TAUTOMERISM OF DERIVATIVES OF AZINES.

17.* EFFECT OF SOLVENTS ON THE POSITION OF THE AZINYL-YLIDENE TAUTOMERIC EQUILIBRIUM OF SUBSTITUED AZINYLMETHANES

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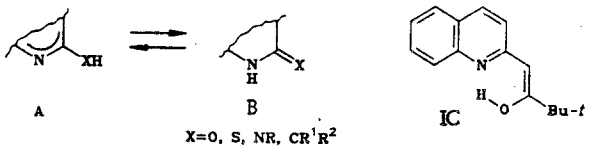
The effect of solvents on the position of the azinyl-ylidene tautomeric equilibrium in series of azinylmethanes was studied. It was shown that an increase in the polarity of the solvent leads to stabilization of the ylidene tautomer; the sensitivity of the tautomeric equilibrium to the effects of the solvent depends on the form of the side fragment that undergoes tautomerization. It was concluded that stabilization of the ylidene tautomeric form by polar solvents is a general tendency in series of prototropic equilibrium of the azinyl-ylidene type as a whole.

Tautomeric interconversions of the azinyl-ylidene A⇄B type [2, 3] play a substantial role in many divisions of the chemistry of heterocycles. One of the most important factors that determine the position of a tautomeric equilibrium is the effect of the medium. The dominating effect of the molecular environment on the tautomerism of hydroxy and mercapto azine (X = O, S) is well known [4, 5]. An increase in the polarity of the solvent leads to a pronounced shift of the equilibrium to favor tautomeric form B [5].



We have previously observed that the tautomeric equilibrium of azinylmethanes (X = CR^1R^2) is sensitive to the nature of the solvent; more polar solvents also promote stabilization of ylidene tautomer B [6, 7]. Moreover, in [8] in a study of the tautomerism of tert-butyl quinaldinyl ketone (I) it was concluded that a tautomer of the A type is stabilized when the polarity of the solvent is increased. This conclusion requires additional substantiation, since the possibility of the formation of a third tautomer — enol IC — was not taken into account in [8]. At the same time, according to the data in [1], the formation of an enol tautomer is observed for acylmethylquinolines; its percentage depends markedly on the polarity of the solvent. The aim of the present research was to study the effect of solvents on the position of the tautomeric equilibrium A⇄B of substituted azinylmethanes. As the subjects of the investigation we used compounds for which enolization of the side fragment is not characteristic [2].

For the theoretical evaluation of the effect of the polarity of the solvent on the A⇄B tautomeric equilibrium we analyzed the effects of nonspecific solvation within the framework of the Germer solvaton model [9]. A modified Hamiltonian that makes it possible to take into account interaction of the nuclei and electrons of a molecule with a set of point charges — solvatons, which model the solvent — is used in quantum-chemical calculations with allowance for solvation in accordance with Germer. By means of this relatively simple computational scheme one can, in a number of cases, obtain a semiquantitative evaluation of the effects of solvation [10]. We calculated the energies of solvation of tautomers of 2-hydroxypyridine and 2-pyridylacetaldehyde (II) with the aid of the CNDO/2 method. The differences in the energies of solvation of the tautomers for various values of the dielectric permeability (ε)

*See [1] for Communication 16.

†Deceased.

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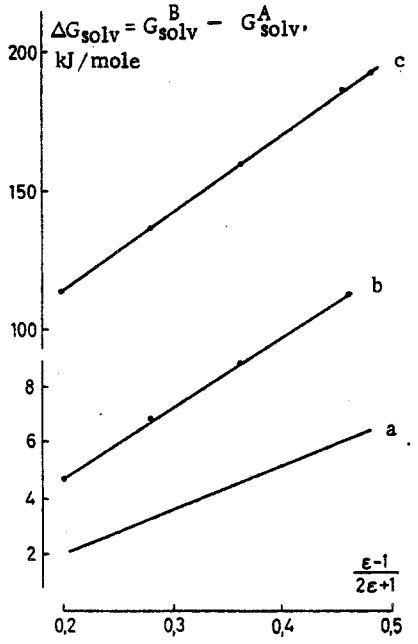

