Dynamic NMR Spectroscopy on Rotation about the C=C Bond in Enamines Containing the N-H Bond

V. I. Bakhmutov and E. I. Fedin

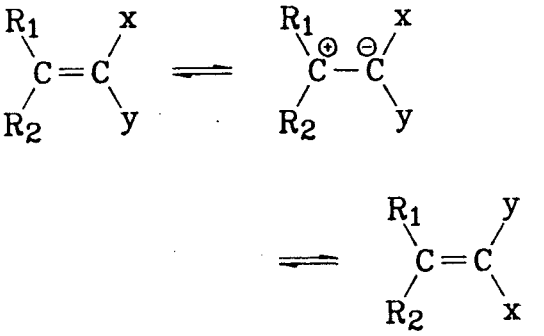
Institute of Organo-Element Compounds
Academy of Sciences of the USSR
Moscow 117312, USSR

I. INTRODUCTION

Dynamic NMR spectroscopy provides a convenient means for studying the kinetics of chemical processes falling within the time scale of the method (1). Depending on the choice of indicator nuclei and on the technique applied, NMR spectroscopy allows one to measure the lifetimes of magnetically non-equivalent positions, ranging from 10^2 s [double resonance with transfer of saturation from one position to another (2)] to 10^{-6} s [pulse methods including $T_{1\rho}$ measurements (3)]. The rate constants of transitions affecting the lineshapes of NMR signals can be readily calculated, assuming two-center exchange, by the Gutowsky-Holm equation

$$k = 1/\tau = \pi\Delta\nu_0\sqrt{2} \qquad (1)$$

at the coalescence temperature of the signals, where $\Delta\nu_0$ is the difference between the resonance frequencies of the signals in the absence of exchange (4). The complete analysis of NMR lineshapes with the use of a computer (1,5) yields the rate constants of the transitions at various temperatures and hence permits one to determine, from the Arrhenius and Eyring equations, activation parameters of the transitions. The dynamic NMR method has found wide use in studying the simplest transformation of polar ethylenes - rotation about the double bond or their thermal Z,E-isomerization (the symbols Z and E correspond, respectively, to the cis and trans arrangement of the 'principal' substituents relative to the double bond). In NMR studies of mainly enamines containing a tertiary amino group, Sandström, Kessler, Shvo et al. (6-17) treated the Z,E-isomerization as a rotation through a dipolar transition state:



The magnitude of $\Delta G^{\ddagger}$ for rotation in such molecules is rather low (from 8 to 30 Kcal/mol) due to delocalization of the electron pair of the nitrogen atom. The principles of rotation about the C=C bond through the dipolar transition state

(the thermal mechanism of the Z,E-isomerization) have been discussed in previous reviews (15, 16) and may be summarized as follows:

1) An increase in electron-donating power of R_1, R_2 and in acceptor capacity of X, Y promotes polarization of the C=C bond in the molecular ground state and stabilizes the charges in the transition state, thereby decreasing the energy barrier to rotation.

2) An increase in size of the substituents at the double bond increases steric strain in the molecular ground state, which also decreases the rotation barrier.

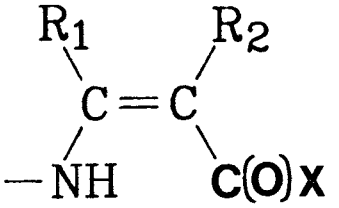
3) An increase in dielectric constant of the medium favors polarization of the C=C bond in the ground state and separation of charges in the transition state, which decreases the barrier to rotation about the C=C bond.

4) The Z,E-isomerization is a unimolecular reaction. It is characterized by a 'normal' magnitude for the pre-exponential factor (logA = 12-13) and a negative entropy change.

Thus, the rotation barrier is a very useful quantitative characteristic of the structure of tertiary enamines. Compared to enamines containing a tertiary amino group, those with an N-H bond are more complicated systems. Indeed, the latter can undergo tautomeric transformations (18-22) with tautomeric equilibrium fully shifted, as a rule, towards the enamine form. Such compounds are protonated and deprotonated to give cations and anions where the order of the C=-=C bond seems to be lower than that in the initial state (18). As a result, enamines containing the N-H bond may exhibit a variety of reaction pathways by which the geometrical isomerization can proceed. These pathways are analyzed in the present review on the basis of the available literature. It is to be noted that the data on enamine isomerization, discussed in this work, have all been obtained from NMR spectroscopy. This unique method permits a simultaneous investigation both of the isomerizations and of proton transfer reactions.

