OXIMES OF AZOLECARBALDEHYDES AND Δ^2-AZOLINE-CARBALDEHYDES AND THEIR DERIVATIVES

III.* syn–anti (E–Z) ISOMERIZATION IN AQUEOUS SOLUTIONS AND RELATIVE THERMODYNAMIC STABILITIES OF THE STEREOISOMERS

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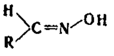
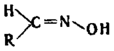
The configurational (kinetic) stability of the anionic and zwitterionic forms of 1-methylpyrazolecarbaldehyde oximes and 1-methylimidazolecarbaldehyde oximes and their quaternary ammonium derivatives in aqueous solutions has been established. In an acid medium, isomerization takes place and an E–Z equilibrium of the cations of the oximes is established. The changes in the relative thermodynamic stabilities of the stereoisomers of the heteroaromatic carbaldehyde oximes as functions of the size and nature of the ring, the position of the oxime group, and the steric loading are due to spatial factors and electrostatic interactions. To substantiate the preferred conformations of the Z aldehyde oximes the differences in the values of the chemical shifts of the α protons of the ring and the rates of their deuterium exchange have been used.

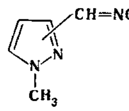
In a preceding paper [1], the PMR spectra of the uncharged and the cationic forms of 1-methylpyrazole-3-, -4-, and -5-carbaldehyde oximes and of 1-methylimidazole-5-carbaldehyde oxime (I-IV, respectively), and also the cations and zwitterions of their quaternary ammonium derivatives, the 3(5)- and 4-hydroxyimino-1,2-dimethylpyrazolium and 4(5)-hydroxyimino-1,3-dimethylimidazolium ions (V-VII, respectively), were described. These oximes arise in the form of mixtures of E (syn) and Z (anti) isomers.



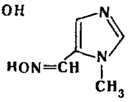
E (syn)



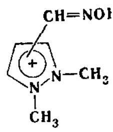
Z (anti)



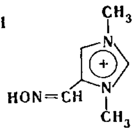
I-III



IV



V, VI



VII

The E/Z ratio found from the spectrum in an organic solvent depends as a rule on the method of oximation [2] and the conditions of isolation, purification, storage, etc. The E/Z ratios in the samples that we had available are given in Table 1. On investigating samples of oximes with different E/Z ratios in alkaline aqueous solutions, we observed no isomerization (at 20-30°C) and no establishment of an E–Z equilibrium. An additional proof of the configurational (kinetic) stability of the anionic and zwitterionic forms of the oximes under these conditions was obtained in an investigation by the PMR method of the deuterium exchange of the $H_{4(5)}$ protons of the E and Z isomers of (VII). In the E isomer (zwitterion in 1 N NaOD), exchange was complete after 3-4 h, while in the Z isomer only 45% exchange was recorded after

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*For Communication II, see [1].

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TABLE 1. Proportion of the E Isomer in 1-Methyl-Substituted Azolecarbaldehyde Oximes and Their Derivatives

Oxime	Proportion of the E isomer in various samples of the oxime[a], % (method of preparation[b])	Equilib. proportion of E isomer in acidic aqueous solutions, % (± 5%)
I	30 (A); 90 (B)	⩽30
II	⩽5 (A); 27—40 (B)	14
III	75 (A); 75 (B)	80
IV	50 (B)	37
V	63—73 (B)	80
VI	38—45 (B)	20
VII	45—65 (C)	35

[a] Determined from the PMR spectra in an organic solvent [1]. The spectra were recorded several hours (sometimes days) after the sample had been dissolved. Since the possibility of slow isomerization was not excluded (see [2] and below), the figures given probably do not always correspond to the compositions of the initial crystalline oximes.

[b] Methods of preparation: A and B, oximation of the aldehydes in acid and neutral media, respectively; C, quaternization of the oxime [2].

nine days. Under these conditions, the E/Z ratio remained unchanged*; it depended only on the composition of the initial sample. It is obvious that with an appreciable velocity of the E ⇌ Z process, a nonequilibrium distribution of the deuterium between the isomers cannot exist over such a long period. The results obtained do not confirm the point of view according to which there is alkaline catalysis of E – Z isomerization [3, 4].

As was to be expected [3], isomerization did take place in dilute solutions of mineral acids. Under these conditions, the E – Z equilibrium of the cationic forms of the oximes (I-VII) was established fairly rapidly (depending on the concentration of the acid) (Table 1).

For the majority of aliphatic [5], aromatic [6], and six-membered heteroaromatic [7,8] aldoximes, the E configuration is thermodynamically the more stable, which is due to the obvious spatial differences of the stereoisomers [4]. Under the usual conditions only the E isomers of 1-substituted benzimidazole-2-carbaldehyde oxime [9], imidazole-2-carbaldehyde oxime, Δ^2-imidazoline-2-carbaldehyde oxime, and Δ^2-pyrazoline-3-carbaldehyde oxime [1,2] are formed. The instability of the Z isomers is shown by the configurational individuality (E) of these oximes under conditions (acidic aqueous solutions) [1] in which the establishment of the E – Z equilibrium is ensured (see below).† In addition to this, it is known that Z-furan-2-carbaldehyde oxime is considerably more stable than Z-benzaldehyde oxime [11], and Z-isothiazole-5-carbaldehyde oxime is more stable than the E isomer [12].