Fig. 1

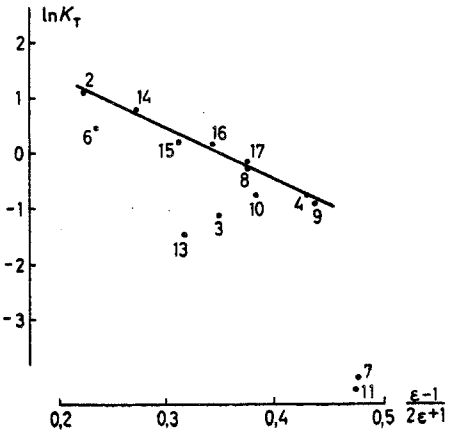

Fig. 2

Fig. 1. Differences in the energies of solvation of the tauometers: a) experimental data [5] for 2-hydroxy-6-chloropyridine; b) calculated data for 2-hydroxypyridine; c) calculated data for 2-pyridylacetaldehyde.

Fig. 2. Dependence of ln K_T for III on the polarity of the solvent. The numbers correspond to the numbers of the solvents in Table 1.

are presented graphically in Fig. 1. For both 2-hydroxypyridine and II, which model the tautomers of substituted azinylmethanes, significant alternation of the charges on the atoms in tautomer B leads to its greater stabilization with an increase in the polarity of the solvent. It should be noted that the calculated data obtained correspond qualitatively to the experimental values with respect to the relative energies of solvation of the tautomers of 2-hydroxypyridine [5]. Considering the monotypic character of the electronic restructuring of the molecules for the entire set of tautomeric equilibria of the azinyl-ylidene type (X = O, NR, S, CR^1R^2) [3] one might expect an increase in the stability of the B form with an increase in the polarity of the solvent due to nonspecific solvation.

The experimental investigation of the effect of solvents was carried out in the case of the tautomeric equilibrium of 5-methoxy-2-pyrimidinylcyanoacetic ester (III). To ascertain the effects of nonspecific solvation we selected slightly polarizable solvents that are not capable of specific solvation (CCl_4, CH_2Cl_2, chlorobenzene, and dichloroethane), as well as a mixture of CCl_4 and CH_2Cl_2 (Table 1 and Fig. 2). We found that, as expected, an increase in the polarity of the solvent leads to a pronounced shift of the tautomeric equilibrium to favor ylidene form B. Whereas the percentage of the aromatic tautomer of III is 76% in CCl_4, it is only 34% in dichloroethane. It should be noted that the ln K_T value correlates well with polarity function $Y = (\varepsilon - 1)/(2\varepsilon + 1)$ in the Kirkwood–Onsager equation [11]. The experimentally found linear dependence of ln K_T on Y for solvents that are not capable of specific solvation makes it possible to ascertain the contribution of other electrostatic interactions that differ from the interactions of the dipole-dipole type. Thus the percentage of the ylidene tautomer for III in benzene is greater than in CCl_4, although these solvents have close dielectric permeabilities. The observed difference in the K_T values (Table 1 and Fig. 2) is evidently associated with the fact that in the easily polarizable benzene the energy of solvation of the more polar ylidene tautomer B increases due to an interaction of the dipole–induced dipole type [11].

The tautomeric equilibrium for III was found to be highly sensitive to the effects of specific solvation. Thus in $CHCl_3$,* ethyl acetate, DMF, and MeOH the percentage of tautomer

*Chloroform is capable of forming hydrogen bonds, thus the energy of the $CHCl_3$–HMPT hydrogen bond is 1.5 kcal/mole [12].

TABLE 1. Tautomeric Equilibrium Constants (K_T = [A]/[B])

№	Solvent name	K_T III	IV	V	VI	VII
1	Isooctane		4,5		3,7	
2	CCl_4	3,2	2,9	41,6	4,7	5,75
3	$CHCl_3$	0,31	4,3	37,5	2,1	4,0
4	CH_2Cl_2	0,53		42,5	2,5	4,5
5	CH_3CN			32,0	3,5	
6	Benzene	1,6	2,9	23,6	2,3	
7	Methanol	0,02	3,45	21,8	3,0	
8	Chlorobenzene	0,72	4,8	33,5	2,0	3,4
9	Dichloroethane	0,49		36,0	2,7	4,0
10	Ethyl acetate	0,54	2,7	18,2	1,6	
11	DMF	0,02	1,9	10,4		
12	Toluene			37,5	2,45	
13	CCl_4+5% MeOH	0,20				
14	CCl_4+10% CH_2Cl_2	2,8				
15	CCl_4+20% CH_2Cl_2	0,88				
16	CCl_4+50% CH_2Cl_2	0,81				
17	CCl_4+70% CH_2Cl_2	0,72				

