STUDY OF EXCHANGE PROCESSES IN 4,4,6-TRIMETHYL-2-PHENYLAMINO-4H-1,3-THIAZINE DERIVATIVES

A. P. Engoyan, Yu. N. Sheinker, T. F. Vlasova, L. A. Ignatova, and A. E. Gekhman

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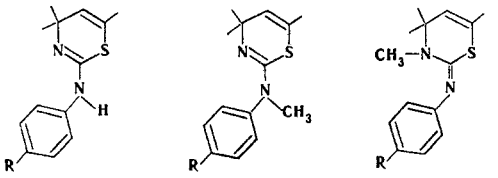
It is shown that, in contrast to model structures with fixed amine and imine forms, the form and position of some of the signals in the PMR spectra of 4,4,6-trimethyl-2-phenylamino-4H-1,3-thiazine derivatives depend on the temperature; this is associated with rotational isomerism about the nitrogen–heteroring bond, which is realized at a higher rate in the model derivative with an amine structure and is slowed down in the tautomeric derivatives owing to the formation of hydrogen bonds with solvent molecules (in deuteroacetone) or in dimeric associates (in deuterochloroform). According to data from the low-temperature spectra, the percentages of the syn and anti forms in acetone solutions are comparable. In chloroform solution, the equilibrium between the two rotational forms is shifted markedly to favor the anti isomer as the temperature is lowered because of the formation of cyclic dimeric structures.

The problem of amine–imine tautomerism in 2-phenylaminothiazines and thiazolines has been examined in a number of papers [1, 2]. In an investigation of 4,4,6-trimethyl-2-phenylamino-4H-1,3-thiazine derivatives we showed that these compounds exist primarily in the amino form. In particular, this conclusion was drawn on the basis of a comparison of the chemical shifts of the signals of the methyl groups of tautomeric derivative I and of a model compound (II) with an amine structure. It was also found that a



Ia-f IIa-f IIIa-f

I–III a R = H; b R = NO_2; c R = Br; d R = CH_3; e R = OCH_3; f R = OC_2H_5

certain broadening of the doublet signal of the ortho protons of the phenyl ring occurs in the PMR spectra of the NH derivative. In acetone solutions, the signal of the ortho protons of the benzene ring is broadened even more as the temperature is lowered, a stage involving coalescence occurs, and at temperatures below −70°C in the region of slow-exchange rates it is split into two doublets (Fig. 1a). Moreover, the intensity of the weak-field doublet is greater by a factor of two to three than the strong-field doublet. Nonequivalence of the meta protons of the phenyl ring also appears over the same temperature interval.

A pronounced dependence of the position and form of the signal on the temperature is also observed for the proton of the NH group. This signal does not appear at room temperature. As the temperature is lowered, a broad signal, which is split into two singlets at temperatures below − 70°, appears at 8.0-8.5

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute. M. V. Lomonosov Institute of Fine Chemical Technology, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 921-924, July, 1975. Original article submitted January 16, 1974.

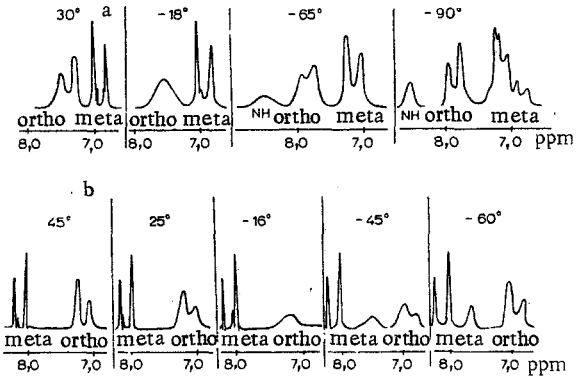


Fig. 1. Signals of the aromatic protons in the spectra of: a) 4,4,6-trimethyl-2-(p-methylphenylamino)-4H-1,3-thiazine in deuteroacetone; b) 4,4,6-trimethyl-2-(p-nitrophenylamino)-4H-1,3-thiazine in deuterochloroform.

