LACTAM ACETALS

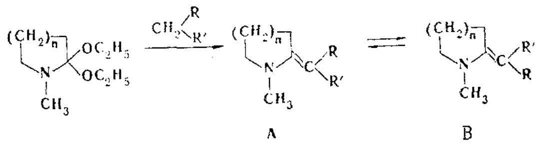
XII.* INVESTIGATION OF THE INTERNAL ROTATION IN CYCLIC ENAMINES BY PMR SPECTROSCOPY

N. P. Kostyuchenko, V. G. Granik,
A. M. Zhidkova, R. G. Glushkov,
and Yu. N. Sheinker

UDC 547.743.1'822.3'892 : 543.422.25

The cis-trans isomerization in a number of enamines – 1-methyl-2-(2'-R-2'-R'-methylene)pyrrolidines, -piperidines, and -hexahydroazepines – depends substantially on the nature of the 2'-substituent and the ring size. The energy barrier to this process decreases as the ability of the substituents to delocalize the anionic center in the transition state increases. The free energy of activation of rotation about the C=C bond is appreciably lower for six-membered enamines than for the corresponding seven- and five-membered analogs.

It is known [2-4] that the energy barrier to rotation about the C=C bond in enamines is relatively low ($\Delta G^{\neq} \leq 13$ kcal/mole), and the free energy of activation of isomerization depends substantially on the character of the substituents. The effect of substituents attached to the β-carbon atom and the size of the ring in which the enamine nitrogen is included on the kinetic parameters of this process was investigated in the present study. The objects of the investigation were enamines synthesized by reaction of N-methylbutyro-, -valero-, and -caprolactam diethylacetals with compounds having active methylene or methyl groups (Table 1):



I–III (I n=1, II n=2, III n=3), a R=CN, R′=$CONH_2$; b R=CN, R′=$COOC_2H_5$; c R=C_6H_5, R′=$COOCH_3$; d R=C_6H_5, R′=CN; e R=R′=$COOCH_3$; f R=R′=$COOC_2H_5$; g R=R′=CN

---

* See [1] for communication XI.

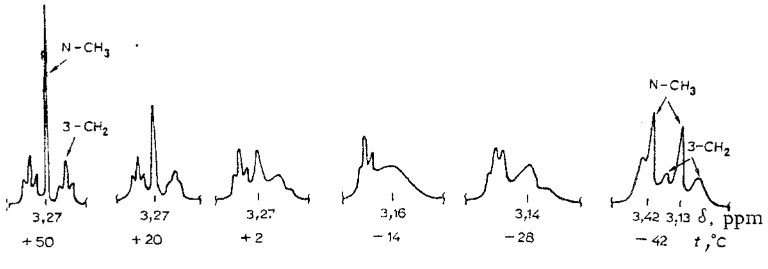


Fig. 1. Change in the form of the signals of the N–CH_3 and 3-CH_2 groups as the temperature changes for IIb.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1212-1219, September, 1974. Original article submitted January 14, 1974.

TABLE 1. Conditions for the Synthesis of and Properties of Previously Undescribed Enamines I-III

Compound	Reaction temp., °C	Reaction time, h	mp or bp (mm)	Empirical formula	Found, %			Calc., %			UV spect., λmax, nm (log ε)	IR spec., cm⁻¹		Yield, %
					C	H	N	C	H	N		CO	C=C	
Ia	60	0,5	209—210 (alcohol)	$C_8H_{11}N_3O$	58,4	6,8	26,0	58,2	6,7	25,4	286 (4,35)	1660	1575	64
Ib	60	0,5	121—122 (cyclohexane)	$C_{10}H_{14}N_2O_2$	61,4	7,1	14,3	61,8	7,2	14,4	284 (4,38)	1690	1580	50
Ic	80	3	47—48 (hexane) 143—144 (2)	$C_{14}H_{19}NO_2$	72,4	7,7		72,1	8,1		295 (4,30)	1675	1560	60
IIe	130	3	165—167 (3)	$C_{11}H_{17}NO_4$	58,4	7,8		58,1	7,4			1670	1550	56
IIIe	100	3	172—173 (3)	$C_{12}H_{19}NO_4$	60,0	7,8		59,8	7,9			1680	1555	42