II. THE MECHANISM OF Z,E-ISOMERIZATION OF ENAMINES CONTAINING THE N-H BOND

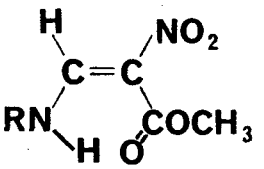
The kinetics of isomerization of enamines containing a primary or secondary amino group were studied mainly by the proton resonance method with enamino ketones and enamino ethers of the general formula:



where X = Alk or OAlk. Determination of the spatial configuration of these compounds by ^{1}H NMR is no problem when $R_1 = R_2 = H$, because the observed magnitude of the spin-spin coupling constant $J_{-CH=CH-}$ clearly reveals the spatial arrangement of the coupled protons (23). In the case of derivatives of tri-substituted ethylenes (for instance, $R_1 = H$, but $R_1 \neq R_2$) the configuration can be ascertained by comparing the observed value of the olefinic proton chemical shift with that calculated by the increment equation (24)

$$\delta_{CH} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}. \quad (2)$$

It should be noted, however, that with unsaturated compounds containing bulky substituents, the difference between the experimental and calculated δ_{CH} is large and frequently equal to the difference between δ_{CH} of the isomers themselves. In such cases a need arises for additional experiments. Thus reference 25 dealt with unsaturated nitro-compounds such as *1*, which are of interest from the viewpoint of synthesis of amino acids and other biologically important species. The resonance signals in the ^{1}H NMR spectra of these compounds were assigned using the shift reagents $Eu(dpm)_3$ and $Eu(fod)_3$. In references 26 and 27 an alternative approach was suggested to establish the configuration of nitroalkenes such as *1* and *3*; the approach is based on



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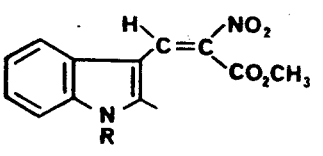

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the observation of the broadening of the olefinic proton signal on heating the sample. This broadening resulted from scalar relaxation of the second kind, which was more pronounced in the Z-configuration due to the trans relationship of the ^{1}H and ^{14}N nuclei.

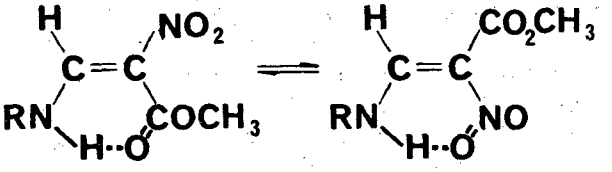
Table 1. The Kinetic Parameters of rotation about the C=C Bond of Enamines *1* in Nitrobenzene (30).*

R	E_{act} Kcal/mol		$\Delta H^{\ddagger}$ Kcal/mol		$\Delta S^{\ddagger}$ e.u.		$\Delta G^{\ddagger}_{298}$ Kcal/mol	
	Z	E	Z	E	Z	E	Z	E
CH_3	-	-	-	-	-	-	20.4[347]	20.0[347]
p-CH_3O-Ph	20.4	20.4	19.7	19.7	-14.2	-14.2	23.9	23.9
p-CH_3-Ph	22.0	22.0	21.6	21.6	-12.0	-12.0	25.2	25.2
Ph	24.7	24.7	24.0	24.0	-6.0	-6.0	26.0	26.0
p-Cl-Ph	25.0	25.0	24.2	24.2	-9.0	-9.0	27.0	27.0

*The estimated errors are 0.4 Kcal/mol for E_{act}, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$ and 1.5 - 2.0 e.u. for $\Delta S^{\ddagger}$.

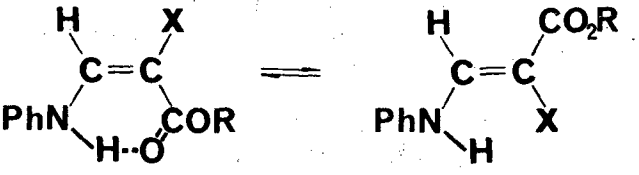
A. The Thermal Mechanism of Rotation about the C=C Bond

Recently, comprehensive ^1H NMR studies were carried out on the kinetics of isomeric transformations in a series of enamines *1* containing the N-H bond (28-32).



E-1 **Z-1**

Table 1 lists the activation parameters for the Z,E-transitions, as calculated from the temperature dependence of the $COOCH_3$ signals through the full lineshape analysis (28-30). As seen from Table 1, the isomerization parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and E_{act} of enamines 1 in nitrobenzene decreases with increasing electron-donating power of R. At the same time, in the series of N-aromatic enamines, a satisfactory correlation is observed between ln $k_{Z,E}$ and σ_p of the substituent in the para position of the aromatic ring (30). These data, together with the fact that the kinetic order of the process is equal to unity, point to a thermal, unimolecular mechanism for the isomerizations. The same thermal mechanism for rotation about the C=C bond, involving formation of a dipolar transition state, has been suggested by Knippel et al. (31) in studies on the temperature dependence of the ^1H NMR spectra of ethyl derivatives of enamines *1* in monitoring the CH= signals. As shown in Table 2, the rotation barrier in dimethylsulfoxide, as determined from the coalescence temperatures, diminishes with increasing electron-donating power of the para substituent of the aromatic ring. Thus, the Z,E-isomerization of enamines *1* containing an NH proton is similar in these cases to the isomerization of enamines containing a tertiary amino group. There are, however, a few differences. As seen from Table 3, an increase in electron-accepting capacity of substitutent X results in simultaneously increasing, rather than decreasing, the energy barrier to rotation about the C=C bond in enamines 2:



