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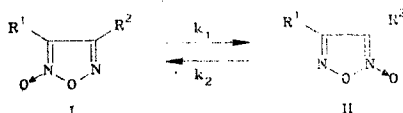
EFFECT OF SUBSTITUENTS ON THE RELATIVE STABILITY OF FUROXAN ISOMERS

V. G. Andrianov, M. A. Shokhen,
A. V. Ereemeev, and S. V. Barmina

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The overall energy of isomers of substituted furoxans has been calculated using the MINDO/3 method. Comparison with experimental results indicated that the calculation correctly predicted the structure of the more stable isomer. Correlation of the difference of the overall energy of the isomers (ΔE) with the induction and resonance constants of the substituents, and comparison of the values of ΔE calculated from the correlation equation with the experimental values have also been carried out.

At elevated temperatures unsymmetrically substituted furoxans are capable of mutual transformation [1, 2]:



The relative stability of the isomers depends on the nature of the substituents R^1 and R^2 . However, the reasons for the stability of one isomer or the other are not clear and the limited amount of experimental material available does not allow a quantitative, nor even a qualitative, correlation of the electronic effects of the substituents with the equilibrium constants of the isomers.

In this connection, we have carried out calculations by the MINDO/3 method, using the original program [3], of the difference in the overall energy of the isomers $\Delta E = E_{II} - E_I$ of a series of furoxans with different substituents (Table 1). In dealing with the geometry of the furoxan ring, x-ray crystallographic data were used [4] and for the substituents R^1 and R^2 , averaged geometrical parameters [5]. Comparison of the calculated difference in the overall energy of the isomers with the experimentally determined values for the free energy difference (ΔG) (Table 1) indicates that the calculation correctly predicts the structure of the isomer with the greater stability, although the difference is exaggerated for isomers with cyano-group substituents. Therefore, calculation without optimization of the geometry is satisfactory for an interpretation of the effect of substituents on the relative stability of the isomers.

In accordance with the principle of the linearity of free energies [6], the dependence of the rate constant of the forward reaction on the induction (σ^o_I) and resonance (σ^o_R) con-

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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TABLE 1. Calculated and Experimental Energy Differences for Furoxan Isomers (kJ/mole)

R ¹	R ²	ΔE , quant.mech	ΔE , from eq.2	ΔG^a	Lit. ref.
CH ₃	H	-6,76	-9,61		
C ₆ H ₅	H		8,90	0 ^b	7
C ₆ H ₅	CH ₃		18,51	-1,92 b	8
C≡CH	H	-0,39			
NH ₂	H	-37,83	-40,69		
NH ₂	C ₆ H ₅		-49,59	-c	9
(CH ₃) ₂ N	C ₆ H ₅		-65,78	-c	9
OH	H	-53,17	-59,51		
OCH ₃	H	-45,88	-46,19		
OCH ₃	CH ₃		-36,57	<-13 ^d	10
OCH ₃	C ₆ H ₅		-55,28	-c	11
OC ₆ H ₅	CH ₃		-31,73 ^e	<-13	10
F	H	-42,90	-38,27		
Cl	CH ₃		-20,35	<-10 ^b	14
Cl	C ₆ H ₅		-38,87	≤-8,2 f	15
Br	C ₆ H ₅		-39,54	≤-5,8 f	15
CH ₃ S	CH ₃		-2,20	-3,46 d	10
C ₆ H ₅ S	CH ₃			-1,26	10
C ₆ H ₅ S	C ₆ H ₅			-2,2 ^b	16
CH ₃ SO ₂	CH ₃		-4,35	-2,63 d	10
CHO	H	15,24	8,50		
COCH ₃	CH ₃	-3,39	18,11	-0,8	2
COOCH ₃	H	5,75	7,23		
COOCH ₃	CH ₃	2,66	16,84		
COOC ₂ H ₅	CH ₃		16,84	-0,73	10
CONH ₂	H	1,38	8,92 ^g		
CONH ₂	CH ₃	3,67	18,53 ^g	2,69	10
C≡N	CH ₃	10,04	8,06	1,04	10
NO ₂	H	-17,18	-16,24		
NO ₂	CH ₃	-6,47	-6,63	-c	10
NO ₂	C ₆ H ₅		-25,14	<-4,4 f	17