Reversible changes in the form of the signals of the $N-CH_3$ and $3-CH_2$ groups were observed in the PMR spectra of I-III as the temperature changed. Doubling of the indicated signals was observed in the spectra of unsymmetrical compounds of the pyrrolidine and hexahydroazepine series (Ia-c, IIIa-c) with carbonyl-containing groups at temperatures close to room temperature, while initially coalescence and then the appearance of a narrow singlet of the $N-CH_3$ group and a distinct triplet of the $3-CH_2$ group were observed as the temperature rose. Doubling of the signals is also retained in the spectra of Id, IId, and IIId, which do not contain CO groups, at considerably higher temperatures; the coalescence point for enamine IId is +149°, while coalescence points were not reached for enamines Id and IIId on heating above 150°. In contrast to Ia-c and IIIa-c, the corresponding changes in the form of the signals for piperidine enamines IIa-c were observed at considerably lower temperatures: t_{coal} from −12 to −14° in place of 45-80° for Ia-c and IIIa-c (Fig. 1). Isomerization for symmetrical enamines Ie,f, IIe,f, and IIIe,f is realized particularly readily, and the coalescence points can be reached only for pyrrolidine derivative Ie at −74 to −90° (according to the signal of the $COOCH_3$ group). The observed facts unambiguously indicate that reversible transformation A $\rightleftharpoons$ B occurs in solutions of I-III. The presence of a quite large set of substituents and the possibility of comparison of the chemical shifts of the $N-CH_3$ and $3-CH_2$ groups for Ia-d, IIa-d, and IIIa-d with the corresponding values for symmetrically substituted enamines Ie-g, IIe-g, and IIIe-g make it possible to make a reliable assignment of each of the groups of signals to the A and B isomers. Thus, the carbalkoxy groups of Ie,f, IIe,f, and IIIe,f are in the cisoid orientation relative to the $N-CH_3$ and $3-CH_2$ groups. The CN groups in enamines Ig, IIg, and IIIg are in a similar situation. A comparison of the spectra of these compounds shows that the $N-CH_3$ group in dinitrile Ig is deshielded more appreciably ($\Delta\delta$ 0.6 ppm), while the $3-CH_2$ fragment is somewhat more shielded ($\Delta\delta - 0.1$ ppm) than in diesters Ie,f, apparently because of the difference in the magnetic-anisotropic effect of these groups. This difference in the chemical shifts of the cis $N-CH_3$ group with respect to the CN or COOR groups makes it possible to clearly distinguish between isomers A and B. For example, the chemical shifts of the $N-CH_3$ groups of the isomers of Ib are 3.47 and 2.8 ppm, i.e., the first value is close to cis-oriented CN or $N-CH_3$, while the second value is close to cis-oriented COOR and $N-CH_3$. Consequently, the first signal at 3.47 ppm corresponds to the A isomer ($R=CN$, $R'=COOC_2H_5$), and the signal at 2.80 ppm corresponds to the B isomer ($R'=COOC_2H_5$, $R=CN$). The assignments of the geometrical isomers of the other enamines can be similarly made. The analysis is usually performed in this way from the signals of the $N-CH_3$ and $3-CH_2$ groups. The difference in the chemical shifts of the $3-CH_2$ signals was not used in the assignment of the isomers of enamines Ia-f, inasmuch as when the isomers were present in smaller amounts, it was not possible to reliably isolate the signals of this fragment. The data from the PMR spectra are presented in Tables 2-4. In examining the spectra of enamines Ic,d, IIc,d, and IIIc,d which contain a phenyl substituent, one's attention is drawn to the shift to strong field of the signals of the $N-CH_3$ and $3-CH_2$ groups in the cis position with respect to the phenyl substituent (for Ic, IIc, and IIIc, $\Delta\delta_{N-CH_3} \sim 0.62-0.76$ ppm and $\Delta\delta_{3-CH_2} \sim 0.69-0.71$ ppm; for Id, IId, and IIId, $\Delta\delta_{N-CH_3} \sim 0.83-0.89$ ppm, and $\Delta\delta_{3-CH_2} \sim 0.34-0.89$ ppm). An examination of Dreiding molecular models shows that because of steric hindrance the benzene ring cannot be found in the plane of the C=C bond, and this is also responsible for the above-noted effects of shielding of cis-oriented $N-CH_3$ and $3-CH_2$ groups.