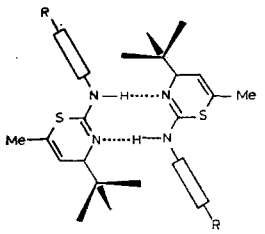


Fig. 2. Cyclic dimers in chloroform solutions.

ppm. The intensity of the weak-field signals is less than that of the strong-field signal by a factor of two to three. The chemical shifts of the signals of the other protons remain practically unchanged.

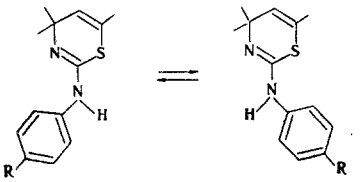
The changes in the form and position of the signals of the phenyl protons and the proton of the NH group of I as the temperature changes are evidently due to the presence in solution of at least two molecular states, between which exchange occurs. The presence of these states in the investigated case may be due to amine–imine tautomerism and retarded rotation of the phenyl ring about the N–Ph bond or of the heteroring about the C–N bond.

At room temperature, the signals of the 4-CH_3 groups of tautomeric derivative I and model amine structure II coincide. The conversion of tautomer I to the imine form should have been accompanied by a weak-field shift, inasmuch as the corresponding signals in the spectra of imine model III are found at weaker field (by 0.15-0.20 ppm) at all temperatures than in the spectra of II. Inasmuch as no change is observed in the position of the signal of the 4-CH_3 groups of the NH derivative as the temperature is lowered, the spectral changes cannot be explained by tautomerism.

Two doublets from the ortho protons of the benzene ring with identical intensities should have been observed in the case of retarded rotation of the phenyl ring about the N–Ph bond at the low temperatures to which slow exchange corresponds. In addition, two doublets with different intensities are present in the PMR spectra of acetone solutions of tautomeric derivatives I at low temperatures. This sort of pattern cannot be consistent with retarded rotation of the phenyl group.

The observed effects find their explanation under the assumption of retarded rotation of the heteroring about the C–N bond. Inasmuch as the C–N bond in the investigated compounds is partially an amide system, its order should be increased, and the increase in the barrier to transition between the two planar states is natural. In analogy with isomerism involving the C=N double bond, we will subsequently call these states syn and anti isomers.

The interconversion of the syn and anti forms at room temperature proceeds at a sufficiently high rate, as a consequence of which only one averaged doublet from the other protons of the benzene ring is observed. As the temperature is lowered, the rate of conversion from one form to the other is slowed down, and signals from the syn and anti isomers appear in the PMR spectra in the range of low exchange rates. In the anti structure the deshielding effect of the cyclic double bond on the ortho protons of the phenyl ring is weaker than in the syn form because of its remoteness. The more intense weak-field doublet can therefore be assigned to the syn isomer, and the less intense strong-field doublet can be assigned to the anti isomer. This assignment is in good agreement with the concept that the syn form is sterically more favorable, inasmuch as the steric interaction of the phenyl ring with the ring nitrogen atom is smaller in this structure than the interaction with the bulky sulfur atom in the anti isomer.



syn anti

The character of the change in the signal of the NH proton makes it possible to assume that at ordinary temperatures the signals of these protons are markedly broadened due to proton exchange and do not appear. As the temperature is lowered and exchange is slowed down, the signals of the protons of the NH groups of the two forms are seen sufficiently distinctly, and their intensity ratio corresponds to the intensity ratio of the doublets of the phenyl ring ortho protons.

It should be noted that the presence in the spectra of one doublet from the ortho protons of the phenyl ring in each of the isomers constitutes evidence that the aromatic ring is either perpendicular to the plane of the ring C=N double bond or, over the entire temperature range, accomplishes rapid (on the NMR time scale) transitions between the possible conformations, among which the planar conformations are less likely because of steric hindrance. On the basis of the literature data [3] it may be assumed that the second assumption is preferable.