In the oximes (I-VII), the two geometric forms exist in the equilibrium in comparable amounts, while for the majority (I, II, IV, VI, and VII) the Z isomer proves to be the more stable. The greatest predominance of the Z configuration is characteristic for the oximes (I, II, and VI) in which both α positions of the ring lack methyl groups. The introduction of methyl groups into the remote β positions (II → VI, III → V, IV → VII) scarcely affects the E/Z ratio, while the methylation of an α position (I → V) leads to the destabilization of the Z isomer.

The tendency to an increase in the stability of the Z isomers on passing from six- to five-membered aromatic systems also reflects the action of the steric factor. A consideration of scale molecular models (Eugon, Hungary) shows that the hindrance in the Z isomers between the oxygen and the proton of the α-carbon, preventing the coplanarity of the ring and the C = N bond [13], diminishes with the contraction of the ring. This takes place because of the increase in the C_0CC and CCH angles (conformation A) or the C_0CN angle and the angle formed by the CN bond and the axis of the orbital of the lone pair of electrons of the ring nitrogen atom (B and C conformations).‡

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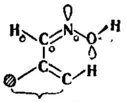
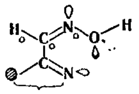
* The recording of the E/Z ratio and of the degree of deuterium exchange was performed simultaneously from the signals of the =CH and the $H_{4(5)}$ protons [1] (scale of recording the spectra 0.2 Hz/mm).

† The Z-1-methylbenzimidazole-2-carbaldehyde oxime recently obtained [10] proved to be unstable and rapidly changed into the E isomer.

‡ The spatial requirements of this orbital are apparently somewhat smaller than for a hydrogen atom attached to an sp^2 carbon [14].


A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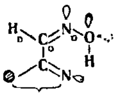
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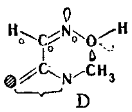
D

A distortion (in the direction of an increase) by 6-7° of the CC_0N_0 and C_0N_0O angles of the oxime group (conformation A) in Z-p-chlorobenzaldehyde oxime as compared with the E isomer [13] indicates the importance of this hindrance.

The steric hindrances in (III-V), (VII), and 1-methylimidazole-2-carbaldehyde oxime are approximately equivalent. The substantial differences in the relative stabilities of the isomers between these two groups of oximes cannot apparently be due to the electronic effects of the nuclei, since quaternization, which sharply changes these effects, does not (unless it increases steric hindrance) lead to an appreciable change in the E/Z ratio. The energy contribution of an intramolecular hydrogen bond (intra HB) between the hydrogen of the hydroxy group and the α-nitrogen atom of the ring to the stabilization of the Z isomers is apparently nonexistent. This bond has been detected only in the thermodynamically unstable Z isomers (pyridine-2-carbaldehyde oxime [7] and benzimidazole-2-carbaldehyde oxime [10]). An analogous intra HB with the α-carbonyl oxygen also proves insufficient to stabilize the corresponding stereoisomers of the α-oxo oximes [15]. It is characteristic that in the stable Z isomers an intra HB of this type is either impossible (II-VII) or should be weaker (I) (because of the low basicity of the ring nitrogen atom) than in the imidazole-2-carbaldehyde oximes. No intra HB is formed in the stable Z-furan-2-carbaldehyde oxime [16]. Apparently, the main reason for this situation is the energetic unfavorableness of the cis orientation of the $C_0=N_0$ and O−H bonds of the oxime group (C) [5, 16, 17].

An attempt has recently been made to base the comparable stabilities of the E- and Z-benzaldehyde oximes (E/Z = 10) on the formation of an intra HB of a different type (A) [18, 19]. Our results on the chemical shifts (CSs) and deuterium exchange of the ring protons (see [1] and below) do not contradict the hypothesis of the existence of such bonds in the Z isomers (I-VII). However, it must be mentioned that an intra HB of this type must be substantially stabilized when the oxime group ionizes. This predicates [20] a considerable increase in the ionization constants of the Z aldoximes which, nevertheless, prove to be lower than for the corresponding E isomers [12, 21]. Finally, the geometrical conditions for intra HBs of both types are more favorable in the six-membered aromatic aldoximes. Because of the differences in the external angles of the ring, the deviations of the axes of the bonds and of the orbitals involved in intra HBs from the optimum are more considerable for five-membered systems [22].