TABLE 2. Data from the PMR Spectra and Activation Parameters for Rotation about the C=C Bond in Enamines Ia-f

Compound	R	R' [a]	δ_{N-CH_3}, ppm	$\delta_{C_3-CH_2}$ [b], ppm	$\Delta\delta_{N-CH_3}$, ppm	t, °C [c]	t_{coal}, °C	Isomer content, %	$\Delta G^{\neq}_{C=C}$, kcal/mole	Solvent
Ia	CN	$CONH_2$	3,44 3,15	3,38 [d] —	0,29	−56	+71	92,5 7,5	19,1 17,4	$CDCl_3$
Ib	CN	$COOC_2H_5$	3,47 2,80	3,29 [d] —	0,67	−50,5	+75	98 2	19,7 17,0	$CDCl_3$
Ic	C_6H_5	$COOCH_3$	3,03 2,27	— 3,28 [d]	0,76	−56	+80	3,5 96,5	17,2 19,5	$CDCl_3$
Id	CN	C_6H_5	3,30 2,47	2,65 2,99	0,83	+20	—	56 44		$CDCl_3$
			3,29 2,50	— [d]	0,79	+20	>+150	55 45	>21	$DCON(CD_3)_2$
Ie	$COOCH_3$	$COOCH_3$	2,83	3,17	—	+20				$CDCl_3$
						−96,5 [e]	−90		9,4	CH_2Cl_2
						−88	−74		10,2	$(CD_3)_2CO$
If	$COOC_2H_5$	$COOC_2H_5$	2,84	3,15		+20				$CDCl_3$
Ig	CN	CN	3,44	3,06		+20				$CDCl_3$

---

[a] The presented orientation of the substituents pertains to the more stable isomer.

[b] The values given are for 20°C.

[c] This is the temperature for which the chemical shifts of the $N-CH_3$ groups are given.

[d] The signals of the second isomer are marked by the other signals.

[e] The temperature for which the chemical shifts of the $COOCH_3$ groups are given: δ_{COOCH_3} 3.66 and 3.75 ppm (CH_2Cl_2), δ_{COOCH_3} 3.67 and 3.55 ppm (CD_3COCD_3). Doubling of the signals of the $COOCH_3$ group was not observed in CD_3OD at ~−100°.

TABLE 3. Data from the PMR Spectra and Activation Parameters for Rotation about the C=C Bond in Enamines IIa-e

Compound	R	R' [a]	δ_{NCH_3}, ppm	$\delta_{C_3-CH_2}$, ppm	$\Delta\delta_{NCH_3}$, ppm	t^b, °C	t_{coal}, °C	Isomer content, %	$\Delta G^{\neq}_{C=C}$, kcal/mole	Solvent
IIa	CN	$CONH_2$	3,32 3,08	3,26 2,88	0,24	−70	−14	22 78	13,1 13,7	$CDCl_3$
IIb	$COOC_2H_5$	CN	3,42 3,13	3,25 2,94	0,29	−42	−14	55 45	13,1 13,0	$CDCl_3$
IIc	Ph	$COOCH_3$	3,01 2,29	2,29 3,01	0,72	−63	−12,5	64 36	12,9 12,6	$CDCl_3$
IId	CN	Ph	3,36 2,47	2,31 3,20	0,89	+20	—	38 62		$CDCl_3$
			3,32 2,46	— [c]	0,86	+20	+149	33 67	20,6 21,2	$DCON(CD_3)_2$
IIe [d]	$COOCH_3$	$COOCH_3$	2,95	2,90						$CDCl_3$
IIg	$COOC_2H_5$	$COOC_2H_5$	2,90	2,95						$CDCl_3$
IIf	CN	CN	3,45	2,76						$CDCl_3$

---

[a] See the note to Table 2.

[b] The temperature for which the δ_{N-CH_3} and $\delta_{C_3-CH_2}$ values are given.

[c] The C_3-CH_2 signals are masked by other signals.

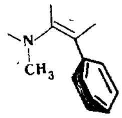
[d] Doubling of the signals of the $COOCH_3$ group at −90 to −100° was not observed for IIe in CH_2Cl_2, $(CD_3)_2CO$, and CD_3OD solutions; $\Delta G^{\neq}_{C=C} < 9.9$ kcal/mole.

