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**Kinetics of Z, E-Isomerization of α -Keto-
 N-Methylnitrones**

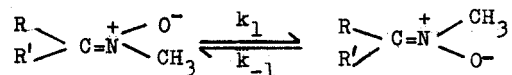
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Rate constants of thermal Z,E - isomerization of five-membered cyclic α -keto-N-methylnitrones in deuteriochloroform (for unimolar solutions) are determined. The structural features of five-membered cycle are shown to affect the value of free activation energy. Thermodynamic activation parameters for 4-N-methylnitrono-2,2,5,5-tetramethyltetrahydrofuran-3-one are determined.

The study of Z,E - isomerization of nitrones is restricted to a small number of examples, the simplest among them (N-methylnitrones) being devoted three works¹⁻³ to only. The free activation energy of Z,E-isomerization of N-methylnitrones with a nitrono group in the open chain is more than 30 kcal/mole. Thus E. Grubbs et al¹ have determined an energy barrier of thermal isomerization of C-(n-tolyl)-C-phenyl-N-methylnitrono (Ia) in tert. butyl alcohol: $\Delta G_{144}^{\#} = 3$ kcal/mol.



Ia: R = n-CH₃C₆H₄, R = C₆H₅

Ib: R = (CH₃)₅C₆, R = H

Ic: R = C₆H₅, R' = H

The other authors² give $\Delta G_{1(147^\circ)}^{\#} = 34.6$ kcal/mol and $\Delta G_{-1(147^\circ)}^{\#} = 33.1$ kcal/mol for compound (Ib). It being

established that benzoic acid exerts a catalytic influence on the conversion rate: $\Delta G_{1(64^\circ)}^\# = 25.4 \text{ kcal/mol}$ $\Delta G_{-1(64^\circ)}^\# = 23.9 \text{ kcal/mol}$.

It should be noted that for nitrones obtained from aldehydes the value of free activation energy is lower. Thus $\Delta G_{85^\circ}^\#$ for C-phenyl-N-methylnitrones (Ia) is 29 kcal/mol .⁴ For unsubstituted at carbon atom nitrones, e.g. for nitrone (2) the $\Delta G_{180^\circ}^\#$ value, determined by the method of dynamic PMR spectroscopy, 23.2 kcal/mol .⁴

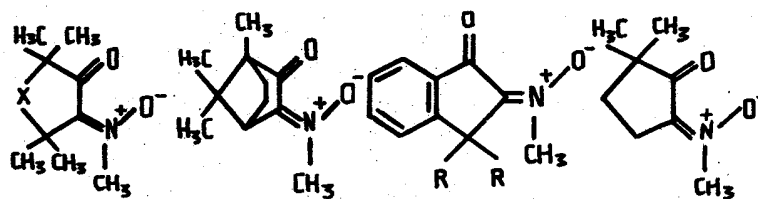


The value of energy barrier of isomerization also decreases considerably with the presence of electron-accepting substituents at carbon atom. Thus for C-cyano-C, N-diphenylnitrono (3) $E_a = 24.6 \text{ kcal/mol}$.⁵

It was shown elsewhere that with methylation of isomeric (E and Z) monoximes of 2,2,5,5-tetramethyltetrahydrofuran-3,4 by diazomethane one N-methylnitrono, viz. E-isomer (4-E), was formed only. On the grounds of this and some other examples 7,8 we have established that Z-isomers of nitrones can be obtained by UV-radiation of E-isomers. When being heated or with long exposition these less stable Z-isomers are capable of converting into E-isomers. The high thermodynamic stability of E-isomers can be accounted for by the mutual repulsion of closely situated negatively charged oxygen atoms in Z-nitrones.