B is substantially greater than one might have expected for solvents with such polarities (Table 1 and Fig. 2). One can see that the ylidene tautomer is stabilized by both proton-donor ($CHCl_3$, MeOH) and proton-acceptor (ethyl acetate, DMF) solvents through the formation of hydrogen bonds at different centers. The effect of specific solvation is substantial even when small amounts of these solvents are added. Thus, when 5% MeOH is added to CCl_4, the percentage of the ylidene tautomer in the equilibrium increases by almost 60% (Table 1).

Thus the position of the tautomeric equilibrium of pyrimidinylcyanoacetic ester III is highly sensitive to the character of the solvent. An increase in the polarity of the solvent leads to a marked shift of the equilibrium to favor the ylidene tautomeric form. Solvents that are capable of specific solvation increase the relative stability of tautometic form B to an even greater extent.

A similar strong effect of solvents on the tautometic equilibrium is also manifested in the case of other azinylcyanoacetic esters. Thus, the transition from solutions in $CHCl_3$ to solutions in a mixture of hexane + 2% $CHCl_3$ substantially increases the percentages of the aromatic tautomers in the equilibria for 2-pyrimidinylcyanoacetic esters [6] and for 4,6-dimethoxy-sym-triazin-2-ylcyanoacetic ester [7], and the transition from $CHCl_3$ to DMSO shifts the tautomeric equilibrium of 6-chloro-2-pyrazinylcyanoacetic ester to favor the ylidene tautomeric form [13].

We also studied the effect of solvents on the tautomeric equilibria of 4-pyrimidinylmalonic ester (IV), 5-nitro-2-pyridylmalonic ester (V), 2-quinoxalinylmalonic ester (VI), and (2-pyridyl)(2,4-dinitrophenyl)acetic ester (VII). In contrast to azinylcyanoacetic esters, IV-VII contain bulky groups in the side fragments — carbethoxy for IV-VI and dinitrophenyl for VII. A comparison of the tautomeric equilibrium constants of azinylmalonic esters IV-VI in solvents that are not capable of specific solvation (CCl_4, CH_2Cl_2, chlorobenzene, and dichloroethane) showed that an increase in the polarity of the solvent leads to a very slight shift of the tautometic equilibria to favor ylidene tautomer B (Table 1, Fig. 3). This difference in the sensitivities of the tautomeric equilibria of azinylmalonic and azinylcyanoacetic esters to the polarities of the solvents can be explained by the peculiarities of the solvation of the bulky side fragments. The transition from aromatic form A to ylidene form B evidently leads to a substantial deterioration in the solvation of the bulky groups of the side fragment because of the steric requirements that develop in the rigid structure of the ylidene tautomer. Although an increase in the polarity of the solvent promotes stabilization of the ylidene heterocyclic fragment, this effect is compensated by deterioration of the solvation of the side substituents. The small effect of the polarities of the solvents on the position of the tautomeric equilibrium of dinitrophenylacetic ester VII can also be explained precisely by the existence of these two opposing tendencies (Table 1, Fig. 3).

The tautomeric equilibria of azinylmalonic esters IV-VI proved to be only slightly sensitive not only to the effects of nonspecific solvation but also to the effects of specific solvation (Table 1, Fig. 3). Thus the percentages of tautomers B in methanol for IV and VI differed by ∿5% from the values expected for solvents with such polarities.

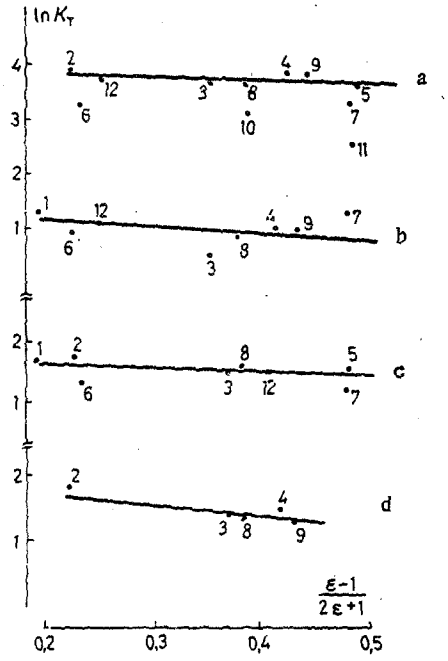

Fig. 3. Dependence of ln K_T on the polarity of the solvent for V (a), VI (b), IV (c), and VII (d).