TABLE 4. Data from the PMR Spectra and Activation Parameters for Rotation about the C=C Bond in Enamines IIIa-e

Compound	R	R'^a	δ_{NCH_3}, ppm	$\delta_{C_3-CH_2}$, ppm	$\Delta\delta_{NCH_3}$, ppm	t^b, °C	t_{coal}, °C	Isomer content, %	$\Delta G^{\ne}_{C=C}$, kcal/mole	Solvent
IIIa	CN	$CONH_2$	3,39 3,08	2,90 3,10	0,31	−34	+45	38 62	16,0 16,3	$CDCl_3$
IIIb	$COOC_2H_5$	CN	3,39 3,09	2,95 3,09	0,30	−20	+45	55 45	16,2 16,0	$CDCl_3$
IIIc	Ph	$COOCH_3$	3,02 2,40	2,34 3,02	0,62	−37	+57	68 32	16,7 16,2	$CDCl_3$
IIId	CN	Ph	3,33 2,46	—c 2,88	0,87	+20		20 80		$CDCl_3$
			3,31 2,50	—c	0,81	+20	>+150	16 84	>21	$DCON(CD_3)_2$
IIIe^d	$COOCH_3$	$COOCH_3$	3,03	2,80		+20				$CDCl_3$
IIIg	$COOC_2H_5$	$COOC_2H_5$	2,96	2,76		+20				$CDCl_3$

---

a-d See the footnotes to Table 3.



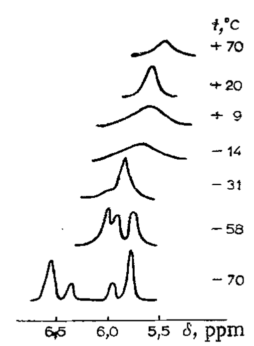
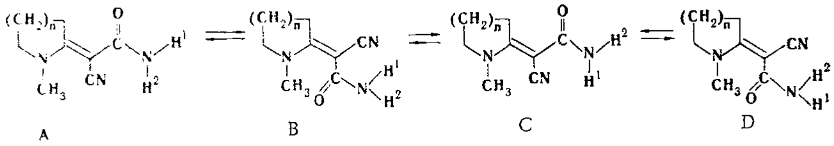


Fig. 2. Change in the form of the signals of the NH2 group as the temperature changes for IIa.

In addition to the already indicated changes in the spectra associated with rotation about the C=C bonds, in the case of enamines Ia, IIa, and IIIa isomerization associated with rotation about the amide C−N bond can also be observed:



For enamines IIa and IIIa, all four isomeric forms (A-D) (see Fig. 2) are (observed according to the NH_2 signals) in the spectra at <−40°. It follows from Tables 2-4 that the relative stabilities of the isomeric forms depend substantially both on the substituents and on the size of the nitrogen heteroring, and the six- and seven-membered enamines differ markedly in this respect from the five-membered enamines. For example, while the ratio of isomers with cis- and trans-oriented $N-CH_3$ and CN groups is 98 : 2 for Ia, these ratios are 45 : 55 and 55 : 45 for enamines IIa and IIIa, respectively. The reasons that make it possible to induce such large differences in the energies of the isomers of the five-membered enamines are not completely clear. An examination of the molecular models makes it possible to assume that steric factors, which consist, for example, in interaction between the electron pair of the N atom and the π (or p) electrons of the substituents, may play an important role in these differences.

On the basis of the spectral data obtained in this study we calculated the rate constants (k) for cis–trans conversion at the coalescence temperatures. The $k = {}^1/_2\tau$ values for equal populations were calculated from the Gutowsky–Holm equation [5]

$$1/2\tau = \frac{\Delta\nu\pi}{\sqrt{2}},$$

where $\Delta\nu$ is the maximum difference in the chemical shifts (in Hz) of the CH_3 groups in the $COOCH_3$ substituents for Ie and the protons of the NH_2 groups for Id, IId, and IIId. The kinetic parameters for different populations of the isomers were calculated from the equations [3]

$$\left(\frac{\delta^2\tau^2-2}{3}\right)^3 = (\Delta P)^2\delta^2\tau^2, \quad \frac{1}{\tau} = \frac{1}{\tau_A} + \frac{1}{\tau_B}, \quad \frac{P_A}{\tau_A} = \frac{P_B}{\tau_B},$$

where $\delta = \Delta\nu \cdot 2\pi$, $P = P_A - P_B$ (where P_A and P_B are the fractions of each of the isomers in the mixture,