The present work deals with the kinetic study of thermal Z,E-isomerization of cyclic (-keto-N-methylnitrones with exocyclic nitrono group. The specific feature of the compounds studied is a rigid S-cis-conformation with the maximum conjugation of carbonyl and nitrono groups. The following nitrones were chosen to be studied: 4-N-methylnitrono-2,2,5,5-tetramethylfuran-3-on (4), 2-N-methylnitrono-7,7,5,5-tetramethylcyclopentanone (5), 3-N-methylnitrono-1,7,7-trimethylbicyclo-[2,2,1]-heptane-2-on (6), 2-N-methyl-

nitroindanone (7), 2-N-methylnitrono-3,3-dimethylindanone (8), and 2-N-methylnitrono-5,5-dimethylcyclopentanone (9).



4: X=O

6

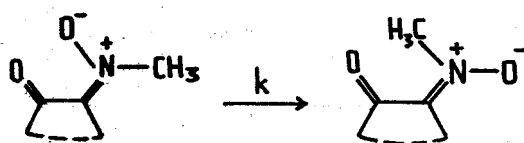
7: R=H

9

5: X-CH₂

8: R=CH₃

The present communication presents the results of measurement of rate constants (*k*) of the thermal Z,E-isomerization of these nitrones:



Experimental

Synthesis of initial Z-isomers of nitrones was done photochemically: by UV radiation of E-forms of nitrones in anhydrous pentane (for nitrones 4 - 6, 8, 9) or diethyl ether (for nitrone 7).^{7,8}

E-isomers of nitrones (4 - 9) all are obtained by methylation of monoximes of the corresponding of (α -ketones by diazomethane. Nitrones 4, 6-8 were described elsewhere^{6,9,10}.

Kinetic measurements were carried out in the solution of deuteriochloroform. To preclude the catalytic influence of an acid on the isomerization studied deuteriochloroform freshly distilled over potash was used. The choice of just this solvent was due to low solubility of Z-isomers in other organic solvents with b.p. needed for thermolysis.

Technique A (for nitrones 4, 6). Isomerization was carried

out in the standard 5-mm-NMR-ampule in the thermostat at various temperatures ((10C) over the range from 32 to 58°C.* Each point was registered 5-7 times and a mean value was calculated. The concentration of isomers was determined to within $Z \pm 2\%$.

Technique B (for nitrones 5, 7, and 8). Isomerization was done in the spectrometer cell, the temperature was measured before and after the reaction. Spectra were taken in 0.5-5 min (46-56 measurements).

The concentration (ratio) of E-and Z-isomers was determined by PMR spectra taken by VARIAN EM-360. The areas of signal peaks of N-CH₃-groups were measured planimetrically** in all the cases. The determination of quantitative ratios of isomers by this method is confirmed by the PMR spectra of the reference isomer mixtures. The slopes of straight lines were calculated by the least-squares method. The values of chemical shifts of N-CH₃ groups of the nitrones studied are listed in Table 1.

* When the experiment had to be stopped, the ampule with the reaction mixture was placed into the Dewar flask with liquid nitrogen.

** The authors are grateful to L. Mendaleva for her assistance in the planimetric measurements.

Table 1
The Values of Chem. Shifts of N-CH₃ Groups in the
PMR Spectra of Nitrones 4-9
(δ , p.p.m.)

Nitrone	E-N-CH ₃	Z-N-CH ₃
4	4.10	3.88
5	4.23	3.90
6	4.05	3.87
7	4.26	4.02
8	4.35	4.03
9	4.10	3.83

The determination of concentrations of E- and Z isomers of nitrone (7) was hindered, since in PMR spectra (see Fig. 1) signals of protons of Z-N-CH₃; Z-CH₂- and E-CH₂ groups were situated close to each other (3.90; 3.90; and 3.83 p.p.m., respectively, chem. shift of E-N-CH₂ signal at 4.23 p.p.m.). The calculation was done by Eq. (7) derived as follows. Denoting the areas of signals by E, E'; Z, and Z', one obtains:

