Spectroscopic Studies of Solvent Effects on Intramolecular Hydrogen Bonding in *N*-Substituted Salicylamides

Michio KONDO

Central Research Laboratories, Sankyo Co., Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140

(Received July 6, 1978)

It has been found from absorption and emission spectra that the intramolecular hydrogen bonds between the phenolic hydroxyl and carbonyl group of *N*-methylsalicylamide and *N*-methyl-5-chlorosalicylamide survive in DMSO as well as in 1,2-dichloroethane, whereas those of *N,N*-dimethylsalicylamide and *N,N*-dimethyl-5-chlorosalicylamide are disrupted in DMSO. The solvent dependence of the ^1H and ^{13}C chemical shifts of these compounds are also well related to the intramolecular hydrogen bonding.

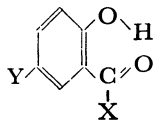
The first absorption bands of benzoic acid, benzamide, phenol, and salicylic acid are located at 280 (heptane),[1] 279 (solvent not identified),[2] 278 (hexane),[3] and 303 nm (0.1 M $HClO_4$),[4] respectively. The red shift of the first band of salicylic acid, compared with those of the other three compounds, have been ascribed to the intramolecular hydrogen bonding between the phenolic hydroxyl and carbonyl groups.

In salicylamide and *N*-methylsalicylamide, the first absorption bands are located very close to that of salicylic acid, suggesting a planar structure involving intramolecular hydrogen bonds as in salicylic acid molecules. In the case of *N,N*-dimethylsalicylamide, on the other hand, steric interaction between the ring proton-6 and the N–CH_3 group distorts the planar structure.

DMSO is known as a powerful solvent capable of forming intermolecular hydrogen bonds with various polar groups of solute molecules. An almost exclusive intermolecular hydrogen bond between the phenolic hydroxyl and DMSO molecules has been assumed for a number of *o*-substituted phenols.[5]

It is well established that a molecule having intramolecular hydrogen bonds, such as methyl salicylate[6] or *N*-methylsalicylamide,[7] undergo the so-called proton transfer in the excited singlet state, resulting in a significantly red-shifted emission band.

These observations suggest that the absorption and emission spectra of salicylamides are dependent upon the solvent wherein the intramolecular hydrogen bond is replaced by intermolecular hydrogen bonds with solvent molecules or not. In this paper, the spectroscopic behavior of *N*-methylsalicylamide (**1**), *N,N*-dimethylsalicylamide (**2**) and the corresponding amides of 5-chlorosalicylic acid (**3** and **4**) will be reported in the binary solvent system of 1,2-dichloroethane (DCE) and DMSO. The ^1H and ^{13}C NMR spectral changes of these compounds, upon changing the solvent from $CDCl_3$ to DMSO, will also be described.



	X=NHCH$_3$	N(CH$_3$)$_2$
Y=H	**1**	**2**
Cl	**3**	**4**

Experimental

N-methyl- and *N,N*-dimethylsalicylamide were prepared by the condensation of methyl salicylate with the appropriate amine in methanol. 5-Chlorosalicylamides were also prepared in a similar way. The absorption and emission spectra were recorded on a Hitachi spectrophotometer, Model 356, and a Hitachi fluorescence spectrophotometer, Model MPF-2, respectively. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100A-15 spectrometer at room temperature. The sample concentrations were 2% for ^1H NMR and 5—10% w/v for ^{13}C NMR measurements, unless otherwise noted. The ^{13}C NMR spectra were recorded at FT mode operation.