TABLE 5. Data from the PMR Spectra and Activation Parameters for Rotation about the C—N Bond in Enamines Ia-IIIa

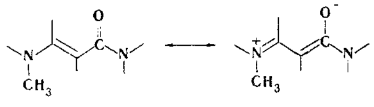
Compound	δ_{NH_2}[a], ppm	Isomer content, %	t, °C[b]	t_{coal}, °C	$\Delta G^{\neq}_{C-N}$, kcal/mole
Ia	6,02 5,55	—[c]	−34	−4	13,2
IIa	6,59 5,79	78	−70	−31	11,6
	6,40 5,99	22		−58	10,5
IIIa	6,31 5,95	62	−44	−24	12,3
	6,48 5,96	38		−40	11,3

---

[a] The solvent was $CdCl_3$.
[b] The temperature for which the δ_{NH_2} values are given.
[c] The isomer with trans-oriented $CONH_2$ and NCH_3 groups predominates.

which were determined by integration of the corresponding signals), and τ_A and τ_B are the lifetimes of the isomers. The rate constants in this case are $k_A = 1/\tau_A$ and $k_B = 1/\tau_B$. The free energies of activation of isomerization were calculated from the Eyring equation, and the transmission coefficient was assumed to be one. The results of the calculations pertaining to rotation about the C=C bond are presented in Tables 2-4 ($\Delta G^{\neq}_{C=C}$), while those pertaining to rotation about the C—N bond are presented in Table 5 ($\Delta G^{\neq}_{C-N}$).

The difference in the $\Delta G^{\neq}_{C-N}$ values for rotation about the C—N bond (amide rotation) as a function of the ring size is apparently due to the differences in the energies of the ground states to a greater degree than in the case of rotation about the C=C bond. Inasmuch as the conditions for the conjugation of the p electrons of the enamine nitrogen atom are most favorable in the six-membered rings and least favorable in the five-membered rings [6], one should have expected a decrease in the free energy of rotation about the C—N bond in the order I > III > II. In fact, the contribution to the resonance hybrid of structure E lowers the double-bond character of the amide C—N bond and promotes a decrease in the barrier to rotation about this bond.



A,C E

As seen from Table 5, the assumptions expressed above are in good agreement with the experimental data. The free energy of activation for rotation about the C—N bond ($\Delta G^{\neq}_{C-N}$) for the five-membered ring (Ia) is a maximum value and differs from the values for six- and seven-membered enamines IIa and IIIa by 1.60 and 0.90 kcal/mole, respectively.*

The difference in the $\Delta G^{\neq}_{C=C}$ values (Tables 2-4) for cis—trans isomerization on passing from enamine Ia to IIa and IIIa is 5.4 and 2.8 kcal/mole, respectively. Shvo and co-workers [2, 3], in a study of a number of noncyclic enamines with COOR and CN groups and several enamines of the pyrrolidine series, expressed the assumption that the main factor that determines the rate of isomerization is the energy of the transition state rather than the energy of the ground state. From our data on the differences in the free energy of activation, $\Delta G^{\neq}_{C=C}$ and $\Delta G^{\neq}_{C-N}$, it can be concluded that although the effect of the energy of the activated complex is more substantial, the differences in the energies of the ground states are not so small that they can be disregarded.

In [2, 3] it was established that replacement of the COOR group by a nitrile group for noncyclic enamines and some enamines of the pyrrolidine series leads to a substantial increase in the free energy of activation for isomerization at the C=C bond. It hence follows that the effect of substituents on the kinetic parameters of the isomerization should follow the trend of the σ_R constants rather than that of the σ con-

---

* The calculation was made for the isomers present in larger amounts.

stants [3]. Inasmuch as the CN group is considerably more inclined to delocalization of electrons than the COOR group [7] (σ_R 0.08 and 0.24, respectively), it might be assumed that replacement of a cyano group by a carbalkoxy group would lead to a decrease in the energy of the activated complex and, consequently, to a decrease in $\Delta G^{\neq}_{C=C}$. Our results are in agreement with these data and make it possible to arrange the substituents (in the order of increasing $\Delta G^{\neq}_{C=C}$) in the following order: COOR ≈ $CONH_2$ < CN ≈ C_6H_5.

