Russian Journal of General Chemistry, Vol. 67, No. 7, 1997, pp. 1082–1087. Translated from Zhurnal Obshchei Khimii, Vol. 67, No. 7, 1997, pp. 1150–1155.

Study of Acid–Base Interaction by Means of Low-Temperature NMR Spectra. Structure of Salicylic Acid Complexes

N. S. Golubev, S. N. Smirnov, P. Schah-Mohammedi, I. G. Shenderovich, G. S. Denisov, V. A. Gindin, and H. H. Limbach

Institute of Physics, St. Petersburg State University, St. Petersburg, Russia
Institute of Organic Chemistry, Independent University, Berlin, Germany

Received November 20, 1996

Abstract—^{1}H NMR spectra of CDF_3–CDF_2Cl (1 : 1) solutions containing partially deuterated (OH/OD) salicylic acid and 2,4,6-collidine enriched with ^{15}N have been obtained. At low temperature (100–120 K), resolved signals of bridging OH/NH protons are observed for all equilibrium forms of the complexes, and they retain structure due to spin–spin coupling with ^{15}N nucleus and also to partial deuteration. Examination of the spectra afforded data on the chemical structure of the 1 : 1, 1 : 2, and 2 : 1 complexes and on the localization of bridging protons therein. Deuterium substitution in one of the hydrogen bonds results in secondary isotope effects, which makes it possible to estimate the strength and sign of mutual influence of several hydrogen bonds in the conjugated system (cooperative and anticooperative effects).

An interaction between molecules of an acid (AH) and a base (B) in aprotic low-polar solvents usually results in formation of a number of H-bonded complexes (namely, molecular AH···B, zwitterionic $A^-\cdots HB^+$, and also complexes involving homo- and heteroconjugated ions of A^- $[BHB]^+$ or $[AHA]^-\cdots HB^+$ type) [1–5]. Along with acidity and basicity (ΔpK_a), the ability of the reacting molecules and products (ions) to form various-type hydrogen bonds [6, 7] and also mutual influence of hydrogen bonds (cooperative and anticooperative effects) decisively contribute to relative stability of these complexes. Complete description of acid–base equilibria in aprotic media requires using various spectroscopic methods. These usually include vibrational (IR and Raman [8–10]) and electronic (UV) spectroscopy [11, 12] and NMR on various nuclei [13–15]. An advantage of ^{1}H NMR spectroscopy consists in the high sensitivity of proton chemical shifts to formation and strength of hydrogen bonds, and also in that the signals are easy to assign. However, there is also a great drawback derived from the fact that, under usual conditions, the lifetimes of hydrogen bonds are short in the NMR time scale; as a result, proton signals of all complexes participating in the readily established equilibrium are averaged. This is also assisted by proton exchange, which is highly efficient in systems containing acids and bases.

In recent years the authors have offered and developed a technique for NMR studies in liquefied gases (Freon mixtures) as solvents, which makes it possible to obtain high-resolution spectra at 100–150 K under conditions of slow exchange and thus to shrply increase their information content [16–20]. The lifetimes of complexes with strong hydrogen bonds under these conditions are 10^{-1}–10 s; hence, the resulting spectra reflect an equilibrium composition of the solutions, signals of all complexes being resolved. This permits qualitative and quantitative analyses to be carried out readily. Using ^{1}H and ^{15}N spectra we studied interactions in one of the simplest acid–base systems pyridine-^{15}N–acetic acid in a CDF_3/CDF_2Cl mixture in the 100–130 K range [19, 20]. We found that complexes formed by a molecule of the base with one, two, and three acid molecules are in equilibrium, and the degree of proton transfer to the nitrogen atom, measured by the constant of scalar ^{1}H–^{15}N spin–spin coupling, the greater the more acid molecules are involved in complex formation. Proton signals of complexes of involved compositions in the spectra of solutions containing the acid, partly deuterated at the OH group, and pyridine were found to be additionally split due to secondary isotope effects. This means that hydrogen bonds in complexes with homoconjugated ions are not independent, and a small weakening of one of the hydrogen bonds caused by H/D replacement results in appreciable change in the strength of the other ones. The sign of the secondary isotope effect is determined by the direction of mutual influence of the hydrogen bonds (cooperative strengthening

