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AMINE—AMMONIUM SALT SYSTEMS IN THE INTERPRETATION OF PMR SPECTRA

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The stepwise protonation of amines can be utilized for the interpretation of the PMR spectra of conjugated pairs consisting of an amine and its salt. A linear dependence of the proton chemical shifts on the composition of the amine—salt system has been demonstrated in the example of 2a-methyl-4-keto-trans-decahydroquinoline, making it possible to determine the proton chemical shifts, which are hidden in one of the partners by other signals, by means of extrapolation. The chemical shifts of the protons nearest the nitrogen atom vary in the following order upon protonation: $\alpha\text{-}H_a^{tert} > \alpha\text{-}He^{tert}_e \approx \beta\text{-}H_a^{tert} > \beta\text{-}H_a^{sec} \approx \beta\text{-}H_e^{sec} \approx \beta\text{-}H^{pr}$.

In the interpretation of the PMR spectra of cyclic amines, especially in the presence of other functional groups and a large number of C—H protons, it is frequently difficult to identify not only the β (δ 1.2-1.7 ppm), but also the α protons (δ 2.4-2.8 ppm). In this case, the protonated bases, i.e., the ammonium salts (generally trideutero- or trifluoroacetates or hydrochlorides), provide significant support in this case. Owing to the significantly larger chemical shift of the protons adjacent to the ammonium group (3.1-4.0 ppm for α-H, 1.7-2.4 ppm for β-H) it is possible to identify the α-protons and sometimes the β-protons. Shift reagents can also be used for the interpretation of bases; however, when other acceptor centers, such as hydroxy or keto groups, are present in the molecule, the picture may become more complicated, rather than simplified, due to the simultaneous complexation at two centers.

In this communication we shall demonstrate the possibility of the use of ammonium salts for the interpretation of the PMR spectra of amines.

The exchange rate of the protons on the nitrogen atom in protic solvents such as water and ethanol is known to be very high on the NMR time scale [1]. Therefore, mixtures of amines and their corresponding salts produce an averaged spectrum with a linear dependence of the shift on the composition of the mixture. A monoacidic base and its salt should thus act toward each other as an ideal shift reagent, which acts only at the amino group. The stepwise protonation of an amine and the construction of shift—composition diagrams may thus make it possible to reliably follow the changes in the chemical shifts of the individual protons and to determine the chemical shifts of the protons which were not identified in the base or, respectively, in the salt.

In this report we shall demonstrate the application of the method of stepwise protonation in the example of 2a-methyl-4-keto-transdecahydroquinoline (α isomer, mp 63°C), whose structure was previously proved by chemical methods [2] (the trans configuration of the methyl group relative to C_8 was confirmed by x-ray diffraction analysis [3]).

The signals of the following protons were identified in the spectrum of a solution of the base 2a-methyl-4-keto-trans-decahydroquinoline in D_2O according to the nature of the splitting of the signals, as well as with the aid of double resonance. A doublet of the 2-CH_3 group with δ 1.34 ($^3J_{2\text{-}CH_3,2\text{-}He}$ = 7.0 Hz) is easily determined in the high-field part of the spectrum. The most low-field signal with δ 3.99, which is a quintet of doublets with spin—spin coupling constants equal to 7.0 and 2.0 Hz, is assigned to the 2-H_e proton. The doublets of doublets with δ 3.10 and 2.44, which are superimposed on the absorption of other protons, can be assigned to the 3-H_a and 3-H_e protons, since they have the same spin—spin coupling constant (13.0 Hz) and, as the double resonance shows, interact with one another and

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TABLE 1. Chemical Shifts and Spin–Spin Coupling Constants of Protons in the System Consisting of 2a-Methyl-4-keto-trans-decahydroquinoline and its Hydrochloride

Proton	Fraction of hydrochloride in mixture, %							$\Delta\delta = \delta_{salt} - \delta_{base}$, ppm
	0	10	20	40	70	90	100	
	δ, ppm							
2-H_e	3,99	4,04	4,05	4,18	4,33	4,11	4,50	0,51
3-H_a	3,10	3,13	3,16	3,20	3,31	3,36	3,38	0,28
3-H_e	2,44	2,48	2,51	2,55	2,69	2,73	2,75	0,31
9-H_a	2,91*			3,28	3,55	3,71	3,80	0,89
10-H_a	2,48*			2,68	2,84	2,94	2,98	0,50
2-CH_3	1,34	1,36	1,38	1,46	1,56	1,62	1,65	0,31
	J, Hz							
2-H_e, 2-CH_3	7,0	7,0	7,0	7,0	7,0	7,0	7,0	
2-H_e, 3-H_a	7,0	7,0	6,5	6,5	6,0	6,0	6,0	
2-H_e, 3-H_e	2,0	2,0	2,5	2,5	3,0	3,5	3,5	
3-H_a, 3-H_e	13,0	13,0	13,5	14,0	14,5	15,0	15,0	
9-H_a, 8-H_a	11,0*				11,0	11,0	11,0	
9-H_a, 10-H_a	11,0*				11,0	11,0	11,0	
9-H_a, 8-H_e	4,0*			4,0	4,0	4,0	4,0	
10-H_a, 5-H_e	3,0*			3,0	3,0	3,0	3,0	
10-H_a, 5-H_a	11,0*			11,0	11,0	11,0	11,0	

*Values of the chemical shifts and spin–spin coupling constants found by extrapolation.

