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Abstract

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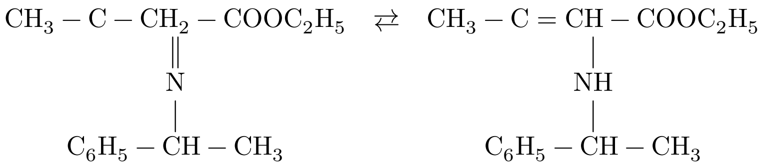
SPECTROPOLARIMETRIC STUDY OF A KETIMIDE-ENAMINE TAUTOMERIC SYSTEM

Having discovered a distinctive effect of the solvent on the dispersion of the optical rotation of *N*-benzoyl-α-phenylethylamine and having explained these observations from the standpoint of amide-iminol tautomerism (^{1}), we became interested in the possibility of using the spectropolarimetric method to study other cases of tautomerism. The first object was the condensation product of optically active α-phenylethylamine with acetoacetic ester, from which one might expect the manifestation of ketimide-enamine tautomerism according to the scheme:



$$\begin{array}{ccc} CH_3-\underset{\underset{\underset{C_6H_5-CH-CH_3}{|}}{\overset{\|}{N}}}{C}-CH_2-COOC_2H_5 & \rightleftarrows & CH_3-C=\underset{\underset{\underset{C_6H_5-CH-CH_3}{|}}{\overset{|}{NH}}}{CH}-COOC_2H_5 \\ \mathrm{Ia} & & \mathrm{Ib} \end{array}$$

Carrying out the condensation at a temperature of −10-15° in ethereal solution, as described for benzylamine (^{2}), we obtained two substances of identical elemental composition, corresponding to formula I: a liquid, distilling in vacuo (150-152°/2 mm), and crystals melting at 64-78°. An exact determination of the melting point is impossible, since the crystals are stable only below zero; if they are kept at room temperature, then after 10-12 hr the crystals turn into a liquid having the same magnitude of rotation as the liquid portion of the condensation product.

Attempts to effect the reverse transition—to isolate the solid form by freezing the liquid—were not successful; however, the existence of an equilibrium (and not merely a one-sided transition) is evidenced by the mutarotation of solutions of the solid and liquid forms in 65% aqueous methanol: it turned out that both solutions approach, from different sides, one and the same equilibrium state (see Fig. 1).

The very fact of the transformation described could not yet serve as proof of the existence of ketimide-enamine tautomerism, since this transformation could

Fig. 1. Mutarotation in 65% methanol of the liquid (I) and crystalline (II) forms

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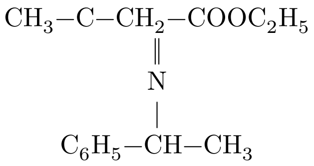
also be associated with a syn-anti transition of the ketimide form Ia or a cis-trans transition of the enamine form Ib. However, establishing the reversibility of the transition seems to us weighty evidence in favor of the presence of ketimide-enamine tautomerism, since in the case of syn-anti or cis-trans isomerism a spontaneous transition is observed only in one direction: in these latter cases the labile form spontaneously passes into the stable one, while the reverse transformation requires an expenditure of energy and ordinarily does not occur spontaneously.

The answer to the question of what the solid form of the condensation product represents,* can be given by comparing its optical rotation with the rotation of substances of known structure. In solutions of the solid form in all solvents a rapid change of rotation with time was observed (Fig. 2); however, in all cases the initially observed rotation (or that extrapolated to the initial time, $\tau = 0$) has a negative sign, i.e., the same sign as the rotation of the starting amine. The rotation of Schiff bases obtained by condensation of fatty aldehydes (acetic, isobutyric) with optically active (−)-α-phenylethylamine has the same character.

Fig. 1. Mutarotation in 65% methanol of the liquid (I) and crystalline (II) forms

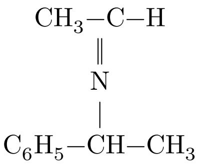
Fig. 2. Mutarotation of the crystalline form: *I* —in dioxane, *II* —in carbon tetrachloride, *III* —in benzene, *IV* —in methanol, *V* —in alcohol, *VI* —in ethyl acetate, *VII* —in a 65% solution of ethylene glycol in methanol

This gives grounds for concluding that, in its structure, the solid form resembles Schiff bases, i.e., it is a ketimide:



$$\begin{array}{c} CH_3-C-CH_2-COOC_2H_5 \\ \| \\ N \\ | \\ C_6H_5-CH-CH_3 \end{array}$$

similar to



$$\begin{array}{c} CH_3-C-H \\ \| \\ N \\ | \\ C_6H_5-CH-CH_3 \end{array}$$

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* We speak of the solid, and not the liquid, form because the latter, evidently, may be not an individual substance but a mixture.