From the above it is understandable why enamines Id, IId, and IIId can be isomerized only at high temperatures and why interconversion of enamines Ie,f, IIe,f, and IIe,f is inhibited only at temperatures $\leq -90°$. In the first case the delocalization of the anionic center in the transition state is not very effective (low σ_R-substituent constants), and this is responsible for the high energy of the activated complex and, consequently, the high activation barrier. In the second case, the presence of two COOR groups, which delocalize the negative charge, leads to a decrease in the energy of the transition state and, consequently, to a low $\Delta G^{\neq}_{C=C}$ value (≤ 10 kcal/mole). The height of the activation barrier is determined both by the effect of the substituents and by the size of the nitrogen heteroring, and the free energies of activation decrease in the order II < III < I. As already noted above, an examination of the ground states of the molecules shows that the order of the C=C bond decreases in precisely this order. In the transition state, a positive charge arises on the α-carbon atom, while a negative charge develops on the β-carbon atom,* and stabilization of the carbonium ion is realized through the unshared electron pair of the enamine nitrogen atom (structure F). Inasmuch as localization of the positive charge on the nitrogen atom is more advantageous from an energy point of view than localization on the carbon atom, the greater degree of interaction of this pair with the vacant orbital stabilizes the activated complex.

F

In addition, the contribution of structure F to the resonance hybrid should be determined by the degree of strained character of a system with an endocyclic double bond, and it is therefore useful to compare this parameter in the cycloolefin. The strained character changes from 2.3 to 0 and 0.7 kcal/mole on passing from cyclopentene to cyclohexene and then to cyclopentene, respectively [8]. While the introduction of a nitrogen atom into the ring does not change the picture qualitatively, in our case the stabilization of the transition state due to contribution of structure F will change in the order II > III > I; this corresponds to the data presented above. One should also note that in a discussion of the basicities of lactams of different ring sizes Huisgen [6] pointed out that the presence of sp^2-hybridized atoms in the 1- and 2-positions of the ring is most favorable for valerolactam, inasmuch as the angle formed by the trigonal atom retains its normal value (120°) only in the case of a six-membered ring.

EXPERIMENTAL

The spectra of 10-20% solutions of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The accuracy in the determination of the coalescence temperatures was ±3°, the accuracy in the measurement of the chemical shifts was ±1 Hz, and the accuracy in the determination of the differences in the chemical shifts was ± 0.1 Hz. Compounds Ia-c, IIe-g, IIe, and IIIe were synthesized by the method in [9, 10].

LITERATURE CITED

1. A. M. Zhidkova, V. Granik, N. S. Kuryatov, V. P. Pakhomov, O. S. Anisimova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., 1089 (1974).
2. J. Shvo and H. Shanan-Atidi, J. Amer. Chem. Soc., 91, 6684 (1969).
3. J. Shvo and H. Shanan-Atidi, J. Amer. Chem. Soc., 91, 6689 (1969).
4. V. G. Granik, I. V. Persianova, N. P. Kostyuchenko, R. G. Glushkov, and Yu. N. Sheinker, Zh. Organ. Khim., 8, 181 (1972).
5. H. S. Gutowsky and C. H. Holm, J. Chem. Phys., 25, 1228 (1956).
6. R. Huisgen, H. Brade, and H. Wals, and J. Glogger, Ber., 90, 1437 (1957).

---

*The anionic center and the vacant orbital are in mutually perpendicular planes.

7. R. W. Taft, Jr., in: Steric Effects in Organic Chemistry, Wiley, New York (1956).
8. N. S. Zefirov and V. I. Sokolov, Usp. Khim., 36, 243 (1967).
9. V. G. Granik and R. G. Glushkov, Zh. Organ. Khim., 7, 1146 (1971).
10. H. Bredereck and K. Bredereck, Ber., 94, 2278 (1961).