1070-3632/97/6707-1082$18.00 © 1997 МАИК Наука/Interperiodica Publishing

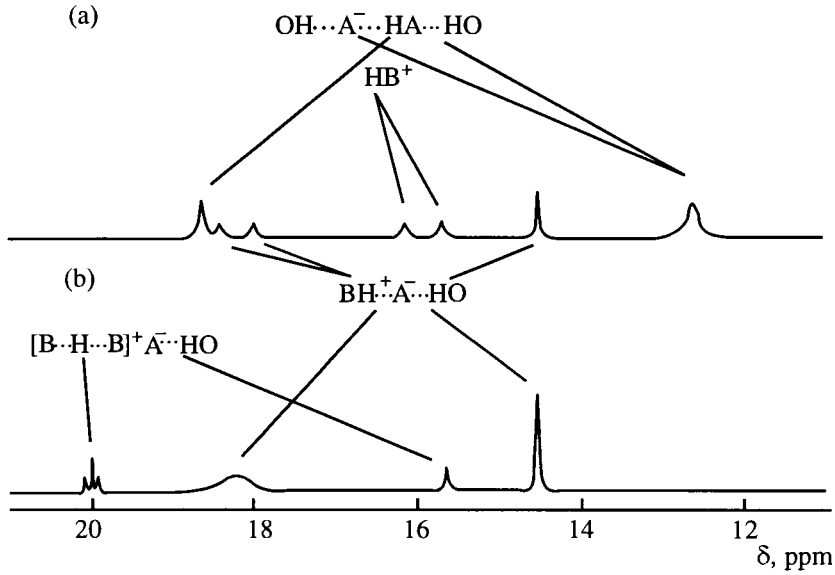
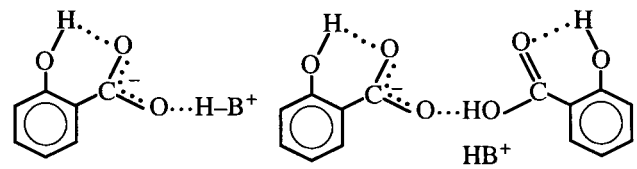


Fig. 1. ^{1}H NMR spectra [(a) 200 MHz, (b) 500 MHz] of solutions containing salicylic acid and collidine-^{15}N [(a) 0.035 and 0.020 M; (b) 0.020 and 0.030 M] in a CDF_3–CDF_2Cl mixture at 110 K.

or anticooperative weakening). This sign is an important characteristic of chains of interacting hydrogen bonds in a number of molecules of biological importance (for example, active centers of ferments), which seem to take part in their functioning [21, 22].

In this work we have studied the acid–base interaction in solutions containing salicylic acid and 2,4,6-trimethylpyridine-^{15}N (collidine) in a CDF_3–CDF_2Cl Freon mixture by low-temperature ^{1}H NMR spectroscopy. Because of the presence of intramolecular OH···O=C hydrogen bond in salicylic acid molecule, effects connected with formation of long chains of interacting hydrogen bonds would be expected in this acid–base system. Owing to this interaction, the signal of the phenol OH proton is an indicator of the position of the central proton in the formally symmetric bridge of the homoconjugated anion. Furthermore, we were able to isolate, as individial crystals, complexes comprising equlibrium mixtures in liquid solutions, and thus to perform their crystallographic analysis.

The low-field part (containing OH and NH proton signals) of the spectra of solutions containing collidine and salicylic acid, one or the other component being in excess, is presented in Fig. 1. In case of a 1.5-fold excess of the acid, the low-temperature (110 K) spectrum (Fig. 1a) consists of two doublets (δ 15.9 and 18.2 ppm, J_{NH} 88 Hz) and three singlets (δ 12.7, 14.6, and 18.7 ppm). At a precisely equimolar composition of the mixture (1 : 1), only two signals, a singlet at 14.6 ppm and a doublet at 18.2 ppm, remain in the spectrum. Clearly, they result from the OH and NH protons of a 1 : 1 ion pair (complex **I**), hence the other signals should be assigned to the 2 : 1 complex **II** with homoconjugated disalicylate anion.