Fig. 3. Dispersion of rotation: of the liquid phase in pyridine (I), acetic acid (II); of the ethyl ester of β(α-phenylethylamino)butyric acid in acetic acid (III), in pyridine (IV)

Figure 3: Fig. 3. Dispersion of rotation: of the liquid phase in pyridine (I), acetic acid (II); of the ethyl ester of β(α-phenylethylamino)butyric acid in acetic acid (III), in pyridine (IV)

It is also seen in Fig. 2 that the rate at which equilibrium is reached depends strongly on the solvent: in polar solvents equilibrium is established slowly (methanol, 23 hours), whereas in nonpolar solvents it is established rapidly (dioxane, 50 min.).

With respect to the influence of solvents on tautomeric systems, there are a number of statements in the literature, relating, it is true, mainly to keto-enol tautomerism. Thus, in the work of A. N. Nesmeyanov and M. I. Kabachnik[3] it is indicated that the position of the tautomeric equilibrium depends on the relative basicity (or acidity) of the forms in a given medium. In particular, in the β-aminocrotonic—iminoacetic ester system the equilibrium is shifted toward the less basic form, which in this case is the amine form. To test how solvents of basic and acidic character affect the equilibrium in the tautomeric system under investigation, we recorded the rotation-dispersion curves of the liquid form in pyridine and acetic acid (in the equilibrium state) and compared them with the rotation-dispersion curves of the ethyl ester of β-(α-phenylethylamino)butyric acid synthesized for this purpose. Comparison of the dispersion curves shown in Fig. 3 indicates that, for the condensation product of α-phenylethylamine with acetoacetic ester, which is capable of ketimide-enamine tautomerism, a sharp change in rotation both in magnitude and in sign is observed upon transition from a basic

solvent toward the acid. At the same time, the small difference between the rotation of the ethyl ester of β-(α-phenylethylamino)butyric acid in pyridine and in acetic acid shows that the change in rotation in the former case is not simply a consequence of salt formation; the reason is evidently that the acidic solvent shifts the equilibrium toward the (more basic) ketimide form Ia, binding it in the form of a salt; the basic solvent leads to predominance of the enamine form Ib.

For additional confirmation of the conclusions reached, the azo-coupling method was used, which Dimroth (4) had at one time applied to keto-enol systems, and the bromination method, recently used by Seher (5) for the study of the tautomerism of β-aminocrotonic ester, although doubts have been expressed (6) concerning the applicability of the latter method to enamines. Both methods showed that the amount of enamine in solutions of the solid form is small at the initial moment and gradually increases, i.e., they qualitatively confirmed the result of the polarimetric study.

Fig. 3. Dispersion of rotation: of the liquid phase in pyridine (I), acetic acid (II); of the ethyl ester of $\beta(\alpha$-phenylethylamino)butyric acid in acetic acid (III), in pyridine (IV)

On the basis of the rotation value of the equilibrium system, the composition of the equilibrium mixture can be calculated if the rotation of the components of the system is known. The rotation of one of the components—the solid, ketimide form—is easily found by extrapolating to $t = 0$ the mutarotation curve in the corresponding solvent. Such extrapolation for the solution in 65% methanol gives the value $[M]_{578}^{\text{ketimide}} = 350^{\circ}$ (see Fig. 1). Similarly, from the mutarotation curve of the liquid form in the same solvent one can find the rotation of the liquid form at the initial moment, $[M]_{578}^{\text{liquid}} + 1600^{\circ}$. However, unlike the solid form, in the present case there is no certainty that the liquid form is an individual (enamine) form rather than a mixture of ketimide and enamine forms or a mixture of geometric isomers of the latter. If it is assumed that the liquid form as a whole is a definite geometric isomer of the enamine (most probably the cis form stabilized by an intramolecular hydrogen bond), then from the above rotation values the enamine content in 65% methanol at equilibrium is calculated to be 68%. This almost coincides with the percentage of enamine (69%) found by Seher (^{5}) for the methanolic solution of β-aminocrotonic ester.

The results presented show the promise of using the spectropolarimetric method for the study of tautomeric systems. Continuing investigations in this direction, we are, in particular, along with studying the behavior of amides and ketimide-enamine systems, extending this method also to keto-enol systems of the acetoacetic ester type.

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Note: Figure translations are in progress. See original paper for figures.