2, R=CH_3, CH_2CH_3

Frank et al. (32) explain this phenomenon in terms of different effects exerted by substituent

Table 2. Barriers to rotation about the C=C bond of Enamines *1* in DMSO*.

R	$\Delta G^{\neq}$ t° C, Kcal/mol	
	Z	E
p-$(CH_3)_2$N-Ph	15.6[32]	15.1[32]
p-CH_3OPh	17.2[65]	16.9[65]
p-CH_3Ph	17.6[72]	17.2[72]
Ph	18.1[81]	17.7[81]
p-Cl-Ph	19.2[98]	18.6[98]
p-CH_3CO-Ph	19.8[117]	19.6[117]

*Reference 31 dealt with ethyl ethers of α-nitro-β-aminoacrylic acid.

Table 3. Barriers to Rotation about the C=C Bond of Enamines *2* in Nitrobenzene for Various Substituents X.

X	$\Delta G^{\neq}$ t° C Kcal/mol	Reference
NO_2	26.6[162], 26.2[88]	30
C≡N	23.4[162]	32
COOEt	19.8[88]	32

X on the energy of the ground and transition states. In our opinion, the observed regularity can be attributed to the formation of an intramolecular hydrogen bond, whose strength rises as the acceptor power of substituent X is increased. The formation of intramolecular hydrogen bonds in enamines *1* and *2* and related compounds has been convincingly demonstrated by ^{1}H NMR studies of the chemical shifts of the amino proton in various solvents (29-36). Further evidence in favor of hydrogen-bond formation is provided by the magnitude of the spin-spin coupling constant in the =CH-NH fragment, which ranges from 13 to 16 Hz, depending on the nature of R, and is indicative of a trans orientation of the interacting nuclei. It should be noted that for enamine *1* with R = H, the constants $J_{CH\text{-}NH}^{cis}$ and $J_{CH\text{-}NH}^{trans}$ measured in pyridine are 8 and 16 Hz, respectively (37).

As mentioned above, an increase of the dielectric constant of the solvent reduces the rotation barrier about the C=C bond in tertiary enamines. It is not observed, however, with enamine *1* when R = CH_3. In this case $\Delta G_{Z,E}^{298}$ decreases, with varying nature of the solvent, in the following order (29):

o-dichlorobenzene	>	nitrobenzene	>
>20		20.0	

acetonitrile	>	pyridine
18.0		17.2

which corresponds to increasing basic properties of the medium. This result also points to the influence of the intramolecular hydrogen bond on the rotation barrier height.

^{13}C NMR studies (29) of enamines *1* have shown that an increase in electron-donating power of substituent R gives rise to a downfield shift of the resonance signal of the carbon atom bound to the amino group. According to reference 38, this results from molecular polarization of the following type:

which explains the decreasing energy barrier to rotation about the C=C bond. The strong interaction between the nitrogen electron pair and the π-system of the enamines is independently demonstrated by the magnitude of the amino group proton geminal constant for compound *1* with R = H, which is equal to ~2 Hz and typical of fragments such as H_2C=C, i.e., of fragments with an sp^2-hybridized central atom (23). Further evidence for this interaction is furnished by ^{13}C (39), ^{14}N (40), and ^{15}N (41) NMR spectra of related compounds.

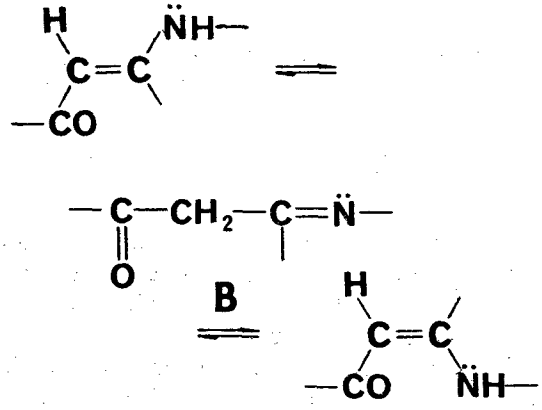
Thus the results reviewed in this section of the paper point toward the probability of the thermal mechanism for Z,E-isomerization of enamines containing the N-H bond. The amino proton is not involved in this isomerization. Indeed, in the ^{1}H NMR spectra of enamine *1*

with R = CH_3 in nitrobenzene, the spin-spin coupling constant of the fragment NH-CH_3 remains unchanged after coalescence of the Z- and E-isomer signals (42).