Results and Discussion

Absorption Spectra. In Fig. 1 are shown the absorption spectra of **1** and **2** in the binary solvent system of DCE and DMSO. The first absorption band of **2** in DCE has a peak at 297 nm and comparison of this value with that for phenol and salicylic acid, suggests the existence of intramolecular hydrogen bonds. With increase in DMSO content, this band shows a progressive decrease in intensity accompanied by the appearance of a new band at 280 nm, an isosbestic point being clearly seen at 285 nm. This observation suggests the existence of an equilibrium between two molecular species in solution. Therefore, the new absorp-

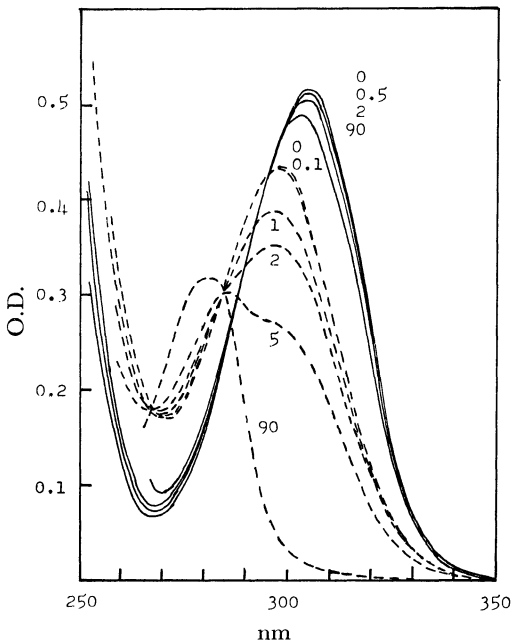


Fig. 1. The absorption spectra of **1** (——; 1.1×10^{-4} M) and **2** (----; 1.1×10^{-4} M) in binary solvent system of DCE and DMSO. The numbers given on the curves indicate the contant of DMSO (% v/v).

ion band may reasonably be ascribed to molecules of which the intramolecular hydrogen bond is replaced by intermolecular hydrogen bonds with DMSO molecules. As anticipated the absorption spectrum of the methyl ether of **2** did not show any variation with the change in solvent composition.

A DCE solution of **1** shows the first absorption band at 304.5 nm, suggesting intramolecular hydrogen bonding. Addition of DMSO to this solution caused no appreciable change in both the position and intensity of this band. Even in a solution composed of 90% DMSO, the absorption maximum of **1** was located at 302 nm, with a trivial decrease in absorbance. The absorption spectrum of the methyl ether of **1** was almost independent of solvent composition and the first absorption band was located at 287 nm, much lower than that of **1** in 90% DMSO and higher by about 10 nm than that of benzamide. It may be concluded from these observations that the intramolecular hydrogen bond in **2** is almost disrupted in DMSO but not in **1**.

Similar behavior was observed for **3** and **4** in the same binary solvent system.

Emission Spectra. In DCE solution, the emission bands of **1**, **2**, **3**, and **4** are located at about 440, 460, 450, and 465 nm respectively. The large Stokes' shifts may be ascribed to the intramolecular proton transfer in the lowest excited state— often observed for many compounds having intramolecular hydrogen bonds.[6-8]

In 90% DMSO solution, **1** and **3** exhibited emission spectra similar to those in DCE solution, both in peak positions (429, 436 nm) and intensities. This similarity suggests that strong intramolecular interactions between the two substituents of **1** and **3** survive in the lowest excited singlet state in DMSO as well as in DCE and that intramolecular proton transfer takes place. The emission spectra of **2** and **4** in 90% DMSO solution were located at 348 and 400 nm, respectively and these large blue shifts suggest species without intramolecular hydrogen bonding between the phenolic OH and the carbonyl oxygen.

^1H NMR Spectra. The ^1H NMR spectral measurements were conducted on **3** and **4** because of easier analysis of the ring proton signals. The results are summarized in Table 1.

The phenolic hydroxyl proton of **3** appeared as a sharp signal at about the same field in $CDCl_3$ and DMSO (δ 12.11 and 12.68, respectively), much lower than the fields where **4** resonates, implying that the intramolecular hydrogen bond of **3** survives even in DMSO. The phenolic OH proton of **4** dissolved in $CDCl_3$ was observed as a very broad signal at about δ 9.6, indicating that the intramolecular hydrogen bond in **4** is much weaker than that in **3**. The broadness of this signal may be ascribed to the average of two molecular conformations, one with intramolecular hydrogen bonds and the other without, on the NMR time scale. Conversely in DMSO, the phenolic OH proton resonates at δ 8.8 as a broad signal. It can be said therefore that intermolecular hydrogen bonds between the phenolic OH of **4** and DMSO molecules exist exclusively.