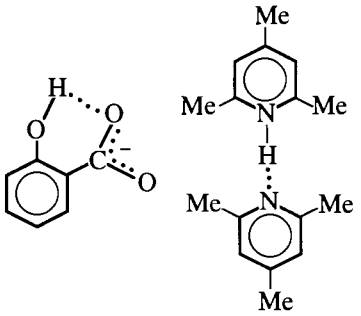


I **II**

Obviously, the singlet at 18.7 ppm belongs to the proton of the central very short hydrogen bridge, the singlet at 12.7 ppm to two phenolic OH protons, and the doublet at 15.9 ppm to the NH proton of the collidinium cation.

Another pattern is observed with solutions containing excess collidine (Fig. 1b). In addition to signals of the 1 : 1 zwitterionic complex (with excess base, the doublet at 18.2 ppm is unresolved), a triplet at 20.0 ppm (J_{NH} 40 Hz), and a singlet at 15.6 ppm are observed in the spectrum. The presence of the triplet means that the bridging proton interacts with two equivalent nitrogen-15 nuclei, and the signal should be assigned to the homoconjugated dicollidium cation $[B\cdots H\cdots B]^+$. Hence, the singlet at 15.6 ppm belongs to the phenolic OH proton of an almost free salicylate ion in complex **III**.

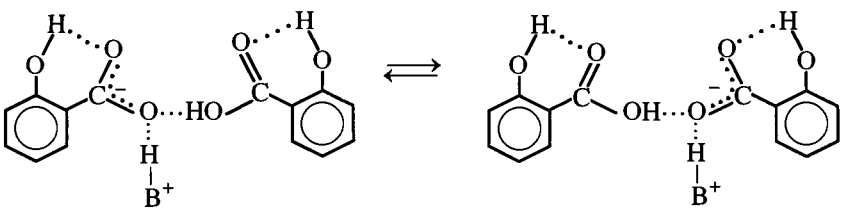
Now we consider localization of the proton in the central hydrogen bridges of the homoconjugated



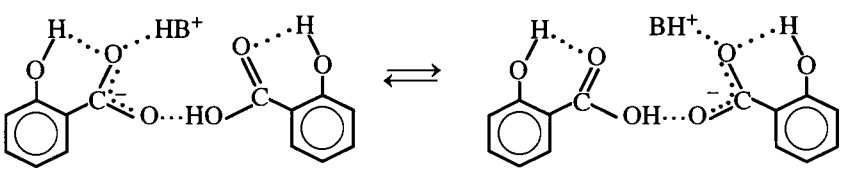
III

cation and anion. The presence of a narrow-band triplet at 20.0 ppm (J_{NH} 40 Hz) means that the proton in the homoconjugated cation is not localized near one of the nitrogen atoms (in this case, a doublet would be observed) or in a potential well bottomed in the center (in this case, the spin-spin coupling constant would be close to zero). The spectrum corresponds to a fast (in the NMR time scale) proton oscillation between two equivalent equilibrium positions.

Such a convenient characteristic of proton position as spin structure is lacking in the case of homoconjugated disalicylate anion; however, the signal of phenolic OH groups can serve as a kind of indicator. If the central proton is located asymmetrically, the two OH groups should be nonequivalent. In fact, the signal of side OH groups of the 2:1 complex in the spectra taken below 110 K (Figs. 2a–2d) at 500 MHz is split. This proves the asymmetric structure of the homoconjugated anion described by formula **II**; degenerate proton transfer in the complex with collidiniun (2:1) occurs at appeciable rate at 100 K. This process appears to be slowed down by an additional $NH^+\cdots O^-$ hydrogen bond with the counterion. Actually, in the spectrum of tetrabutylammonium hydrogen disalicylate in which such hydrogen bond is absent, the signal of side (phenolic) OH groups appears as a narrow singlet even at 100 K (Fig. 2e). Thus, in the case of collidinium disalicylate, reversible proton transfer occurs, which is controlled by the process of rupture–formation of hydrogen bond with the counterion, according to schemes (1) or (2):



(1)



(2)

Moreover, it is difficult to say whether proton oscillation takes place in an isolated homoconjugated ion. The structure of the latter may well be described by a symmetric formula with a central equilibrium proton position, while the hydrogen bond with the counterion creates effective asymmetry and two equivalent forms of the complex.