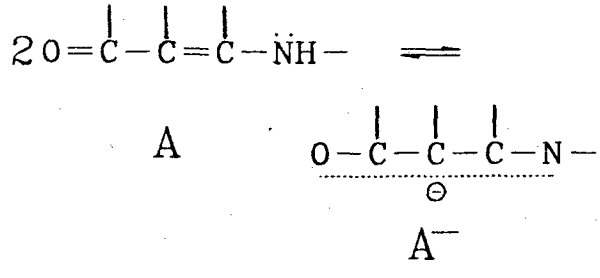
B. The Proton-transfer Induced Z,E-isomerization of Enamines

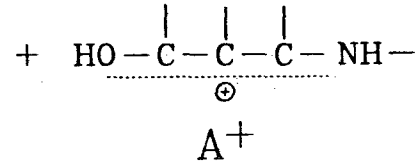
1. Associative Mechanism

When studying the ^1H NMR spectra of enamines of the general formula



Dabrowski et al. (43, 44) observed that in D_2O and ND_3 these compounds could undergo isomerization and, simultaneously, isotopic exchange of the olefinic proton, proceeding, as commonly accepted, via a tautomeric transition Compounds containing a tertiary amino group exhibited no isomerization under the same conditions. This fact allowed the authors to conclude that the isomerization proceeded through a tautomeric transition to yield an unstable but 'freely rotating' imino form B. (The relation between isomeric transformations and isotopic exchange of the olefinic proton was also discussed in references 45, 46). The rate of the isomerization proved, however, to be well above the rate of isotopic exchange (qualitative estimates), which provided evidence for competing mechanisms for the process. Dabrowski and Terpinski (44) believe that one enamine molecule can act as a base on another molecule to eliminate a proton from the nitrogen atom. The double bonds of the resulting anion A^- and cation A^+





lose partly their double bond character, which facilitates rotation about the C---C bond. The isomerization mechanism involving formation of the active (in the sense of rotation) forms due to interaction of two enamine molecules should be referred to as the 'associative' mechanism. This mechanism was supported kinetically by dynamic NMR spectroscopy in studies of isomerizations of enamine *1* with R = H in pyridine (29). It should be noted that the structure of this compound has one amino proton not involved in formation of the intramolecular hydrogen bond. As seen from Figure 1, the lineshape of $COOCH_3$ signals depends on enamine concentra-

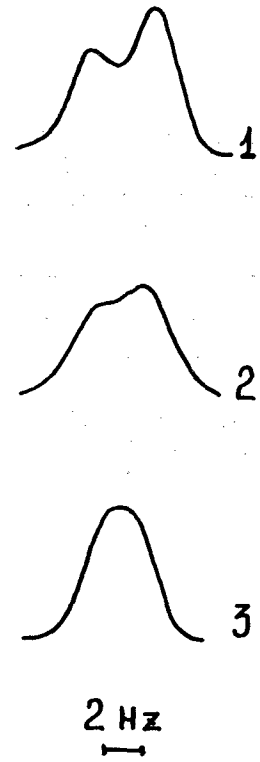


Figure 1. The lineshapes of $COOCH_3$ signals of enamine *1* with R = H in pyridine at 70° C and various concentrations (1.0 - 0.1 M, 2.0 - 0.3 M, 3.0 - 0.4 M).

Table 4. Activation Parameters for Z,E-isomerization of Enamines *1* in Pyridine.

R	E_{act} Kcal/mol		$\Delta H^{\ddagger}$ Kcal/mol		$\Delta S^{\ddagger}$ e.u.		$\Delta G^{\ddagger 298}$ Kcal/mol	
	Z	E	Z	E	Z	E	Z	E
CH_3	12.2	12.4	11.6	11.7	-20.2	-18.4	17.7	17.2
H	10.2	8.5	9.5	7.8	-26.4	-30.8	17.4	17.0

tion. The kinetic order of the Z,E-isomerization, *n*, determined from equation 3 (47)

$$1/\tau_{Z(E)} = dZ(E)/dt[Z(E)] = k[Z(E)]^{n-1} \quad (3)$$

by calculating the lifetimes $\tau_{Z,E}$ at various concentrations of enamine *1* with R = H was found to be, at the indicated temperature, between 1.7 (100° C) and 2.0 (50° C). This corresponds to two enamine molecules being involved in the kinetically controlled stage of the process. It should be noted that the decrease in the isomerization parameters E_{act}, $\Delta H^{\mp}$, $\Delta S^{\mp}$ (Table 4) observed on going from the thermally isomerizing enamine *1* with R = CH_3 to enamine *1* with R = H is at variance with the effect of the substituent at the nitrogen atom. This could not be explained by the thermal rotation mechanism and also suggests that the isomerization mechanism has changed.