We assume that the differences in the E/Z ratios of the aldoximes considered are determined mainly by spatial factors and electrostatic interactions. Thus, for the Z isomers of the 1-methylimidazole-2-carbaldehyde oximes in the s-cis conformation B, the electrostatic interaction of the lone pairs of electrons of the oxygen and the ring nitrogen atoms is apparently so great that the s-cis conformation C with an intra HB proves to be the more stable [10], although this conformation, too, is energetically unfavorable (see above) because of the "repulsion of the lone pairs of the oxygen and the nitrogen of the oxime group" [5]. The s-trans conformation D is probably impossible for steric reasons.* In the Z isomers of (I-VII), of furan-2-carbaldehyde and of isothiazole-5-carbaldehyde oximes there are the favorable s-cis conformations A. For furan-2-carbaldehyde oxime, the predominance of this conformation has theoretical and experimental bases [16]. Information [1] on the CSs of the neighboring ring protons in (I-VII) permit the predominance of the A conformations to be demonstrated at any ratios of the ion-forming groups of these oximes. Table 2 gives the difference of the CSs of these protons between the Z and E isomers ($\Delta\delta = \delta_Z - \delta_E$) in each case. This difference is a measure of the influence of the magnetic anisotropy of the oxygen of the oxime group on the neighboring positions of the aromatic ring. With free rotation of the oxime group around the $C_{ring}-C_{oxime}$ bond, this influence must be distributed proportionally to the relative population of the two possible coplanar (or close to coplanar [13]) conformations. The overall effect of anisotropy can be evaluated from compounds with two neighboring protons: by the summation of the values of $\Delta\delta$ for two nonequivalent protons (II) or by the doubling of the values of $\Delta\delta$ for equivalent protons (VI). In oximes with a single neighboring proton (I, III-V, VII), with a considerable predominance of conformations A the values should be close to those corresponding to the combined effect which, as a rule, is in fact the case. The possibility of this, naturally rough approach is confirmed by information [23] relating to oximes of acylferrocenes. The values of the combined effect estimated on three compounds with two

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* The instability of the Z isomers of the azoline-2-carbaldehyde oximes mentioned can be explained similarly.

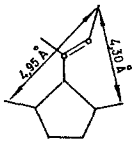
TABLE 2. Differences in the Chemical Shifts of the Ring Protons Adjacent to the Oxime Group of the 1-Methyl-Substituted Azolecarbaldehyde Oximes, $\Delta\delta = \delta_Z - \delta_E$

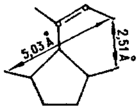
Oxime	$\Delta\delta$, ppm[a]			
	uncharged form in acetone	cation		zwitterion in water
		in DMSO	in water	
I	0,50	—	—	—
II[b]	0,51	—	0,69	—
III	0,60	—	0,43	—
IV	0,59[c]	—	0,56	—
V	—	0,40	0,49	0,60
VI[d]	—	0,44	0,60	0,90
VII	—	0,43	0,62	0,95

[a] For the values of the chemical shifts, see [1]. [b] $\Delta\delta_{H_3} + \Delta\delta_{H_5}$. [c] In DMSO. [d] $2\Delta\delta_{H_{3(5)}}$.

neighboring protons are 0.54-0.76 ppm. The mean value (0.65 ppm) agrees well with the value of 0.61 ppm for the single neighboring proton in a compound with a rigidly fixed orientation.

The stereospecificity of the deuterium exchange of the ring proton in (VII) mentioned above also indicates a predominance of conformation A. Because of electrostatic hindrance to the attack of an OD⁻ ion on the ring proton from the side of the negatively charged oxygen of the oxime group, this attack will be most effective at the maximum distances between the oxygen and the proton. For the zwitterion (VI) with two equivalent protons these distances are practically identical in the E and Z isomers (4.95 and 5.03 Å), which is confirmed by the comparable rates of exchange. (At pD 12-13, exchange in 10-15 min amounts to 72% for the E form and 82% for the Z form.) The extremely low rate of exchange in the Z isomer of (VII) as compared with the E isomer (see above) excludes any appreciable participation whatever in the conformational equilibrium of the s-trans conformation D, for which the distances between the oxygen and the proton in the E and Z isomers are similar (4.95 and 5.03 Å).





Returning to the figures of Table 2, it can be seen that the values of $\Delta\delta$ for aqueous solutions of the oximes (III) and (V) are less than the corresponding total effect of anisotropy. This deviation can hardly be ascribed to the participation in the conformational equilibrium of the sterically hindered s-trans conformations D. It remains to be assumed that in the equilibrium nonplanar conformations play a considerable part for the Z isomers. The realization of these isomers is connected with the disturbance of the conjugation in the system which may probably lead to a change in the energy balance in favor of the E isomer. In actual fact, in the series (I-VII) only in the case of the oximes (III) and (V) is the E isomer more stable than the Z isomer (Table 1). A source of differences in the E/Z ratios between the pyrazole derivatives (III, V) and the imidazole derivatives (V, VII), in which steric hindrances are approximately the same, may be connected with differences in the vectors of the electric moments of the rings.

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