$$(1) E = E-N-CH_3 \quad Z = Z-N-CH_3$$

$$(2) E = E-CH_2 \quad Z = Z-CH_2$$

Hence

$$(3) E/3 = E'/2$$

$$(4) Z/3 = Z'/2$$

E and Y were measured planimetrically

$$(5) Y = Z + Z' + E'$$

where [Z] value was calculated by Eq. (6)

$$(6) [Z] = \frac{Z}{Z + E}$$

The areas of peaks corresponding to groups Z and E were determined from Eqns. (4) and (3) and the values obtained were substituted into Eq. (6). Thus

$$(7) [Z] = \frac{3Y - 2E}{3Y + 3E}$$

It should be noted that Eq. (7) can be applied for $0.25 < [Z] < 0.87$ only. Out of these limits the error of determination of $[Z]$ increases significantly.

Reaction rate constants* were found from the slopes of

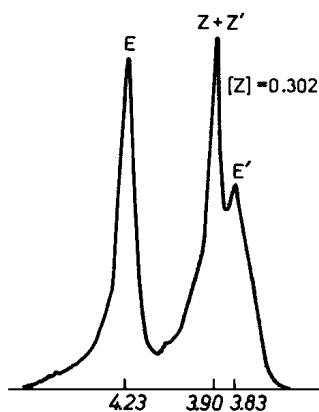


Fig. 1 PMR spectrum of the reaction mixture of thermal isomerization of nitrone 7-Z.

straight lines in the plot of concentration \lg of initial substance vs. time (Figs. 2 and 3).

ΔG^\ddagger was calculated by Eq. (8)¹¹.

$$\Delta G^\ddagger = 4.576 \cdot T (10.319 + \lg T - \lg k) \quad (8)$$

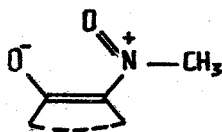
Results and Discussion

The results obtained are given in Table 2 and Figs. 2 and 3.

As a whole, the values of free activation energy of Z,E-isomerization obtained for nitrones studied are within 23-28 kcal/mol i.e. somewhat lower over those given in the literature for compounds with nitrone group in the open

* Under the experimental conditions (thermolysis) the equilibrium is shifted to the formation of E-isomer so much, that PMR method does not permit to registrate the presence of Z isomer and therefore the reverse reaction is not taken into account.

chain¹⁻³. The lower values of free activation energy of thermal Z,E-isomerization of the five-member cyclic ketonitrones studied can be accounted for by the electron-accepting properties of carbonyl group in α -position to nitron function decreasing electron density of C=N bond and entailing thus decrease in ΔG^\ddagger value. In other words this indicates a considerable contribution into electron structure of (α -ketonitrones of mesomeric form.



According to our experimental data Z-nitrones (4, 5, and 8) are more stable over their unsubstituted homologues (9 and 7). The highest isomerization rate is observed for nitron (7) unsubstituted in α -position to nitron groups.

It should be noted that when radiating E-isomer of nitron (9) at room temperature, we failed to isolate its Z-isomer, though at first one could observe a residue which is a characteristic attribute of the formation of Z-isomers with lower solubility over initial E-nitrones in the series studied.

Table 2

Kinetics Measurements of Z,E - Isomerization of Nitrones							
NN Comp.	Concentration (mol/l)	t°C	$\lg \alpha \cdot 10^4$	$k \cdot (10^5 \text{ sec}^{-1})$	$\tau_{1/2}$ (hour)	ΔG^\ddagger d (kcal/mol)	r
4	1.00	32.5	-0.046±0.001	1.06±0.02	18.16	24.9	-0.990
"	"	35.6	-0.081±0.001	1.75±0.02	10.94	24.8	-0.9998
"	"	50.0	-0.378±0.005	8.69±0.12	2.21	25.0	-0.9997
"	"	5.0 ^a	-0.415±0.003	9.57±0.07	2.01	24.9	-0.9998
"	"	58.0	-1.01 ± 0.03	23.2 ±0.7	0.82	25.0	-0.998
5	0.85	34.5 ^b	-0.502±0.008	11.6 ±0.2	1.66	23.6	-0.994
6	1.03	58.0	-0.100±0.003	0.231±0.008 ^c	83.49	28.0	-0.995
7	0.90	35.2 ^b	-2.37 ±0.037	54.6±0.09	0.35	22.7	-0.996
8	0.94	36.0 ^b	-0.706±0.012	16.3±0.3	1.18	23.5	-0.993