It is interesting to compare the proton chemical shifts in various complexes formed by salicylic acid with bases **I–III**. These shifts can be taken as an approximate measure of comparative strengths of hydrogen bonds in similar molecular fragments. Thus, it is evident that the strongest intramolecular hydrogen bond is formed in free salicylate anion; this bond is weakened by formation of an additional hydrogen bond, with a counterion (collidinium cation); the third hydrogen bond with an acid molecule in the 2:1 complex results in significant weakening the intramolecular bridge (δ 15.6, 14.5, and 12.7 ppm, respectively). The NH proton in collidinium ion forms an extremely strong hydrogen bond with collidine molecule and a less stong hydrogen bond with salicylate anion. Homoconjugation of the anion results in further weakening of the interionic hydrogen bond [δ(NH) 20.0, 18.2, and 15.9 ppm, respectively].

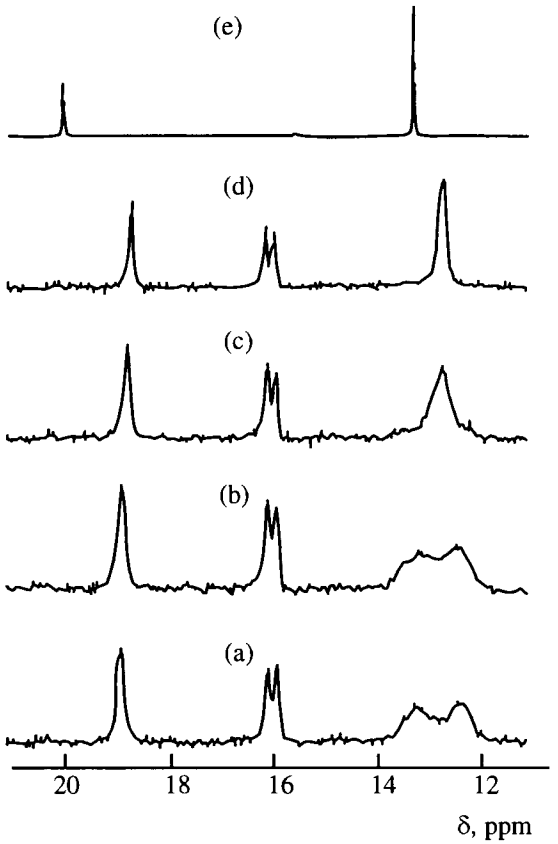
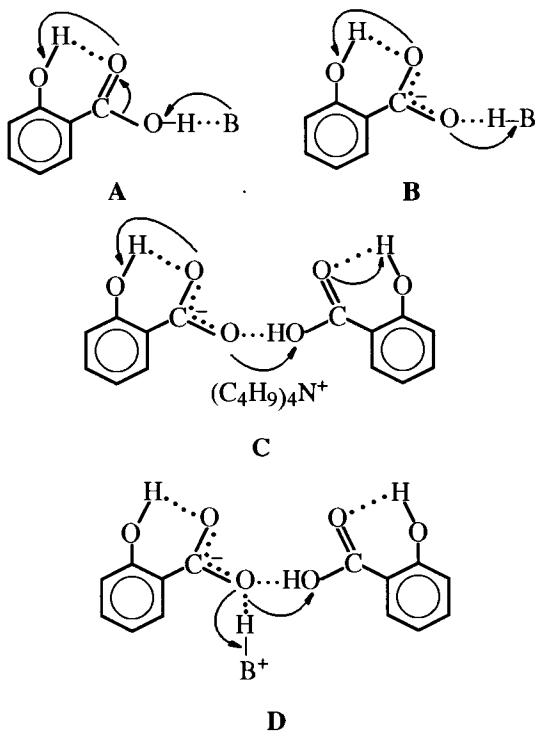


Fig. 2. ^{1}H NMR spectra (500 MHz) of solutions containing salicylic acid (0.02 M) and collidine (0.01 M). Temperature, K: (a) 100; (b) 103; (c) 111; (d) 116. (e) Spectrum (200 MHz) of a solution of tetrabutylamonium hydrogen disalicylate at 100 K.

