INVESTIGATION OF THE TAUTOMERISM OF 3-AMINO-2-ACETYL-2-CYCLOHEXENE-1-ONES BY THE NMR METHOD*

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Amino derivatives of 2-acetylcyclohexane-1,3-diones, which are ascribed the structures (I) and (II), have recently been attracting attention as interesting polyfunctional compounds, invested with rich synthetic possibilities. In addition, they are interesting from the theoretical standpoint, as vinylog amides, containing a supplementary keto function, which expands the chain of $p-\pi$ -conjugation. The indicated enaminodiketones can serve as objects for the clarification of a number of questions of tautomerism. Some of the questions have been considered for certain enaminodiketones of the series (I) described in the literature [2, 3]. However, up to this time there has been no systematic investigation of substances of this type, in view of their poor accessibility, especially vinylog amides of the series (II). Recently we developed a simple and extremely effective method of producing these compounds,



permitting the insertion of practically any amino function into the C_3 -position of the cyclohexane molecule [4, 5]. The possibility of the existence of such enaminodiketones in one or several tautomeric forms or an equilibrium mixture of them [Eq. (1)] prompted us to investigate these compounds by the NMR method



DISCUSSION OF RESULTS

It is quite evident that the theoretically possible tautomeric equilibrium described by Eq. (1) should be expected only for primary (II; $R_1 = R_2 = H$) and secondary (II; $R_1 = H$) vinylog amides. In full agreement with the structure under consideration, signals are observed in the PMR spectra of the tertiary enaminodiketones that we obtained (II; R_1 , $R_2 \neq H$), corresponding to the protons of all the structural fragments of these molecules in the expected regions, and the signals of olefin protons are absent.

The spectra of primary and secondary enaminodiketones (II) are characterized by the presence of at least one signal in a rather weak field, $\delta \sim 11-14$ ppm (Table 1), which served as the basis for concluding

* For a preliminary communication, see [1].

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d No.	R2	R3	R₄	Isotope of nitrogen	Solvent	Concentration, mole η_0	Chemical shift, ppm		Spin - spin inter- action constants, Hz			the H ¹ ,
Compoun							δ _H ′	^δ R ²	$J_{\mathrm{R}_2},\mathrm{H}^1$	J _{N15} , H1	JN15, R2	Width of signal of Hz
1	H	н	н	N ¹⁴ N ¹⁵ N ¹⁵	CDCl ₃ CDCl ₃ C ₆ H ₅ CN	8,0 3,3 3,1	11,12 10,87 10,80	7,77 7,45	6,0 6,0		90 —	8;16
2	н	CH₃	CH₃	N ^{'14} N ¹⁵ N ¹⁵ N ¹⁵	CDCl ₃ CDCl ₃ C ₆ H ₅ CN DMSO	7,8 5,5 5,0 3,1	11,15 10,97 10,30 10,77	7,50 7,57 7,60	6,0 6,0 5,5		91 92	8; 15
3 5 6 7 8 9 10 11	CH ₂ C ₆ H ₅ CH ₃ cH ₈ o-C ₆ H ₄ NH ₂ COCH ₃ COCH ₃ N (C ₆ H ₅) ₂ o-C ₆ H ₄ CH ₃ C ₃ H ₅	CH ₃ H CH ₃ CH ₃ H CH ₃ CH ₃ CH ₃ H	CH ₃ H CH ₃ CH ₃ H CH ₃ CH ₃ CH ₃ H	N 14 N 14 N 14 N 14 N 14 N 14 N 14 N 14	$\begin{array}{c} CDCl_3\\ CDCl_3\\ CDCl_3\\ CDCl_3\\ CCl_4\\ CCl_4\\ CDCl_3\\ CDCl_3\\ CDCl_3\\ CDCl_3\\ CDCl_3\\ CDCl_3\\ CDCl_3\\ Cdcl_5\\ C_6H_5CN\\ DMSO \end{array}$	8,0 6,4 6,5 3,7 7,3 6,8 4,1 4,6 3,2 3,0 3,1	11,80 12,15 12,41 12,85 13,35 13,42 13,75 13,90 13,78 13,68 13,88 13,92	4,50 3,01 3,02	6,0 4,5 5,0			10 10 16 6 10 8 5 8 10
12	C_6H_5	CH3	CH3	N ¹⁴ N ¹⁵ N ¹⁵	CDCl ₃ CDCl ₃ C ₆ H ₅ CN	4,2 4,7 4,3	14,03 13,86 14,03	5 3		85 87		7

TABLE 1. Parameters of the NMR Spectra of Enaminodiketones (IIa) at Room Temperature

that a definite tautomeric form exists. As has already been noted, the method that we found for synthesizing a variety of enamines (II) permitted an investigation of the compounds containing various amino groups, including those with the N¹⁵ isotope, which substantially facilitated the solution of the problem posed. As it follows from Table 1, which presents data for primary and secondary enaminoketones (II), the signals from the H¹ proton are situated in the region of δ 10.30-14.05 ppm; this indicates the existence

of a rather strong chelate type hydrogen bond $-OH^1 \dots O = C \le$, $-OH^1 \dots N = or > NH^1 \dots O = C \le$.