a) Thermolysis of the reaction mixture obtained after radiating nitrone in methanol (under argon flow) was carried out

b) The temperature at which PMR spectra (Method B) were registered is given

b) When extrapolating this value at t 35.6° C the value for $k - 0.010 \cdot 10^{-5}$ was obtained, respectively, $\tau_{1/2} - 1930$ hour

d) The determination error is ± 0.1 (kcal/mol)

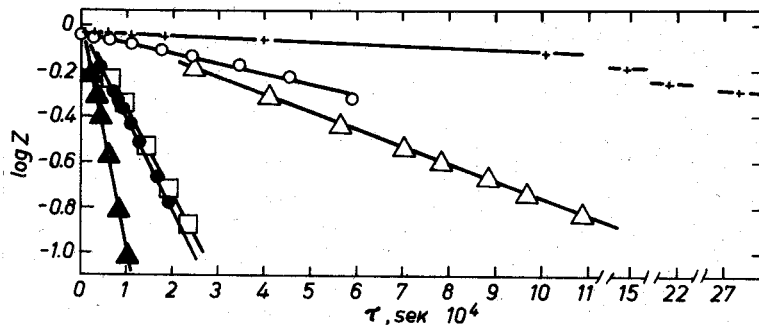


Fig. 2. Kinetic measurements of Z,E – isomerization of Z-nitron 4: (\blacktriangle) - at 58.0° ; (\square) - at 50.0° ; (\triangle) - at 35.6° ; (\circ) at 32.5° ; Z - nitron (6): ($+$) - at 58.0°

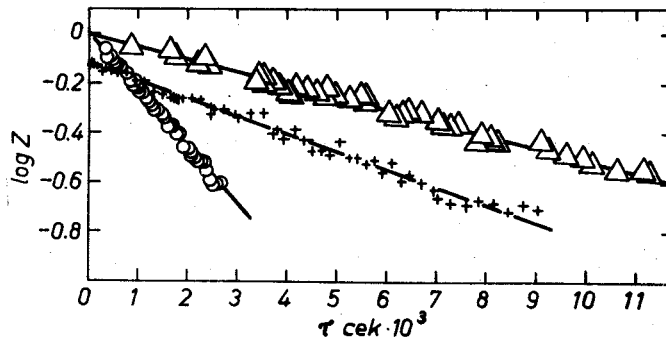


Fig. 3. Kinetic measurements of Z,E -isomerization (\circ) - for nitron (7) at 35.5° ; ($+$) - for nitron (8) at 36° ; (\triangle) - for nitron (5) at 34.5° .

The generation of Z- isomer of nitron (9) was registered successfully with UV radiation of E - nitron (9) at negative temperatures only: -23° (4%) and -58° (17%). Photoisomerization was carried out in CO_3OD just in the ampule for registering PMR spectra*. This fact enables to assume that the free activation energy of isomerization of Z - nitron (9) should be lower than 23 kcal/mol (see Table 2).

The higher values of $\Delta G^{\#}$ of nitrons with two methyl groups alpha-position to nitron group (4, 5, and 8) are, probably, due to steric interactions of these substituents with N-methyl group in the transition state of the isomerization process. This can be traced easily with steric models, the rotation of substituents at nitrogen atom is hindered by a strong steric influence of alpha-alkyl groups at nitron group.

Somewhat higher value of the free activation energy of Z,E - isomerization of oxacyclic Z - nitron (4) over its carbocyclic analogue (5) is caused, probably, by the presence of oxygen atom in the cycle.