Further information on the structure of complexes and mutual influence of hydrogen bonds therein was obtained from consideration of secondary isotope effects. The spectra of several various-type complexes of partly deuterated salicylic acid at 120 K are given in Fig. 3. The deuteration degrees for all groups containing OH (NH) protons were determined by integration of the corresponding signals with respect to the aromatic ring CH proton signals (the resulting values noticeably differ from each other for different hydrogen bonds even of the same complex in the same solution because of the so-called isotopic fractionation: stronger hydrogen bonds are depleted in deuterium owing to the lower zero vibration energy).

The spectrum in Fig. 3a belongs to a molecular complex (OH···AH···B) of salicylic acid with dimethyl sulfoxide. The signal with δ 11.8 ppm of phenolic OH group is split into a doublet; the relative intensity of the high-field component corresponds to the deuteration degree of the carboxylic OH group (35%). It should be assigned to a "half-deuterated" complex OH···AD···B. The direction of the isotope shift points to weakening of intramolecular hydrogen bond upon deuterium substitution of the carboxylic proton. The natural interpretation of this effect consists in the following. It has long been shown by X-ray and neutron diffractometry [23] that deuteration of an AH···B hydrogen bridge produces certain shortening of A–H covalent bonds and lengthening (weakening) of H···B hydrogen bonds. A theoretical explanation of the latter effect (the Ubbelohde effect) has been given in [34–27] (see also a qualitative consideration in [20]). (The case of central hydrogen bond in symmetric bridges of the $[F\cdots H\cdots F]^-$ type, whose hydrogen bond is somewhat shortened, seems to be an exception). The weakening of the intermolecular hydrogen bonds results in slight electron displacement (reduction in charge transfer from the oxygen atom of the base to the acid molecule) and, hence, in certain reduction in the charge density on the carboxylic group (scheme **A**), that manifests itself in weakening of the intramolecular hydrogen bond. Thus, the negative sign of the secondary isotope effect points to a cooperative nature of the interaction between two hydrogen bonds (mutual strengthening).

The spectrum of a zwitterionic 1 : 1 complex of partially deuterated salicylic acid with collidine is given in Fig. 3b. In this case, isotope splitting of both the OH and NH signals is observed, the positive sign of secondary isotope effect indicating an anticooperative interaction of two hydrogen bonds, which corre-



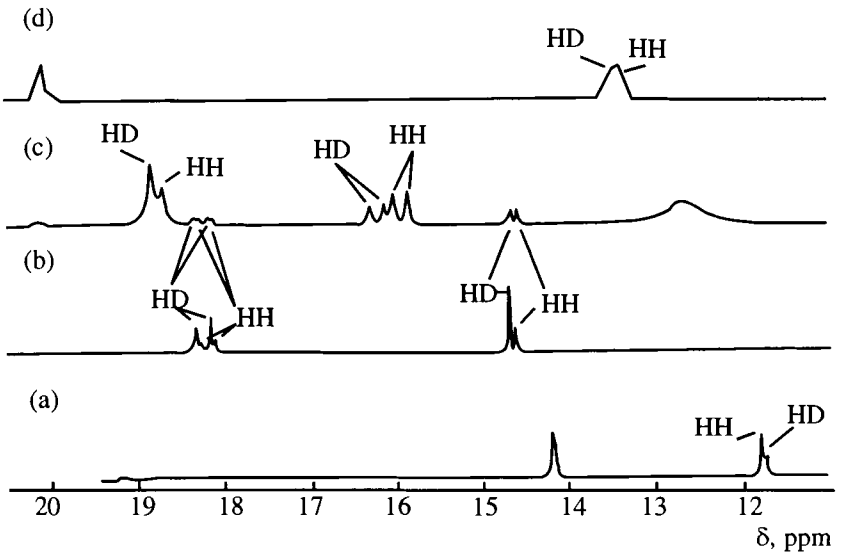


Fig. 3. ^{1}H NMR spectra [(a) and (d) 200 MHz; (b) and (c) 500 MHz] of solutions containing salicylic acid (0.02 M) with partially deuterated OH group and (a) dimethyl sulfoxide (0.03 M), (b) collidine (0.02 M); (c) collidine (0.01 M), (d) tetrabutylammonium salicylate (0.02 M).

sponds to the character of electronic displacements shown in scheme **B**. The two hydrogen bonds compete with each other; charge transfer from the carboxylic oxygen atom to the cation reduces the negative charge density on the second oxygen atom and, hence, results in weakening of the intramolecular hydrogen bond.