The results obtained are evidence that all the substances studied are characterized by the last of the bond types cited, in other words, the compounds exist primarily in the form (IIA). We arrived at this conclusion on the basis of the following experimental data.

1. In the spectra of enaminodiketones, the nitrogen atom of which is bonded directly to a methylene or methyl group (see Table 1, compounds 3-5 and Figs. 1 and 2), the signals of the corresponding protons represent a doublet with spin-spin interaction constant J_{CH_2,H^1} or J_{CH_3,H^1} , 4.5-6.0 Hz; the signal from H^1 is noticeably broadened, to 10-16 Hz. The presence of spin-spin coupling between the indicated protons was demonstrated by the method of double proton-proton resonance. As a result of irradiation with a supplementary field of the signal from the H^1 progon, "uncoupling" of the signals from the protons of the methylene and methyl groups at the nitrogen atom is observed; the doublets corresponding to these protons are converted to singlets.

2. For other secondary compounds, for example, anilides, as well as primary enaminoketones (II), in the spectra of which the signals of N-H are appreciably broadened, the localization of the H¹ proton at the nitrogen atom was demonstrated by replacement of the isotope N¹⁴ by N¹⁵ (compounds 1, 2, 11, 12 and Figs. 3 and 4). Such replacement leads to the appearance of the constant J_N^{15} , H¹ ~ 85-89 Hz in the NMR spectrum, rather large if we consider that their observable maximum values are 92-93 Hz [6].

These data, in conjunction with the results of a measurement of the relative integral intensities of the signals of H^1 , permit us to consider that in the enaminodiketones (II) discussed above, there is practically no contribution of the tautomeric structure (IIb). An analogous phenomenon was observed earlier for the anilide (I; $R_1 = H$; $R_2 = C_6H_5$; $R_3 = R_4 = CH_3$), although in other cases, depending on the nature of the substituents, vinylog amides can exist in the form of an equilibrium mixture of tautomers [3]. As for the remaining five secondary enaminodiketones cited in Table 1, they should also be ascribed the structure (IIA), since this agrees with the observed position and shape of the signal of H^1 . It should be mentioned here that in enaminodiketones (IIA), the chemical shift of H^1 depends substantially on the nature of the



ene-1-one (IIA; $R_2 = CH_3$; $R_3 = R_4 = H$).

substituents R_2 at the nitrogen atom, increasing (see Table 1) in the series: $H < CH_2C_6H_5 < CH_3 < o-C_6H_4$ $\cdot NH_2 < COCH_3 < N(C_6H_5)_2 < o-C_6H_4CH_3 \le C_6H_5$. An analogous sequence, which in a first approximation can probably be correlated with the inductive effect of the substituent, was noted recently for mercaptoaldimines of the thiophene and furan series [7].

From Table 1 it is evident that δ_{H^1} is practically independent of the nature of the solvent. Thus, in the case of the imine and anilide (compounds 2, 11) the replacement of CDCl₃ by dimethyl sulfoxide (DMSO) leads to an increase in δ_{H^1} by an average of ~0.25 ppm.

The broadening of the signal of H^1 noted above is due either to spin-spin interaction or to quadrupole relaxation of N^{14} nuclei. Broadening of the lines is removed by replacing N^{14} by N^{15} , or by irradiating the N^{14} nuclei with the resonance frequency ~4.333 MHz (see Fig. 2).

In the spectra of primary enaminodiketones (compounds 1 and 2), the two protons bonded to the nitrogen atom are characterized by different chemical shifts, and the signal from H^1 is situated an average of ~3.5 ppm in the weaker field direction. Such a shift is still another evidence in support of the existence of an intramolecular hydrogen bond, leading to the formation of a strong chelated ring. Interesting in this respect is the fact that the spin-spin interaction constant $J_N^{15}_{,H^1}$ in the compounds under consideration is 3-5 Hz lower than the constant $J_N^{15}_{,H^1}$. Just as we should have expected, the signs of these constants proved to be the same, which was established by the use of selective double resonance for the N¹⁵-imine (compound 2). In the case of irradiation of the weak field doublet in the quartet of the H¹ proton, uncoupling of the weak field doublet in the quadruplet from H is also observed.

