the existence of a correlation between the $\log(I_{(M-N_2)^+}/I_{M^+}$ values and σ^+-substituent constants in the series of 1-(p-substituted)phenyl-5-methyltetrazole, [14], which reflects increasing stability of the azide structure in the presence of the electron-withdrawing substituents in the $N(_1)$ position [9]. Finally, the cited hypothesis is consistent with the general thermodynamic principle that any increase in the energy of a system (in any form, including under electron impact conditions) stabilizes higher entropy states; the azide structural form is the only state which would satisfy this thermodynamic requirement. This thermodynamic principle is also supported by thermo- and photochromic effects [15, 16], color changes accompanying opening of the tetrazole ring upon heating or photoirradiation.

The subsequent reaction (Scheme 1), elimination of a molecule of nitrogen via expulsion of the $N(_2)N(_3)$ atoms of the tetrazole, is supported by a mass spectral study of 1-methyl-5-phenyltetrazole labelled with the ^{15}N isotope [17].

And finally, the last characteristic of these processes, formation of a nitrene and its cyclization to a benzimidazole, is consistent with the data of another study [11], where it was found that the spectra of the metastable ion $(M - N_2)^{+\cdot}$ produced from 1-phenyl-5-methyltetrazole were identical to that of 2-methylbenzimidazole (using the "direct analysis of daughter ions" technique [18]); this observation indicates that the structures of these two cation radicals are superimposable.

Not all of these arguments are equally convincing. The most persuasive argument is the latter one, since it can be regarded as evidence in favor of decomposition of the azide form, and consequently, of the existence of tautomeric conversion as well.

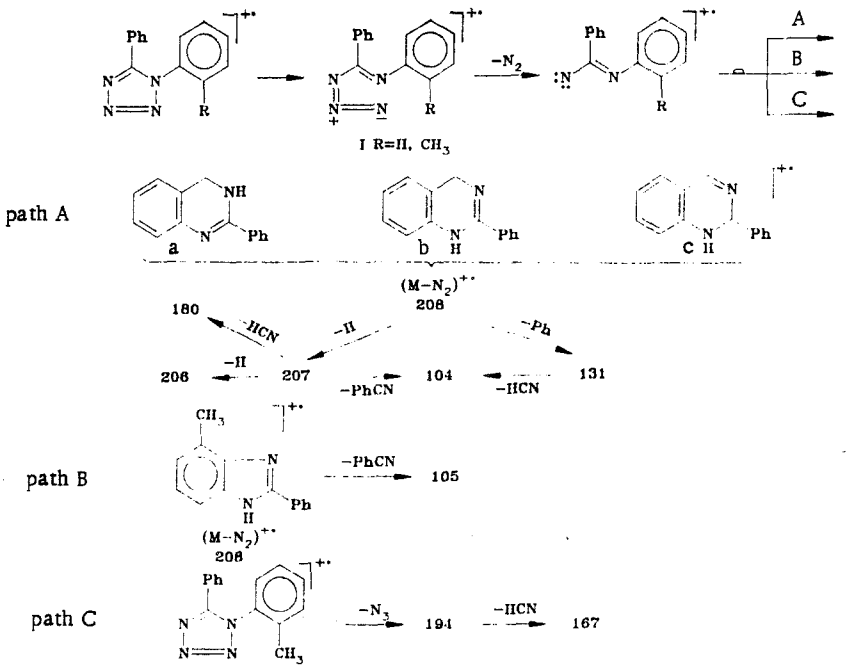
It should be noted, however, that the interdependence of structure and reactivity, and on this basis the conclusion that the structures are identical, is not unequivocal. As an example, consider parallel reactions, such as, in part, isomerization of the nitrene intermediate to give benzimidazole and carbodiimide (scheme 1). In addition, the possibility of carbodiimide formation in study [11] was not verified. Finally, the spectrometry of metastable ions assumes, frequently on an inadequate basis, that the structure of the starting material (in this case, 2-methylbenzimidazole) does not undergo isomerization from the moment of its formation via electron impact to the time of its fragmentation decomposition.

Taking into account these limitations, and also recognizing that mass spectrometry is not conducive to independent methods of structural analysis, it is difficult to say with absolute certainty that the thermolysis and mass spectrometric fragmentation processes are identical. However, if the reactions discussed above do indeed correspond to reality, and if in fact a nitrene is formed upon elimination of nitrogen (scheme 2), then one would expect to observe certain characteristic chemical properties for this nitrene. Since the most characteristic and typical reaction of a nitrene is its insertion into a C–H bond [19, 20], then one would expect to encounter, upon introduction of a CH_3 group in the o position of the $N(_1)$-phenyl substituent in 1,5-diaryltetrazole (R = CH_3), the appearance of a new, alternative pathway, namely, cyclization (of the nitrene) to form isomeric dihydroquinazolines (scheme 2, path A, intermediates a-c). In this regard a low energy of activation is anticipated, which differentiates it from isomerism with respect to the position of the double bond [21].