Fig. 3 shows the spectrum of a solution that presumably contains a complex of two molecules of partially deuterated salicylic acid with collidine. A very strong (+ 0.27 ppm) positive shift of the NH proton signal, caused by H–D substitution of the central (OH···O) proton, is observed. A somewhat weaker, but significant opposite effect (a shift of the signal of the central proton) is also observed upon NH/ND substitution. Though both possible structures of collidinium disalicylate should exhibit anticooperative effect, its very large value makes us to prefer the first formula with the central and interionic hydrogen bonds formed by the same oxygen atom. Unfortunately, the signal of phenolic protons is much broadened, on account of the fact that the rate of degenerate central proton transfer falls in the range of dynamic NMR; this renders impossible observation of both isotope splittings and opposite effects in this signal.

Finally, let us consider secondary isotope effects in a hydrogen salt (tetrabutylammonium hydrogen disalicylate, Fig. 3d). Only the high-field signal is split, the relative intensity of the narrow low-field component corresponding to the deuteration degree of phenolic OH groups (45%). Thus, this splitting is caused by anticooperative interaction of two intramolecular hydrogen bonds through the central hydrogen bridge. Deuterium substitution of the central proton (19%) results in appearance of a low-field wing in the phenolic OH signal, and the positive sign of isotope effect points to the fact that an isolated disalicylate ion, too, should be described by an asymmetric structure with bridging proton oscillation (immeasurably fast in the NMR time scale). In fact, had movement of this proton been described by a potential function with one central minimum, its D substitution would result in certain strengthening of hydrogen bonds (as is the case with the FHF^- ion) and, owing to anticooperative interaction, in a high-field shift of the phenolic proton signal. Thus, in principle, secondary isotope H/D effects can provide valuable structural information.

EXPERIMENTAL

2,4,6-Trimethylpyridine (collidine) enriched with ^{15}N isotope (96%) was synthesized from trimethylpyrilium tetrafluoroborate and ammonium-^{15}N chloride (96%, Deuterio, Germany). Pyrilium salt (8.0 g) was dissolved with heating to 30°C in 150 ml of water. A solution containing 3,5 g of $^{15}NH_4Cl$ and 4.0 g of NaOH in 40 ml of water was added to this solution stirred with a magnetic stirrer, after which the mixture was stirred for 0.5 h at 30°C and then for 0.5 h at 50°C, saturated with K_2CO_3, and extracted with ether (5 × 50 ml). The ether extract was dried with anhydrous K_2CO_3, the ether was distilled off,

and the residue was dissolved in 10% HCl. Tarry substance was filtered off, the filtrate, after addition of K_2CO_3, was extracted with ether, and dried. Distilling off the ether gave 4.2 g (yield 63% per initial ^{15}N) of labeled collidine (96% ^{15}N; purity ≤ 97%, according to NMR).

The CDF_3–CDF_2Cl Freon mixture was obtained by the procedure described in [19]. The solutions and samples were prepared using a high-vacuum line [19]. The spectra were recorded on Bruker AC-200 and AMX-500 instruments in special hermetic ampules with a Teflon valve, rated at 50 bar.

ACKNOWLEDGMENTS

This work was financially supported by the Volkswagen Stiftung Foundation (Hannover, Germany), the Russian Foundation for Basic Research (project no. 96-03-32846), and the Foundation of the State Comitee for Higher Education of the Russian Federation (grant no. 95-0-90-241).