with the 2-H_e proton. In the case of the former signal, the constant of the spin–spin interaction with the 2-H_e proton is equal to 7.0 Hz, and in the case of the latter signal, it is equal to 2.0 Hz. Since the $C_{(3)}$–$C_{(4)}$–$C_{(10)}$ and $C_{(2)}$–N–$C_{(9)}$ bond angles are significantly greater than 109° (the former is 120°, and the latter is 114° [3, 4]), the piperidine ring flattens, the H_e–$C_{(2)}$–$C_{(3)}$–H_a dihedral angle decreases, and the H_e–$C_{(2)}$–$C_{(3)}$–H_e angle increases. Therefore, the signal with the larger spin–spin coupling constant (δ 3.10, J = 7.0 Hz) may be assigned to the 3-H_a proton, and the signal with the smaller constant (δ 2.44, J = 2.0 Hz) may be assigned to the 3-H_e proton. The signals of the 9- and 10-H protons, which are superimposed on the signals of the 3-H_a and 3-H_e protons, could not be identified.

The signals of all the protons indicated (see Table 1), as well as of the 9-H_a and 10-H_a protons (δ 3.80 and 2.98, respectively), which have the form of triplets of doublets with ^3J = 11.0 Hz. Such a large constant corresponds to the a,a configuration of type 9- and 10-H protons and attests to the trans annelation of the rings in the hydrochloride of the amino ketone under investigation.

Mixtures containing successively increasing amounts of the hydrochloride (0, 10, 20, 40, 70, 90, 100%), which correspond to the stepwise protonation of the amine, were prepared from the base and the hydrochloride. The spectra obtained reflect the gradual transition from the base to the salt, the shifts of the signals of each proton being linearly dependent on the composition of the mixture. This makes it possible to determine the chemical shifts of the 9- and 10-H protons in the base by extrapolation δ 2.91 and 2.48 (these shifts are marked with asterisks in Table 1). Since the spin–spin coupling constants of the 9- and 10-H protons in the mixtures are not dependent on the composition of the mixture, it may be concluded that they are the same in the base and in the salt (see Table 1), and their values attest to the a,a configuration of these protons, and therefore, to the trans annelation of the rings in the amine.

Along with the rapid proton exchange at the nitrogen atom under the conditions for the recording of the spectra, there was also very slow isotopic exchange of the protons in the α position to the carbonyl group. The spectrum of the deuterated amine supported the validity of the assignment of the signals, especially of the 9- and 10-H protons [the signals of the 3-H_a, 3-H_e, and 10-H_a protons vanished, and the nature of the splitting of the 9-H (doublet of doublets) and 2-H (quadruplet) changed].

The method of stepwise protonation can be applied to any pair consisting of an amine and its salt and permits the more complete interpretation of the PMR spectrum of one of the components of the pair.

When the method of stepwise protonation is used, it should be kept in mind that simple averaging of the spectrum will occur only in cases in which the conformations of the base and the salt are identical. If the conformations of the base and the salts are different, the conformational changes will also be reflected in the averaging process.

In the case which we described, the conformations of the base and the salt are identical; therefore, the method employed permits the evaluation of the gradients of the changes in the chemical shifts of the signals of the protons located near the nitrogen atom. From Table 1 it is seen that the strongest change in the chemical shift $\Delta\delta$ is experienced by the 9-H_a proton ($\Delta\delta$ 0.89), which is followed by the 10-H_a and 2-H_e protons ($\Delta\delta$ 0.50-0.51) and they by the 3-H_a, 3-H_e, and 2-CH_3 protons ($\Delta\delta$ 0.28-0.31). It is not difficult to see that the axial α-proton located on the tertiary carbon atom undergoes the greatest shift upon protonation. The signals of the 2-H_e and 10-H_a protons undergo smaller changes of the chemical shift. The 3-H_a and 3-H_e protons have significantly smaller values of $\Delta\delta$. The protons of the 2-CH_3 group have the same change in the shift as the 3-H protons. Thus, according to the change in the chemical shift experienced upon protonation of the nitrogen atom, the protons closest to the nitrogen atom may be arranged in the following series: α-H_a^{tert} > α-H_e^{tert} ≈ β-H_a^{tert} > β-H_a^{sec} = β-H_e^{sec} = β-H^{pr}.

It is noteworthy that upon the transition from 2α-methyl-trans-decahydroquinoline hydrochloride to the base, the spin–spin coupling constants of the protons are basically maintained, with the exception of $^3J_{2e3e}$ (it changes from 3.5 to 2.0 Hz), $^3J_{3a2e}$ (it changes from 6.0 to 7.0 Hz), and $^2J_{3a3e}$ (it changes from 15.0 to 13.0 Hz). The changes in the first and second constants may be attributed to changes in the H_e—$C_{(2)}$—$C_{(3)}$—H_a and H_e—$C_{(2)}$—$C_{(3)}$—H_e dihedral angles due to the change in the endocyclic $C_{(2)}$—N—$C_{(9)}$ angle from 109° in the salt to ~ 114° in the base [4]; however, such a change in the endocyclic angles could hardly influence the exocyclic H—$C_{(3)}$—H angle. Therefore, it may be assumed that the constants of the interaction are also influenced by the spatial configuration of the protons relative to the orbitals of the free electron pair of the nitrogen atom and the π electrons of the carbonyl group [5].

EXPERIMENTAL

The PMR spectra were recorded on a BS-487 spectrometer (80 MHz). The solvent was D_2O, the concentration of the solutions was 10%, and the external reference was HMDS. The temperature was room temperature.

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