Further decomposition or fragmentation of the rearranged ions (a-c) is not difficult to propose, based on the known properties of similar compounds.

The susceptibility of dihydroquinazoline derivatives to aromatization [22] would be expected to have an analogy in the elimination of a hydrogen atom or, to a lesser degree, considering the difference in energy between a C–H and C–Ph bond [23], of a phenyl radical. Subsequent fragmentation of the resulting ions at m/z 207 and 131, in agreement with thermodynamic principles (the even-electron ions rule [24, 25]), can be envisioned as expulsion of benzonitrile and HCN molecules (scheme 2, path A). An independence fragmentation pathway for the m/z 207 and 131 ions, leading to the formation of a stable aromatic quinazoline structure, would require additional cleavage of a hydrogen atom (formation of ions with m/z 206, and, to a lesser degree, m/z 130).

Scheme 2*



The reactions considered above should distinguish between tetrazole I and its isomers II and III. In addition, the processes which have been enumerated should correspond to the mass spectra of dihydroquinazolines, which have been reported in the literature.

Comparison with the experimental data, which is summarized in Table 1, indicates that compound I is distinguished by the presence of ion peaks at m/z 207, 206, 180, 131, and 104, which are either absent in the mass spectra of its m- and p-isomers II and III, or else are present in substantially lower intensity in these isomers. Accurate mass measurements (exact mass determinations) (see Table 1) confirm the elemental composition of the ions shown in Scheme 2, path A, and the sequential fragmentation observed in the low resolution mass spectrum (see Experimental) reflects the presence of metastable ion peaks with m* = 156.6 (m/z 207 → 180), 83 (m/z 207→131 and m/z 131 → 104), and 52.2 (m/z 207→104).

It should be mentioned that these processes do not contradict the results of mass spectrometric investigations of nitrogen heterocycles. Thus, elimination of a hydrogen atom and aryl substituent has been described previously for aryl-substituted dihydroquinolines (and isoquinolines) [26, 27]; the thermodynamic basis for the even-electron ion rule, as well as deviations from this rule (in our case, the reaction m/z 207 → 206, Scheme 2, path A), have been considered in great detail in reviews [24, 25]. And finally, the predicted fragmentation characteristics of tetrazole I are in accord with the known mass spectra of several dihydroquinazoline derivatives [28-30].

In addition to these already noted differences in the mass spectra of isomer I and isomers II and III, another characteristic deserves mention, namely the unpredicted reaction corresponding to formation of an ion with m/z 117, which can be attributed to elimination of $CH_3C_6H_4^{\cdot}$ radical, in the scheme m/z 208 →117, also noteworthy is the sequential decomposition along pathway C (Scheme 2). Fragmentation of the molecular ion formed from 1,5-disubstituted tetrazoles via expulsion of a N_3 particle species has been reported previously as a minor process [11]. In the present case the probability of this reaction process is increased due to the o position of the CH_3 group. Subsequent fragmentation of the $(M - N_3)^+$ ion is apparently associated with rearrangement, a detailed explanation of which is difficult at present.

Along with these predicted reactions, there is another general fragmentation tendency which is general for all of the tetrazoles I-III examined herein, namely, Scheme 2, path B,

*The numbers characterizing the ions are their m/z values.

TABLE 1. Mass Spectra of Isomeric 1-(o-, m-, and p-tolyl)-5-phenyltetrazoles I-III and the Thermolysis Products for Compound I (Ia and Ib)

Ion	m/e	Ion mass*		Composition	I_{rel}, %				
		measured	calculated		I	II	III	Ia	Ib
$M^{+\cdot}$	236	236,1070	236,1062	$C_{14}H_{12}N_4$	1,7	1,5	1,3	—	—
$(M-N_2)^{+\cdot}=A$	208	208,0993	208,1000	$C_{14}H_{12}N_2$	84,0	100,0	100,0	100,0	100,0
$(A-H)^+=B$	207	207,0920	207,0922	$C_{14}H_{11}N_2$	84,8	12,3	35,7	63,7	55,3
$(B-H)^{+\cdot}$	206				12,6	—	—	10,2	
$(M-N_3)^+=C$	194	194,0974	194,0970	$C_{14}H_{12}N$	3,6	—	—	—	—
$(B-HCN)^+$	180	180,0810	180,0813	$C_{13}H_{10}N$	13,3	—	—	7,6	—
$(C-HCN)^+$	167	167,0860	167,0861	$C_{13}H_{11}$	11,8	—	—	—	—
$(A-Ph)^+$	131	131,0600	131,0609	$C_8H_7N_2$	55,2	—	8,0	29,3	—
$(A-CH_3C_6H_4)^+$	117	117,0570	117,0571	C_8H_7N	25,0	—	—	3,2	—
$(A-PhCN)^{+\cdot}$	105	105,0585	105,0579	C_7H_7N	28,4	26,0	35,1	3,2	42,9
$(B-PhCN)^+$	104	104,0510	104,0500	C_7H_6N	100,0	36,4	33,7	11,4	11,4
$(PhCN)^{+\cdot}$	103	103,0430	103,0421	C_7H_5N	21,1	7,2	9,7	6,4	—
$(CH_3C_6H_4)^+$	91	91,0550	91,0548	C_7H_7	48,9	46,3	87,9	12,2	1,4