2. Dissociative Mechanism

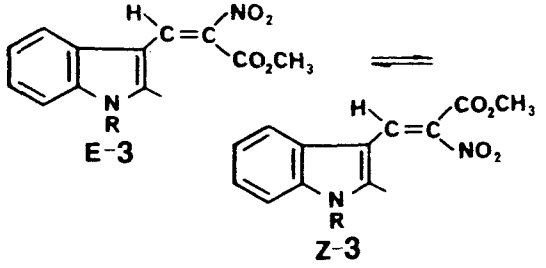
The anion A^- in the above scheme can be generated by interaction of an enamine containing an N-H proton with a base whose role may be played by the solvent. Such a mechanism of Z,E-isomerization of enamines should be referred to as the 'dissociative' mechanism. The existence of the dissociative mechanism was confirmed by dynamic NMR studies of enamines *1* with N-aromatic substituents in dichloromethane-pyridine mixtures (30, 37). The lifetimes of the Z- and E-isomers were found by full analysis of the lineshapes of the $COOCH_3$-signals. The effect of substituent R on the Z,E-isomerization barrier height in enamines *1* with R = Ar (Table 5), the partial first order kinetics of the reaction in enamine and pyridine (37), as well as the kinetic isotopic effect found from the lineshape of the $COOCH_3$ groups of enamine *1* with R = Ph, deuterated at the nitrogen atom, all pointed to a mechanism involving cleavage of the N-H bond, followed by rapid rotation in the anion

$$A_Z \rightleftarrows A_Z^- + H^+$$

$$A_Z^- \rightleftarrows A_E^-$$

$$A_E^- + H^+ \rightleftarrows A_E.$$

The dissociative mechanism was also supported by the kinetics of isomerization of enamine *3* with R = H (48).



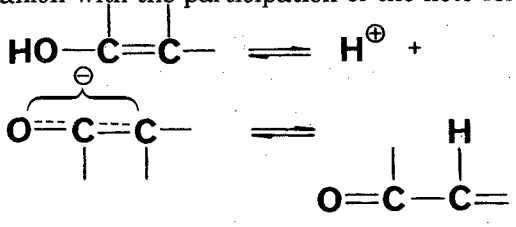
In acetonitrile and pyridine the compound showed isotopic effects (as established by analyzing the lineshapes of $COOCH_3$-signals, see Table 6 and Figure 2). Substitution of the radicals CH_3 and CH_3CO for the nitrogen proton resulted in a sharp increase of the rotation barrier ($\Delta G_{Z,E}^{298}$ = 17.5 Kcal/mol for R = H in

Table 5. The Effect of Substituent R on Barriers of Z,E-isomerization of Enamines *1* in a CH_2Cl_2:Pyridine Solution (30).

R	p-NO_2-Ph	p-Cl-Ph	Ph	p-CH_3-Ph	p-OH-Ph
$\Delta G_Z^{\ddagger}{}_{298}$ Kcal/mol	14.2±0.2	15.6±0.2	15.9±0.2	16.5±0.2	16.8±0.2
$\Delta G_E^{\ddagger}{}_{298}$ Kcal/mol	14.3±0.2	15.4±0.2	15.7±0.2	16.3±0.2	16.5±0.2

acetonitrile and pyridine and $\Delta G_{Z,E}^{423} > 24$ Kcal/mol for R = CH_3, CH_3CO in dimethylsulfoxide). Finally, it is only the dissociative mechanism that can explain the inhibiting effects of an acid on the rate of isomerizations of enamine *3* with R = H in acetonitrile (Figure 3), where the acid reduces the lifetime of the anionic form (48).

The conformational lability of the anionic forms of enamines can be accounted for by the decreased order of the C---C bond. As demonstrated by MO LCAO calculations, the dissociation of the N-H bond in enamine *1* (R = CH_3) leads to CC double bond nonbonding interaction and to a threefold decrease of the rotation barrier about the C=C bond in the anionic form (49a). It should be noted that the decreased order of the C---C bond in the anionic form is not sufficient perhaps for the isomerization of the enolic systems. As demonstrated by the dynamic NMR spectroscopy in reference (49b,c) the fast isomerization of the enolic systems is achieved by the protonation-deprotonation reaction of the enolic anion with the participation of the keto form:



i.e., by the transformation from a double bond to a single bond.