Thus, in the series of substituted azinylmethanes an increase in the polarity of the solvent leads to stabilization of the ylidene tautomer. The sensitivity of the tautomeric equilibrium to the effects of the solvent decreases significantly when there are bulky substituents attached to the methyl group. Taking into account the data on the effect of the polarity of the solvent on the tautomerism of hydroxy and mercapto azines, the elucidated tendency — stabilization of the ylidene form by polar solvents — is extremely general in series of prototropic equilibria of the azinyl-ylidene type as a whole. This similarity is due to the similarity in the electronic restructuring in the tautomeric transitions of the A⇄B azinyl-ylidene type.

EXPERIMENTAL

The tautomeric equilibrium constants of III-VIII were determined by UV spectroscopy from the intensities of the long-wave absorption of the ylidene tautomers, as in [14]. The molecular extinction coefficients of the ylidene tautomers for the analytical wavelengths were calculated on the basis of the absorption intensities in the UV spectra (solutions in $CHCl_3$) and the tautomeric equilibrium constants in $CDCl_3$, which were obtained by PMR spectroscopy. The molecular extinction coefficients (in centimeters per mole per liter) of the B forms were as follows: ε_{max}^{305} = 32,000 for III, ε_{max}^{300} = 17,800 for IV, ε_{max}^{400} = 19,000 for V, ε_{max}^{300} = 16,400 for VI, and ε_{max}^{307} = 12,700 for VII. The accuracy in determination of K_T was ±5%.

The UV spectra of $1\cdot10^{-4}$ M (III, IV, VI) and $2\cdot10^{-4}$ M (V and VII) solutions were recorded with a Beckmann DU8 spectrophotometer at 20°C. The PMR spectra were recorded with a Bruker WP200SY spectrometer. The solvents were purified in accordance with the methods in [15]. The quantum-chemical calculations by the CNDO/2 method were made with the program in [16] with a BÉSM-6 computer. The geometries of the molecules were selected in accordance with [17].

The synthesis of III was described in [18], the synthesis of IV was described in [14], and the synthesis of V was described in [19].

2-Quinoxalinylmalonic Acid Methyl Ester (VI). This compound was obtained by a method similar to that in [18] from 2-chloroquinoxaline and the Na salt of malonic ester in a ratio of 1:3 in DMF at 60°C. The reaction time was 3 h, and the product, with mp 85-87°C, was obtained in 70% yield. UV spectrum (in $CHCl_3$), λ_{max} (log ε): 300 (4.07), 408 (3.71), and 425 nm (3.72). Found: C 50.4; H 4.4; N 11.0%. $C_{13}H_{12}N_2O_4$. Calculated: C 50.8; H 4.6; N 10.8%.

(2-Pyridyl)(2,4-dinitrophenyl)acetic Ester (VII). A 0.36-g (7 mmole) sample of a 50% suspension of NaH in oil was added to a solution of 0.45 g (3 mmole) of 2-pyridinylacetic acid ester in 10 ml of absolute ether. After hydrogen evolution had ceased, 0.6 g (3 mmole) of 2,4-dinitrochlorobenzene was added, and the mixture was stirred at 20°C for 2 h. It was

then poured into 50 ml of water, and the aqueous mixture was neutralized with HCl and extracted with chloroform. The extract was washed with water, dried with $MgSO_4$, and evaporated. The residue was purified by chromatography with a column packed with silica gel by elution with chloroform ($R_f \sim 0.3$) to give 0.2 g (20%) of a red oil. PMR spectrum ($CDCl_3$): 7.1-8.8 (7H, protons of the pyridine and phenyl rings), 5.86 (1 H, s, $-\overset{\diagdown}{\underset{\diagup}{}}CH)$, 4.2 (2H, m, CH_2), and 1.21 ppm (3H, m, CH_3). UV spectrum (in $CHCl_3$), λ_{max} (log ε): 259 (4.18) and 307 nm (3.40). Found: C 54.3; H 4.0; N 12.5%. $C_{15}H_{13}N_3O_6$. Calculated: C 54.4; H 3.9; H 12.7%.

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