*The results of exact mass measurements of ions in the mass spectra of I are given; the elemental composition of the ions, which are general for compounds I-III, correspond to the indicated masses, within the error limitations of the experiments.

which can be rationalized easily in terms of independent insertion of the intermediate nitrene into an aromatic C–H bond, leading to the formation of benzimidazole derivatives, as has been noted in earlier studies [11]. The feasibility of this type of insertion reaction is supported by the apparent similarity in the elimination of benzonitrile and the mass spectra of methyl-substituted benzimidazoles [31-33].

Testing the feasibility of using the theoretical framework of organic chemistry to solve problems arising in mass spectral interpretation has thus revealed that the most characteristic features of the fragmentation pattern of isomer I could, in fact, be predicted, without resorting to empirical "structure–mass spectra" correlation experiments. This was possible due to the analogy which exists between dissociative ionizations and thermal reactions. If this analogy is not merely random in character, we would expect to observe these reactions (Scheme 2, paths A and B) in the thermal reactions of isomer I as well.

In fact, a chromatographic–mass spectrometric experiment (see Experimental) carried out at an injector temperature of 380°C, which leads to thermal decomposition of tetrazole I at the moment of sample introduction, revealed that upon exit from the chromatographic column the peaks of two compounds Ia and Ib were observed; these compounds have been identified as 2-phenyldihydroquinazoline (unknown position of the double bond) and 2-phenyl-5-methylbenzimidazole (see Table 1). These compounds exhibit completely the sequence of fragmentation reactions shown in Scheme 2 (paths A and B), and their corresponding analogs (see [28-30] and [31-33]).

EXPERIMENTAL

Low resolution mass spectra of 1-(o-, m-, and p-tolyl)-5-phenyltetrazoles I-III (see Table 1) were recorded on a single focusing LKV-2091 mass spectrometer (Sweden) under standard acquisition conditions. The elemental composition of the molecular and fragment ions was determined using a Varian MAT-331A mass spectrometer (USA), at a resolution of M/ΔM of 15,000, with PFK as the reference standard.

The chromatographic–mass spectrometric experiment relative to the thermal decomposition of tetrazole I and identification of the resulting products of 2-phenyldihydroquinazoline Ia and 2-phenyl-5-methylbenzimidazole Ib was performed on an LKB-2091 apparatus (standard assembly) under the following conditions: 1.5% OV-101 packed column on chromosorb WHP (100/120 mesh) support; injector temperature, column temperature, and separator temperature 380, 150...300 (10 deg/min), and 270°C, respectively; He carrier gas at a flow rate of 20 ml/min. The retention times and concentrations of products Ia and Ib (based on the ratio of their total ion currents) were 12.8 and 18.6 min, and 63.2 and 36.8%, respectively.

Product identification was carried out using authentic substances and/or literature data for the mass spectrometry of the appropriate analogs (see text).

Tetrazoles I-III [34]. To a solution of 10.55 g (50 mmole) of the appropriate benzoyltoluidine in 50 ml absolute methylene chloride was added 10.4 g (50 mmole) PCl_5, and the mixture was refluxed until hydrogen chloride evolution was complete. The solvent and phosphorus oxychloride were removed under vacuum, and the residue was dissolved in 30-50 ml absolute DMF and added to a suspension of 4.55 g (70 mmole) NaN_3 in 30 ml absolute DMF, dropwise over a 40-60 min period. The mixture was stirred at room temperature for 1-1.5 h and poured into water. The resulting precipitate was filtered and washed with water, and recrystallized from isopropyl alcohol.

Compound I. Yield 52%, bp 97-98°C. Found: C 71.0; H 5.1; N 23.9%. $C_{14}H_{12}N_4$. Calculated: 71.1; H 5.1; N 23.8%.

Compound II. Yield 65%, bp 93-95°C. Found: C 71.1; H 5.2; N 23.6%. $C_{14}H_{12}N_4$. Calculated: C 71.1; H 5.1; N 23.8%.

Compound III. Yield 66%, mp 122-124°C. Found: C 71.1; H 5.2; N 23.7%. $C_{14}H_{12}N_4$. Calculated: C 71.1; H 5.1; N 23.8%.

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