Table 1. ^1H CHEMICAL SHIFTS IN ppm DOWNFIELD FROM TMS

Compd	Solvent	OH	NH	NCH_3	H-3	H-4	H-6
3	$CDCl_3$	12.11[s]	6.24[b]	3.02	*ca* 6.9	7.33	7.26
	DMSO	12.68[s]	8.95[b]	2.83	6.92	7.40	7.89
4	$CDCl_3$	9.6[b]	—	2.74	6.86	7.28	7.79
	DMSO	8.8[b]	—	2.59	6.67	7.17	7.63

s: Sharp. b: Broad.

The $N-CH_3$ signal for **4** was observed as a singlet in both solvents, $CDCl_3$ and DMSO. Hirota *et al.*[9] observed a singlet signal for the $N-CH_3$ groups of **2** in CD_2Cl_2 at room temperature but at low temperature discovered two discrete signals. The signal coalescence at room temperature was ascribed to the rapid rotation, on the NMR time scale, of the $N(CH_3)_2$ group around the amide bond, CO–N. From the MO calculation the bond, CO–N, is expected to have a reduced double bond character owing to the intramolecular hydrogen bonding of the carbonyl group with the phenolic OH group.[9] In DMSO the intramolecular hydrogen bond of **2** and **4** are considered to be disrupted from the UV spectroscopic point of view. Therefore, in terms of ^1H NMR spectroscopy it is expected that **2** and **4** dissolved in DMSO are very similar to *N,N*-dimethylbenzamide (**5**). It has been reported for **5** that $N-CH_3$ is a broad singlet at room temperature, when dissolved in $CDCl_3$.[10] However, two discrete signals were observed for an aqueous solution of **5**.[11] The methyl ether of **2**, the UV spectrum of which is very similar to that of **2** in DMSO, showed two discrete signals for the two $N-CH_3$ groups in both solvents, $CDCl_3$ and DMSO, at room temperature. This indicates that the intramolecular interaction of the phenolic OH with the $CON(CH_3)_2$ group in **2**

Table 2. ^{13}C CHEMICAL SHIFTS IN ppm DOWNFIELD FROM TMS

Carbon	**1**		**2**		**3**		**4**	
	$CDCl_3$	DMSO	$CDCl_3$[a]	DMSO	$CDCl_3$[a]	DMSO	$CDCl_3$[a]	DMSO
C-1	114.6	115.2	117.3	124.4	115.3	116.6	118.5	126.3
C-2	161.8	160.4	159.2	153.2	160.1	158.6	157.7	152.1
C-3	118.8	117.5	118.0	115.6	120.2	119.3	119.4	117.3
C-4	134.5	133.6	132.5	129.9	134.0	133.1	132.4	129.5
C-5	119.0	118.5	118.3	118.9	123.3	122.2	123.2	122.5
C-6	125.7	127.5	128.6	127.8	124.9	127.0	128.0	127.3
C=O	171.1	169.8	171.9	168.6	169.5	168.1	170.6	166.9
$N-CH_3$	26.5	26.0	38.2	b)	26.5	26.0	38.4	b)

a) Saturated solution. b) A very broad signal.

and **4** can not be neglected even in DMSO.

When the solvent was changed from $CDCl_3$ to DMSO the ring proton-6 of **3** shifted downfield, whereas that of **4** shifted a little upfield. With the same solvent change the amide proton signal of **3** shifted downfield as much as 2.71 ppm, while the phenolic OH signal shifted downfield much less. This indicates that strong intermolecular interactions of this compound with DMSO molecules occur through the amide proton. This intermolecular hydrogen bonding makes the ring proton-6 subject to the electric field due to the polar S–O group of the intermolecularly hydrogen bonded DMSO molecule, resulting in the lower field resonance of this proton. For the ring proton-6 in **4**, this type of deshielding may be negligible in DMSO. Possible internal rotation around the C_{ring}–CO bond, induced by the disruption of the intramolecular hydrogen bond, may be responsible for the slight upfield shift of proton-6.