For a number of enaminodiketones (II) studied, it was shown that the nature of the spectra varies substantially with the temperature. For example, heating solutions of N¹⁵-imines (compounds 1 and 2) in CDCl₃ and benzonitrile leads to broadening of the signal from H₁ and its fusion with the zero line at only 80°. It should be mentioned that the value of δ_{H^1} remains almost unchanged in this case. A similar phenomenon was observed earlier for mercaptoaldimines [7]. By analogy, the result obtained here can evidently be explained by the appearance of another tautomer, in this case (IIB), and by the establishment of equilibrium between it and the tautomer (IIA). When N¹⁵-anilides (compounds 11, 12) are heated in benzonitrile to 190°, the width of the signals from H¹ and the constants J_{N^{15},H^1} remain almost constant, but a shift of the signal of H¹ by ~0.6 ppm is observed. These data once again are evidence of substantial strength of the hydrogen bond in the chelated ring of enaminodiketones (IIA), also confirmed by the data of other physicochemical methods [5].







EXPERIMENTAL METHOD

The spectra of solutions of the enamines (II) were obtained on RS-60 [8] and "Varian DA-60" spectrometers with a working frequency of 60 MHz. Hexamethyldisiloxane was used as the internal standard; the chemical shifts are cited in parts per million (ppm) relative to tetramethylsilane ($\delta = 0$).

The synthesis of enaminodiketones (IIA) was published in our earlier works [4, 5]. To identify the substances described below we used thin-layer chromatography on an unfixed layer of Al_2O_3 (activity II).

<u>3-N¹⁵-Amino-2-acetyl-2-cyclohexene-1-one (IIA; $R_2 = R_3 = R_4 = H$)</u>. A solution of 340 mg 3-methoxy-2-acetyl-2-cyclohexene-1-one [9] in 80 ml of 0.03 M N¹⁵H₃ in C₆H₆ was left at room temperature for 1 h, then concentrated, and the precipitate formed crystallized from benzene. We obtained 230 mg (90%) of the N¹⁵-imine in the form of needles with mp 136-137° (subl.), giving no depression of the melting point in a mixed sample with the corresponding N¹⁴-imine and chromatographically identical with it.

 $3-N^{15}-Amino-2-acetyl-5,5-dimethyl-2-cyclohexene-1-one (IIA; R₂ = H; R₃ = R₄ = Me).$ Produced analogously with a yield of 88% from 2-acetyl-5,5-dimethyl-3-methoxy-2-cyclohexene-1-one [9] in the form of needles with mp 162-163° (from benzene); gives no depression of the melting point in a mixed sample with the corresponding N¹⁴-imine and identical with it chromatographically.

 $2-A \operatorname{cetyl-3-N^{15}-phenylamino-2-cyclohexene-1-one}$ (IIA; $R_2 = Ph$; $R_3 = R_4 = H$). A solution of 310 mg 3-methoxy-2-acetyl-2-cyclohexene-1-one [9] and 165 mg N¹⁵-aniline in 10 ml of benzene was left at room temperature for 1 h, then concentrated, and hexane added. We obtained 380 mg (92%) of the N¹⁵-anilide in the form of needles with mp 115-116°, giving no depression of the melting point in a mixed sample with the corresponding N¹⁴-anilide and identical with it chromatographically.

 $\frac{2-\text{Acetyl}-5,5-\text{dimethyl}-3-N^{15}-\text{phenylamino}-2-\text{cyclohexene}-1-\text{one (IIA; R}_2 = \text{Ph; R}_3 = \text{R}_4 = \text{Me})}{\text{uced analogously with a yield of 86\% from 2-acetyl}-5,5-\text{dimethyl}-3-\text{methoxy}-2-\text{cyclohexene}-1-\text{one [9] in the form of needles with mp 135-136° (subl.) (from a benzene-hexane mixture); gives no depression of the melting point in a mixed sample with the corresponding N¹⁴-anilide and identical with it chromatographically.$

CONCLUSIONS

1. According to the data of the NMR spectra, primary and secondary 3-amino-2-acetyl-2-cyclohexene-1-ones exist primarily in a tautomeric form, including a strong intramolecular hydrogen bond.

2. The chemical shifts of the proton of NH in the chelated ring depend substantially on the nature of the substituent at the nitrogen atom and depend little on the nature of the solvent.

3. In primary enaminodiketones, the chemical shifts of the two NH protons differ by ~3.5 ppm, while the spin-spin interaction constants J_N^{15} H differ by 3-5 Hz, and possess the same sign.

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