a) In cases where the absolute value of ΔG was not determined, only its sign is given. b) Calculated from the equilibrium constant. c) Equilibrium not fixed. Indicated that isomerization proceeds quantitatively. d) Experimental value determined for R¹ = OC₂H₅, SC₂H₅, or SO₂C₂H₅, respectively. e) For the group OC₆H₅, $\sigma_I = 0.37$ [12], $\sigma_R = -0.36$ [13]. f) Calculated from percentage isomer content. g) Calculated from orientation for $\sigma_N = 0.20$ and $\sigma_I = 0.21$ [12].

stants of the substituents R¹ and R² with allowance for their different positions on the ring can be expressed by the equation

$$\lg(k_1/k_0) = \rho_1\sigma_{R1}^0 + \rho_2\sigma_{R2}^0 + \rho_3\sigma_{I1}^0 + \rho_4\sigma_{I2}^0,$$

where the constants $\rho_1, \rho_2, \rho_3, \rho_4$, characterize the sensitivity of the position to the corresponding effect. Then the equation for the rate constant of the reverse reaction takes the form

$$\lg(k_2/k_0) = \rho_1\sigma_{R2}^0 + \rho_2\sigma_{R1}^0 + \rho_3\sigma_{I2}^0 + \rho_4\sigma_{I1}^0.$$

Hence, the equilibrium constant K is equal to

$$\lg K = \lg(k_1/k_2) = (\rho_1 - \rho_2)(\sigma_{R1}^0 - \sigma_{R2}^0) + (\rho_3 - \rho_4)(\sigma_{I1}^0 - \sigma_{I2}^0)$$

or in another form

$$-RT \ln K = \Delta G = \Delta H - T\Delta S = \rho(\sigma_{R1}^0 - \sigma_{R2}^0) + \rho'(\sigma_{I1}^0 - \sigma_{I2}^0). \quad (1)$$

The entropy difference ΔS could not be evaluated but, because in our case the forward and reverse reactions are in fact the same process, and the differences are connected with the arrangement of the substituents, which do not take direct part in the reaction, it seems valid in this and similar cases to take $\Delta S = 0$ so that the values of ΔG and ΔH are determined only by the difference in the internal energy ΔE of the isomers [18].

The coefficients ρ and ρ' in Eq. (1) were determined by the least square method:

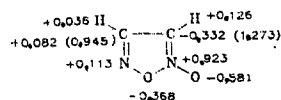
$$\Delta E = 80.1 \Delta \sigma_R^0 - 33.8 \Delta \sigma_I^0 \quad (2)$$

($R=0.981$; $S=5.4$; $r_R=0.929$; $r_I=0.501$).

Comparison of the values of ΔE calculated from Eq. (2) with the experimental free energy differences shows that Eq. (2) correctly predicts the greater stability of isomer II for $R^1 = \text{NH}_2$, $(\text{CH}_3)_2\text{N}$, CH_3O , $\text{C}_6\text{H}_5\text{O}$, Cl , Br , CH_3S , CH_3SO_2 , NO_2 and $R^2 = \text{CH}_3$, C_6H_5 , and the greater stability of isomer I for $R^1 = \text{CONH}_2$ and $\text{C}\equiv\text{N}$ and $R^2 = \text{CH}_3$. When $R^1 = \text{C}_6\text{H}_5$, COCH_3 , C_6H_5 and COOC_2H_5 and $R^2 = \text{CH}_3$, the experimental results do not conform in sign to those calculated. It has been suggested [2] that in the case of methylphenylfuroxans the equilibrium position is determined not so much by electronic as by space effects. For furoxans with $R^1 = \text{COCH}_3$, and COOC_2H_5 and $R^2 = \text{CH}_3$, the difference in the stability of the isomers is in general small (-0.8 and -0.73 kJ/mole) and could be due to solvation effects.