^{13}C NMR Spectra. The ^{13}C chemical shifts of the four compounds are given in Table 2. Signal assignments for **3** and **4** could be readily made on the basis of the chemical shifts given for methyl salicylate in $CDCl_3$,[12] the chlorine-substituent constant, and the relative intensities. However, identification of the C-3 and C-5 signals of **1** and **2** is not so simple because of the close proximity. Fortunately, the C-3 signal showed additional fine splitting due to long range spin coupling with the OH proton when it was fixed by the intramolecular hydrogen bond with the carbonyl oxygen. This identified the C-3 signal in $CDCl_3$. Recording several ^{13}C spectra of **2** in mixed solvent systems of $CDCl_3$ and DMSO with varied compositions was applied to correlate the two sets of signals of C-3 and C-5 in $CDCl_3$ and DMSO solutions.

The pronounced DMSO-induced shifts (Table 3) were observed for C-1, C-2, and C–O in **2** and **4**; the carbonyl carbon and C-2 shifted upfield while the C-1 shifted downfield. These shifts can not be attributed to the usual solvent effects and since these carbons are closely related to the intramolecular hydrogen bond, it is reasonable to attribute the observed shifts to the replacement of intramolecular hydrogen bonds by the formation of intermolecular hydrogen bonds with DMSO molecules. It is reasonable to explain the observed upfield shifts of the carbonyl carbons in terms of the disruption of the intramolecular hydrogen bonds, since the carbonyl carbon of salicylaldehyde was shown to resonate at lower fields by 3.6 and 3.0 ppm than those of the *m*- and *p*-isomers, respectively.[13] Similarly, the upfield shifts of the carbonyl carbon, upon changing from acid to ester, has been ascribed to impossibility of hydrogen bond formation in the latter.[14]

Table 3. DMSO-induced shifts ($\delta_{DMSO} - \delta_{CDCl_3}$)

Carbon	**1**	**2**	**3**	**4**
C-1	0.6	7.1	1.3	7.8
C-2	−1.4	−6.0	−1.5	−5.6
C-3	−1.3	−2.4	−0.9	−2.1
C-4	−0.9	−2.6	−0.9	−2.9
C-5	−0.5	0.6	−1.1	−0.7
C-6	1.8	−0.8	2.1	−0.7
C=O	−1.3	−3.3	−1.4	−3.7
N–CH_3	−0.5	—	−0.5	—

Secondary effects, such as changes in the degree of conjugation between the ring and the substituents induced by the disruption of the intramolecular hydrogen bond, may be responsible for the observed shifts for the other carbons.

References

1) J. Tanaka, *Bull. Chem. Soc. Jpn.*, **36**, 833 (1963).
2) C. J. Seliskar, O. S. Khalil, and S. P. McGlynn, "Excited States," ed by E. C. Lim, Academic Press, New York and London (1974), Vol. 1, p. 278.
3) M. Ito, *J. Mol. Spectrosc.*, **4A**, 125 (1960).
4) S. G. Schulman and H. Gershon, *J. Phys. Chem.*, **72**, 3297 (1968).
5) M. T. Tribble and J. G. Traynham, *J. Am. Chem. Soc.*, **91**, 379 (1969).
6) A. Weller, *Z. Elektrochem.*, **60**, 1144 (1956).
7) M. Kondo, *Bull. Chem. Soc. Jpn.*, **49**, 2679 (1976).
8) H. Shizuka, K. Matsui, T. Okamura, and I. Tanaka, *J. Phys. Chem.*, **79**, 2731 (1975).
9) M. Hirota and K. Todokoro, *Chem. Lett.*, **1974**, 777.
10) P. K. Korver, K. Spaargaren, P. J. van der Haak, and Th. J. de Boer, *Org. Magn. Reson.*, **2**, 295 (1970).
11) M. Nakano and T. Higuchi, *J. Pharm. Sci.*, **57**, 183 (1968).
12) Y. Takeuchi and H. Ishizuka, "C-13 NMR, Kiso to Ōyō," ed by S. Fujiwara, Kodansha, Tokyo (1976), p. 278.
13) A. Mathias, *Tetrahedron* **22**, 217 (1966).
14) D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **45**, 225 (1967).