The highest obtained value of free activation energy, $\Delta G^{\#}=28.0$ kcal/mol, for nitron (6) is, apparently, due to the structural features of the nonbornane system and presence of methyl substituents in the cycle.

Comparison of the values of $\Delta G^{\#}$ for nitron with aromatic ring (7, 8) with those of $\Delta G^{\#}$ of carbocyclic analogues (5, 6, 9) shows that the presence of an aromatic ring in compounds 7 and 8 influences the value significantly.

From the plot of isomerization rate of Z - nitron (4) (see Table 2) vs. temperature, thermodynamic activation parameters of Z,E - isomerization were calculated.

This plot is illustrated in Fig. 4.

Table 3 lists thermodynamic parameters obtained as usually¹².

* PMR spectrum is registered by the VARIAN HA-100 apparatus.

The value of activation entropy obtained by us is close to zero which is also characteristic of other examples of thermal Z,E - isomerization at C=N bond. It is known that for reactions of the first order thermal Z,E - isomerization involving rotation in the transition state the activation entropy is also close to zero¹³.

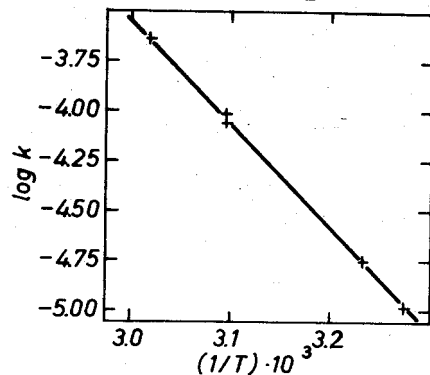


Fig. 4. The plot of isomerization rate of nitrone (4) vs. temperature.

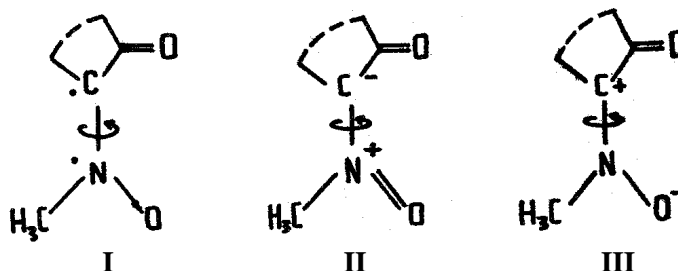
Table 3
Thermodynamic Activation Parameters of Z,E -
Isomerization of Nitrone (4)

tg α	lg A	A	E _a (kcal/mol)	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (kcal/mol. degr)
5212±148	12.1±0.46	1.25·10 ¹²	23.9±0.7	23.2±0.6	-5.2±2.2

A small negative value of entropy can indicate that the moving force of isomerization should be an enthalpy of the process. Hence, in the transition state of the isomerization studied, electron factors (in the first place, electron - chemical nature of the substituents at C- and N- atoms of

nitron group) should exert the strongest influence. This plays an especially important role in the case of torsion (rotary) mechanism with heteropolar transition state.^{14, 15}

It should be noted that for nitrones an inversion mechanism of isomerization is excluded (due to the absence of a free electron pair at heteroatom and a torsion mechanism with homopolar (biradical) /I/ or heteropolar (II or III) transition state is possible only:



Apparently, for nitrones studied one should accept transition state II with partial positive charge at the nitrogen atom and enhanced electron density on the carbon atom, whose stabilization is favored, accordingly, by methyl substituent at nitrogen and carbonyl group in alpha-position to carbon atom.

Besides, the steric factors (increase in the steric volume of substituents at a double bond) are known to increase the free activation energy (ΔG^\ddagger) in the case of at least partial contribution of a rotary mechanism¹⁵. The examples of nitrones given (4, 5, 8) just allow one to observe the increase in ΔG^\ddagger values with the presence of geminal methyl groups in alpha-position to nitron group.

A small negative value of the entropy also agrees with the torsion (rotary) isomerization mechanism.¹⁵

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