Table 6. The Lifetimes of Z,E-isomers of Enamine *1* with R = Ph in a CH_2Cl_2:Pyridine Solution and of Enamine *3* with R = H in Pyridine and their N-deutero-derivatives under the Same Conditions.

Compound	$\tau_{eff}^{t°C}$ (H)* s	$\tau_{eff}^{t°C}$ (D) s	Ref.
1 with R=Ph	0.014^{40}	0.028^{40}	30
3 with R=H	0.03^{60}	0.09^{60}	48

*$\tau_{eff} = \tau_Z\tau_E/(\tau_Z + \tau_E)$.

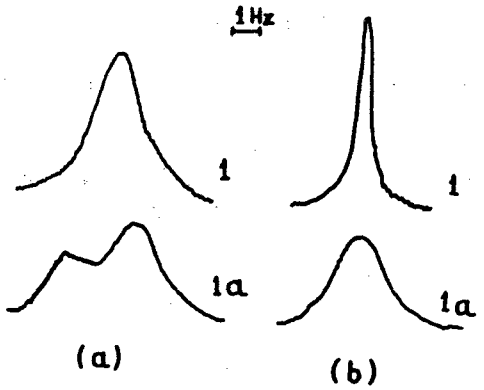


Figure 2. $COOCH_3$ signals of enamine *3* with R = H (1) and its deutero-analog (1a) in pyridine (a) and acetonitrile (b).

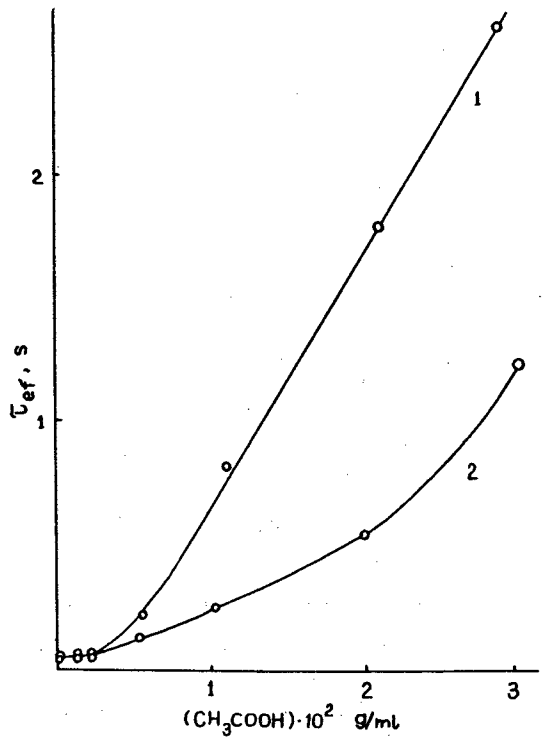
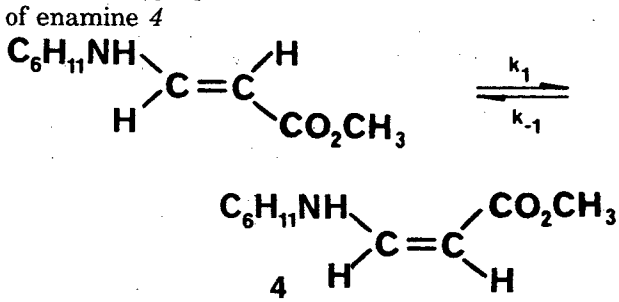


Figure 3. Isomerization of enamine *3* with R = H in CH_3CN at 20° C in the presence of acetic acid: 1.0 - 0.09 M solution, 2.0 - 0.18 M solution.

C. Catalysis of Z,E-isomerization in Enamines Containing the N-H Bond

Inasmuch as enamines containing a primary or secondary amino group can undergo isomerization via migration of the N-H proton, a relationship should be expected to exist between the rate of Z,E-isomerization of these systems and acidic-basic properties of the solvent. In studies of enamine *4*



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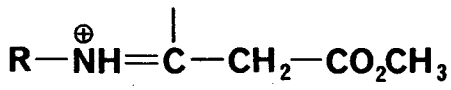
Huisgen et al. (50) showed that the rate of its isomerizations in benzene is extremely small ($k_1^{25} = 8.6\times10^{-6}$ s^{-1}, $k_{-1}^{25} = 1.7\times10^{-6}$ s^{-1}). Addition of acetic acid in catalytic quantities produced a dramatic increase in the reaction rates (the above constants become equal to 1.1×10^{-4} s^{-1} and 0.24×10^{-4} s^{-1}, respectively). The authors rationalized the observed phenomenon in terms of isomerization proceeding via a short-lived imino form:



The acid catalysis of the Z,E-isomerization of enamines was also reported by Frank et al. (32). In the cited work the addition of trifluoroacetic acid to chloroform and nitrobenzene solutions of enamines *2* was found to decrease the coalescence temperature of the $COOCH_3$-group signals in the ^1H NMR spectra. The effect of the acid on the rate of isomerizations of enamines was also investigated in reference 51. Table 7 lists the isomer lifetimes calculated by full analysis of the lineshapes of the $COOCH_3$ signals. It is seen that an increase in acid concentration speeds up the isomeric transitions. Thus these results, too, can be accounted for by protonation of enamines to give the above imino form. It should be noted that the deceleration of Z,E-isomerization observed with enamine *1* with R = Ph at low acid concentrations implies suppression of the dissociative mechanism discussed above.

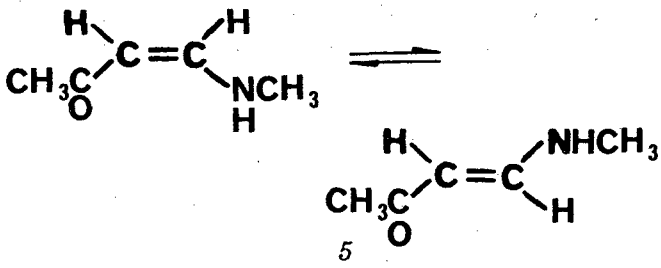
Unlike acids, triethylamine does not catalyze the isomerization of enamine *4* in benzene (50). The addition of triethylamine does not, however, have a catalytic effect in the case of enamines *3* with R = H and of enamines *1* with R = Alk or Ar which contain two powerful electron-accepting groups increasing the acidity of the N-H proton (29, 48). This catalytic effect can be explained in terms of the dissociative mechanism of Z,E-isomerization, as was observed in the presence of pyridine. Thus, from the above data it may be concluded that the effect exerted by an acid or a base on the rate of isomerizations of a particular enamine containing the N-H bond is not simple and depends on the structure of the enamine.

Table 7. The Lifetimes of Z- and E-isomers of *1* with R = CH_3 and Ph in Acetonitrile at Various Concentrations of CF_3COOH (51).

[CF_3COOH] Mol/L	R = CH_3		R = Ph	
	τ_E t°C s	τ_Z t°C s	τ_E t°C s	τ_Z t°C s
0.0	0.16[53]	0.30[53]	0.82[53]	1.0[53]
0.027	0.17[53]	0.32[53]	-	-
0.135	0.14[53]	0.27[53]	>>0.82[53]	>>1.0[53]
0.27	0.073[53]	0.13[53]	-	-
2.7	0.127[-25]	0.39[-25]	0.035[53]	0.053[53]
5.4	0.037[-25]	0.11[-25]	0.095[53]	0.019[53]

III. Z,E-ISOMERIZATION AND PROTON EXCHANGE

As mentioned above, NMR spectroscopy offers an unique means for revealing the mechanisms of isomerizations in enamines containing the N-H bond. In particular, by using this method a relationship was found between the isomerizations and intermolecular proton exchange reactions. Kozerski et al. (52) studied the temperature behavior of the ^1H NMR spectra of enamines *5*



5

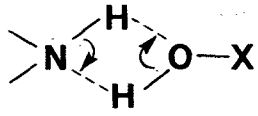
in the region of the CH_3CO signals, which are responsive to the isomerization, and the NCH_3 signals, which are indicators for intermolecular proton exchange due to the splitting on the NH proton. It was demonstrated that in aprotic solvents the activation energy parameters for both processes ($\Delta G^{\ddagger}$) were practically the same (Table 8). This coincidence allowed the authors to conclude that the isomerization occurs with participation of the NH proton, i.e., proceeds via formation of ionic forms. Similar results were reported in reference 42 for enamine *1* with R = Ar, where the full analysis of the lineshapes of the $COOCH_3$ and CH_3 group signals showed the rate of the isomerization in a dichloromethane-pyridine mixture to be very close to the rate of the N-H bond cleavage. The partial first order

Table 8. The values of $\Delta G^{\ddagger}$ for Rotation about the C=C Bond and for Proton Exchange in Enamine *5* in Various Solvents (52).