REFERENCES

1. Gusakova, G.V., Denisov, G.S., and Smolyanskii, A.L., *Zh. Obshch. Khim.*, 1986, vol. 56, no. 3, pp. 600–607.
2. Gusakova, G.V., Denisov, G.S., and Smolyanskii, A.L., *Zh. Obshch. Khim.*, 1989, vol. 59, no. 10, pp. 2343–2348.
3. Barczynski, P., Dega-Szafran, Z., and Szafran, M., *J. Chem. Soc., Perkin Trans. 2*, 1987, no. 7, pp. 901–906.
4. Dega-Szafran, Z., Dulewicz, E., and Szafran, M., *J. Mol. Struct.*, 1988, vol. 177, pp. 317–325.
5. Ilczyshyn, M. and Ratajczak, H., *J. Mol. Liq.*, 1995, vol. 67, pp. 125–131.
6. Denisov, G.S., Mikheev, V.A., Sokornova, T.V., and Shraiber, V.M., *Khim. Fiz.*, 1984, vol. 3, no. 8, pp. 1109–1113.
7. Denisov, G.S., Mikheev, V.A., Sokornov, A.B., Sokornova, T.V., Terushkin, B.S., and Shraiber, V.M., *Zh. Prikl. Spektrosk.*, 1985, vol. 42, no. 1, pp. 66–72.
8. Maiorov, V.D., Kislina, I.S., Sysoeva, S.G., and Temkin, O.N., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1995, no. 9, pp. 1757–1463.
9. Schreiber, V.M., Kulbida, A.I., Rospenk, M., Sobczyk, L., Rabold, A., and Zundel, G., *J. Chem. Soc., Faraday Trans.*, 1996, vol. 92, no. 14, pp. 2555–2561.
10. Barnes, A.J., Larsson, E., and Nielsen, C.J., *J. Mol. Struct.*, 1994, vol. 322, nos. 1/3, pp. 165–174.
11. Borisenko, V.E., Denisov, G.S., Zavjalova, Y.A., and Furin, G.G., *J. Mol. Struct.*, 1994, vol. 322, nos. 1/3, pp. 151–156.
12. Schullery, S.E., Hemati, N., and Scott, R.M., *J. Solut. Chem.*, 1995, vol. 24, no. 8, pp. 771–793.
13. Bogachev, Yu.S., Serebryanskya, A.I., Khutsishvili, V.G., Kurenkova, V.M., and Shapet'ko, N.N., *Zh. Obshch. Khim.*, 1986, vol. 56, no. 4, pp. 909–915.
14. Zeegers–Huyskens, Th. and Sobczyk, L., *J. Mol. Liq.*, 1990, vol. 46, pp. 263–284.
15. Franchuk, I.F., *Ukr. Khim. Zh.*, 1986, vol. 52, no. 7, pp. 680–686.
16. Golubev, N.S., and Denisov, G.S., *J. Mol. Struct.*, 1992, vol. 270, pp. 263–276.
17. Golubev, N.S., and Denisov, G.S., *Dokl. Akad. Nauk SSSR*, 1981, vol. 258, no. 5, pp. 1142–1146.
18. Golubev, N.S., Denisov, G.S., Kuzina, L.A., and Smirnov, S.N., *Russ. J. Gen. Chem.*, 1994, vol. 64, no. 7, pp. 1048–1053.
19. Golubev, N.S., Smirnov, S.N., Gindin, V.A., Denisov, G.S., Benedict, H., and Limbach, H.H., *J. Am. Chem. Soc.*, 1994, vol. 116, no. 26, pp. 12055–12056.
20. Smirnov, S.N., Golubev, N.S., Denisov, G.S., Benedict, H., Schah-Mohammedi, P., and Limbach, H.H., *J. Am. Chem. Soc.*, 1996, vol. 118, no. 17, pp. 4094–4101.
21. Golubev, N.S., Gindin, V.A., Ligay, S.S., and Smirnov, S.N., *Biochemistry (Moscow)*, 1994, vol. 59, no. 5, pp. 447–452.
22. Denisov, G.S., Golubev, N.S., Gindin, V.A., Limbach, H.H., Ligay, S.S., and Smirnov, S.N., *J. Mol. Struct.*, 1994, vol. 322, pp. 83–91.
23. Ubbelohde, A.R. and Gallagher, K.G., *Acta Crystallogr.*, 1955, vol. 8, pp. 71–88.
24. Novak, A., *Structure and Bonding*, Dunitzet, J.D., Ed., Berlin: Springer, 1974, vol. 18, pp. 177–234.
25. Olovsson, I. and Jonsson, P.G., *The Hydrogen Bond*, Amsterdam: North Holland, 1976, pp. 393–469.
26. Jameson, C.J. and Osten, H.J., *Ann. Rep. NMR Spectrosc.*, 1986, vol. 17, pp. 1–118.
27. Jameson, C.J., *Isotopes in the Physical Sciences*, Amsterdam: North Holland, 1991, vol. 2, pp. 1–219.