There are certain differences in the spectra of chloroform solutions of the I derivatives. As the temperature is lowered, the broad doublet of the ortho protons of the benzene ring, after passing through a coalescence stage, is shifted to strong field and takes on the structure of a single doublet (Fig. 1b). The signal of the NH proton appears in the spectra as a broad singlet at 7.5-8.0 ppm only as the temperature is lowered. It then undergoes contraction and is shifted to weak field (8.0-8.5 ppm). A decrease in the temperature leads to a strong-field shift of 0.1-0.15 ppm of the singlet of the 4-CH_3 groups.

The changes in the chemical shifts of the signals in the spectra of I (in $CDCl_3$) become even more noticeable when they are compared with the model compounds. Thus the chemical shift of the two 4-CH_3 groups of amine model IId increases by 0.07 ppm as the temperature is lowered,* while the signal of these same groups of the NH derivative is shifted to strong field by 0.15 ppm. Consequently, the shift of the signal relative to the amine model will be 0.22 ppm.

Inasmuch as only one doublet is observed in the spectra of chloroform solutions for the ortho protons of the phenyl ring after the coalescence stage, whereas the signal of the proton of the NH group remains a singlet at all temperatures, the observed change in the form of the spectrum is apparently associated with a shift, under these conditions, of the equilibrium to favor only one of the forms. Judging from the strong-field shift of the signal of the ortho protons, this form is the anti structure. In addition, the chemical shift of the signal practically coincides with the chemical shift of the doublet of the ortho protons of the phenyl ring of the anti isomer observed in acetone solution. The shift of the conformational equilibrium in $CDCl_3$ to favor the anti form as the temperature is lowered is due, in our opinion, to association of the molecules due to the formation of hydrogen bonds.

In fact, two absorption bands of the N–H bond (3440 and 3380 cm^{-1}) are observed in the IR spectra of I, and the intensity of the low-frequency band increases as the concentration increases [3]. The change in the PMR spectra of the form and position of the signal of the NH proton with temperature also indicates the formation of strong hydrogen bonds. The appearance of both linear hydrogen bonds of the N...H–N type and of hydrogen bonds arising in cyclic dimeric structures [2] is possible in $CDCl_3$ solutions (Fig. 2). The strong-field shift of the signal of the 4-CH_3 groups constitutes evidence in favor of the latter, inasmuch as the indicated groups fall into the region of anisotropic shielding of the phenyl ring because of the nonplanar orientation of the phenyl rings in the cyclic dimers (Fig. 2). Concentration measurements confirm these conclusions. Thus, for example, when the concentration of p-methyl derivative Id in chloroform changes from 4 to 20% at −5°, the change in the chemical shift of the signal of the 4-CH_3 groups is 0.13 ppm and corresponds to the strong-field shift of the signal of these groups when a 4% solution is cooled from −5 to −45°. Thus a decrease in the temperature promotes an increase in the percentages of the cyclic dimers, and, consequently, conversion of the syn form to the anti form.

*The signals of all of the protons of the model compounds with amine and imine structures undergo a weak-field shift of 0.05-0.075 ppm as the temperature is lowered to −60°, and this is evidently associated with a change in the properties of the solutions.

Similar temperature and concentration measures were also made for solutions of the model compound pounds with an amine structure (II) in $CDCl_3$ and deuteroacetone. However, no change in the form and position of the signals of the ortho protons of the phenyl ring and the protons of the $N-CH_3$ group was observed over the entire temperature range. This is apparently due to the fact that the molecules of the amino model cannot form dimeric structures (in $CDCl_3$) or associates with the solvent (in acetone) through hydrogen bonds. For this reason, the syn–anti conversion in them is accomplished with a low energy barrier.

It follows from the data presented above that the dependence of the form and position of some of the signals on the temperature in the PMR spectra of the tautomeric derivatives is due to rotational isomerism in conjunction with intermolecular association processes.

LITERATURE CITED

1. J. Rabinowitz, Helv. Chim. Acta, 52, 255 (1969).
2. P. Sohar and L. Toldy, Acta Chim., Acad. Sci. Hung., 75, 99 (1973).
3. H. Kessler, Ber., 103, 973 (1970).