Solvent	Process	$\Delta G^{\ddagger}$ t°C Kcal/mol
in bulk	isomerization	19.6[102]
	NH exchange in cis form	19.5[94]
	NH exchange in trans form	19.6[98]
C_2Cl_6	isomerization	20.6[116]
	NH exchange in trans form	19.9[102]
	NH exchange in cis form	18.9[84]
C_2Cl_6: pyridine	isomerization	19.8[99]
	NH exchange in trans form	19.0[85]
	NH exchange in cis form	18.2[70]
H_2O	isomerization	18.6[34]
	NH exchange in both forms	14.7[8]

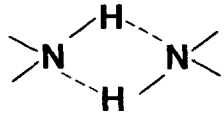
kinetics in enamine and pyridine, observed for both Z,E-isomerization and proton exchange, as well as the similar effect exerted by the substituent in the para position of the aromatic ring, suggested that the transfer of the NH proton between molecules of enamine *1* with R = Ar was catalyzed by pyridine and followed by the loss of conformational stability of the compounds. Thus, with aprotic solvents simultaneity may be

expected for the isomerizations and NH proton exchange in enamines *1* with R = Ar and *5*. A very different situation is observed with proton-donating solvents. As seen from Table 8, in aqueous solution the isomerization of enamine *5* necessitates much greater energy than does the proton exchange reaction. Dynamic NMR studies of the isomerization and proton exchange kinetics for compounds *1* (R = Ar) and *3* (R = H) in CH_3OH (53), CH_3OH-$CHCl_3$ (54), and pyridine-water mixtures (55) demonstrated that enamines with N-H bonds are isomerized in the proton-donating solvents through a unimolecular transition state (thermal mechanism, Section II.A). On the other hand the proton transfer reactions go through a bimolecular transition state, containing one molecule of proton-donating solvent:



X = H, CH_3

Perhaps the difference in the rates of the discussed processes can be accounted for by this fact. The relation between Z,E-isomerization and proton exchange in enamines conaining the N-H proton depends not only on the nature of the solvent but also on the structure of the enamine. Thus in studies of the temperature behavior of the ^1H NMR spectra of enamine *1* with R = CH_3 in pyridine (29), it turned out that the lineshape of the $COOCH_3$ signals - indicators for isomerizations - was independent of concentration of the isomerizing compound. However, for NCH_3 signals whose lineshape depends on the rate of proton exchange, such concentration dependence was clearly observed (Figure 4). Analysis of the spectra showed that Z,E-isomerization and proton exchange were characterized by first and second kinetic orders, respectively. In other words, the intermolecular NH exchange in enamine *1* with R = CH_3 seems to occur through a closed transition state



while the isomerizations proceed by the mechanism of thermal rotation about the C=C bond, discussed in Section II. Thus kinetic studies of NH exchange in isomerizing enamines may provide a better insight into the mechanism of their

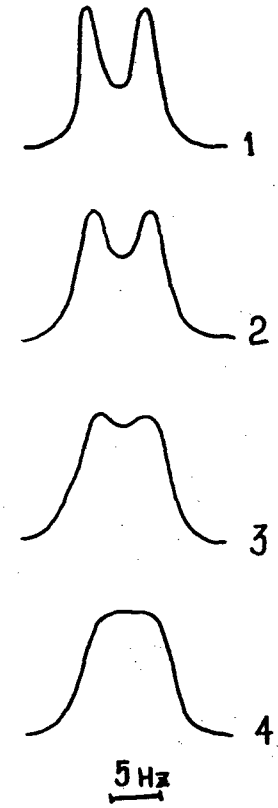


Figure 4. The lineshapes of CH_3N signals of enamine *1* with R = CH_3 in pyridine at 110° C and various concentrations (1.0 - 0.1 M, 2.0 - 0.2 M, 3.0 - 0.5 M, 4.0 - 0.8 M).

Z,E-transitions.

IV. CONCLUSIONS

The data reviewed in this paper suggest that Z,E-isomerization of enamines containing a N-H bond do not follow a single mechanism. Depending on a number of factors, isomerizations of the enamines may proceed through the thermal mechanism and through the proton exchange reaction. Among the factors affecting the isomerization rate and pathway are the nature of N-substituents and those at the double bond as well as the properties of the solvent (first of all, its acidic-basic properties). It seems that in the general case, solutions of the enamines may exhibit several simultaneous pathways of

Z,E-isomerization. An increase in the ability of N-substituents and those at the double bond to be involved in delocalization of negative charge, as well as an increase in basic properties of the solvent, should raise the probability of the dissociative mechanism of the Z,E-isomerizations. An increase in enamine concentration should in turn favor the associative mechanism. The diversity of the mechanisms of 'rotation' about the C=C bond in enamines containing the N-H bond implies that the rotation barriers calculated from the temperature dependence of the NMR spectra cannot be used as a characteristic of the double bond if the 'rotation' mechanism is unknown. Thus in the case of enamines *1* with R = Ar these barriers characterize the cleavage of the N-H bond.

Considering enamines containing the N-H bond as model compounds, we believe that the data reviewed in this paper will aid in recognizing the nature of isomerization reactions of tautomeric molecules which are extensively investigated by NMR spectroscopy.

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