In accordance with the signs of the coefficients of $\Delta \sigma_R^0$ and $\Delta \sigma_I^0$ in Eq. (2), $+R$ and $-I$ effects of the substituted R^1 lead to greater stability of isomer II compared to isomer I and conversely $-R$ and $+I$ effects of substituent R^1 lead to greater stability of isomer I. This is shown by the observation that in the case of furoxans containing such groups as OR , NR_2 , Cl , Br ($+R$ and $-I$ substituents) the 4-substituted derivatives prove to be considerably more stable than the 3-substituted. For $-R$ and $-I$ substituents (NO_2 , COOR , COR , CONH_2 , $\text{C}\equiv\text{N}$, RSO_2), i.e., when the effects are compensated, the difference in the stability of the isomers is usually small.

The reason for the opposite action of induction and resonance effects becomes intelligible if one takes into consideration the dual character of the N-oxide group as a substituent. On the one hand, as a strong resonance electron donor it considerably increases the population of the $2p_z$ AO of the α -carbon atom in comparison with the β -carbon (the charges on the atoms are shown with the $2p_z$ AO populations in brackets):



Hence a $+R$ effect of the substituted R^1 destabilizes isomer I and a $-R$ effect stabilizes it. On the other hand, the positively charged nitrogen atom of the N-oxide group is a strong acceptor of σ -electrons which is particularly clearly displayed in the increase of positive charge on the hydrogen of the α -carbon. As a result of this, a $+I$ effect in substituent R^1 must stabilize isomer I, and a $-I$ effect must destabilize it.

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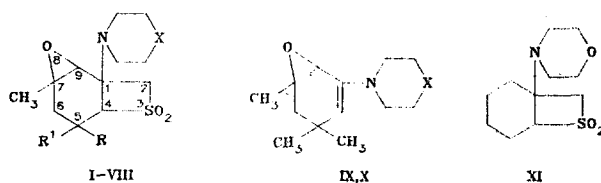
MASS SPECTRA AND ^{13}C NMR SPECTRA OF THE ADDUCTS OF EPOXYENAMINES WITH SULFENE

G. I. Polozov, I. G. Tishchenko,
and V. P. Suboch

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The behavior of the adducts of alicyclic epoxyenamines with sulfene under electron impact and also their ^{13}C NMR spectra were studied. The initial fragmentation of these compounds, which takes place with the ejection of sulfene, is accompanied by a specific hydrogen rearrangement of the molecular ion. The degree of substitution of the cyclohexane ring has a significant effect on the nature of the subsequent dissociation, which leads to extensive degradation of the oxirane ring.

The readily occurring reaction of sulfene with alicyclic epoxyenamines leads to the formation of aminoepoxythietane dioxides [1], which represent a new type of previously uninvestigated heterocyclic system including three and four-membered heterocycles annellated with the cyclohexane ring. It seemed of interest to determine which of the heterocycles would be decomposed first by the action of electron impact and to trace the main directions in the mass-spectrometric fragmentation of the compounds. In this connection in the present work we investigated the mass-spectrometric behavior of 1-amino-8-oxa-3-thiatricyclo[5.2.0.0^{7,9}]nonane 3,3-dioxides (I-VIII) by means of the DADI technique and the high-resolution mass spectra and studied their ^{13}C NMR spectra.



I R=H, II-X R=CH₃; I-IV R¹=H, V-X R¹=CH₃; I, II, V, IX X=O, III, VII, X
X=CH₂, IV, VIII X=(CH₂)₂ (VI X=-)

The molecular ion peaks (M^+) in the mass spectra of adducts I-VIII (Table 1) have low intensity, which demonstrates the low stability of the molecules to electron impact. In the general case the stability of M^+ depends little on the nature of the amine substituent and decreases with increase in the number of methyl groups at position 5 (Table 2) on account of the appearance of new energetically favorable dissociation paths for M^+ on account of possible rearrangement.

The initial dissociation of M^+ is extremely similar to the previously investigated fragmentation of the cyclic adducts of sulfene and enamines [2-4], involving retro[2+2]-cleavage

Scientific-Research Institute of Physicochemical Problems, V. I. Lenin Belorussian State University, Minsk 220080. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 2, pp. 267-271, February, 1986. Original article submitted October 19, 1984.