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Studies on the Conformations of Antimicrobial Salicylanilide Derivatives by Spectroscopy

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Conformations of variously substituted salicylanilides were determined by NMR spectroscopy. The salicylanilide molecules are fairly rigid, taking either the OH···O=C hydrogen bonded (I) or the NH···O hydrogen bonded (II) conformation. The preference between the two intramolecularly hydrogen bonded conformations is affected by the 3- and/or 2′(6′)-substitutent(s). In general, conformation (I) exists overwhelmingly, while conformation (II) becomes predominant in 3-chloro or 2-*O*-acetylated salicylanilide in inert solvents. These two intramolecular hydrogen bonds were weakened or destroyed to a great extent in dimethyl sulfoxide.

Our previous studies on the physicochemical properties (pK_a, P, σ, etc.) of pharmaco-active salicylanilide derivatives showed that both the hydrophobicity and the presence of electron-withdrawing substitutents on the rings are requisite to antibacterial activity.[1] We also studied the intramolecular hydrogen bonding of the salicylanilides by infrared spectroscopy, and reported that the changes in structure and conformation of the salicyloyl moiety could be correlated with the physical and biological properties.[2]

This study showed that the unsubstituted salicylanilide **1** forms a six-membered conjugate chelate ring by very strong OH···O=C hydrogen bonding, and takes a fairly rigid planar *s-trans*-conformation (I) about the amide C–N bond. This hydrogen bond occurs between the OH and O=C groups on the same ring ("intra-ring" hydrogen bond) and strengthens the coplanarity of the aryl and carbonyl group. Almost all substituted derivatives without a 3- or 2′(6′)-substituent were suspected to preferably take a similar conformation (I) based on infrared spectroscopy. 3-Chloro-substituted salicylanilide, however, has been shown to take two conformations; the more predominant one is the OH···O=C hydrogen-bonded conformation (I), and the other is the NH···OH hydrogen-bonded conformation (II) from the two amide $\nu_{C=O}$ band in their infrared spectra (Chart 1).[3] In the case of conformation (II), the hydrogen bond persists between the NH donor and RO (R = H, Me,Ac, etc.) on different rings ("inter-ring" hydrogen bond) and maintains the coplanarity of the whole molecule.

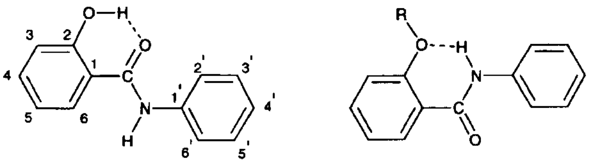


Chart 1.

In this connection, it is interesting to examine how the two hydrogen-bonded conformations of these anilides are affected by the steric and hydrogen-bonding effects caused by the *ortho*-substituents on either or both of anilino or/and aroyl rings.

Infrared spectroscopy is very useful to clarify the conformation about the amide group and the hydrogen bond involved.[4] NH stretching bands of a secondary amide is particularly useful in determining the discrimination of the *cis* and *trans* conformers.[5,6] However, it is rather inappropriate for an extensive study on the conformation of other parts of the molecule and the solvent effect. NMR spectroscopy is another effective tool for determining the geometry of amide molecules.[7,8] We thus employed NMR spectroscopy in order to further confirm the conformational preferences of these anilides in solvents having different influences on the hydrogen-bonding properties.

Experimental

The preparations of the materials were reported elsewhere.[9] ^{1}H Chemical shifts and NOE spectra were obtained using a JEOL EX-270 spectrometer in DMSO-d_6 and $CDCl_3$ at 25 °C. In order to prevent the effect of associated species, the concentrations of the solutions were maintained at ca. 0.05 mol dm^{-3} or less. The absence of associated species was shown by a dilution experiment. The shift of δ_{NH} from 0.2 M (saturated, 1 M = 1 mol dm^{-3}) to 5×10^{-4} is only 0.04 ppm in contrast to a rather large downfield shift caused by the addition of hydrogen acceptor solvents. Its chemical shift is in the range of normal unassociated anilides. The NOE enhancement values given in the tables are the averages of three measurements under different conditions. The accumulation times, irradiation power (db), and irradiation time (s) are 64, 390, and 8 for the first run; 64, 385, and 7 for the second run; and 32, 380, and 8 for the third run, respectively. ^{15}N and ^{13}C Spectra were obtained using a JEOL FX-90Q spectrometer in DMSO-d_6 at ca. 0.5 mol dm^{-3} at room temperature. Infrared spectra were obtained in a CCl_4 solution using a Perkin Elmer Spectrum 2000 infrared spectrophotometer. The concentration of the sample solution was kept below 3×10^{-3} mol dm^{-3}.

Results and Discussion

The chemical shifts and NOE enhancements of *o*-substituted benzanilides are given in Table 1, and various salicylanilides and their 2-*O*-acetyl derivatives are given in Table 2. Anilino ^{15}N and carbonyl ^{13}C chemical shifts generally fall within the normal range of benzanilides. The NOE enhancement of H_X induced by the irradiation of the signal of the nucleus S will be denoted f_{HX}(S); i.e., f_{H6}(NH) implies the observed NOE of H_6 by irradiating the NH proton signal. Infrared spectra of some of salicylanilide derivatives are given in Table 3.

Planar Conformations and Solvent Effect of Salicylanilides. The f_{H6}(NH)of the parent unsubstituted salicylanilide **1** is about twice or three-times stronger than *ortho*-unsubstituted benzanilide **6** or those for *ortho*-substituted benzanilides **2**—**5**. The f_{H3}(OH) is very weak with all salicylanilides measured in $CDCl_3$. The amide moiety of anilide usually takes a planar *s-trans* conformation; the salicylamide group (o-OHC_6H_4CONH) is assumed to be fixed rigidly to the coplanar conformation by the strong intramolecular hydrogen bond between OH and O=C groups, in which OH and C_3 lie *antiperiplanar* to each other and the NH proton is close to H_6, in agreement with the above-mentioned NOE results. As expected, the OH signal of salicylanilide **1** appears to be very low (about 12 ppm) compared with *p*-OH substituted benzanilide (5.17 ppm) in $CDCl_3$. The steric effect by the *ortho*-substituent to the amide carbonyl group causes a considerable torsion around the C_{Ar}–$C_{carbonyl}$ bond, which hinders the coplanarity of the whole molecule. In turn, it strengthens the amide resonance and increases the positive charge of the amide nitrogen atom, causing a down-field shift of the ^{15}N chemical shift as a result. This phenomenon does not occur with salicylanilides, because of a mesomeric effect due to the OH···O=C intramolecular hydrogen bond, which weakens the amide resonance by its cross-conjugation effect.[10] In practice, *o*-substituted benzanilide **2**—**5** have ^{15}N signals at a significantly lower field; however, in salicylanilide **1** it is higher than in unsubstituted benzanilide **6**.

The NH absorption band of salicylanilide **1** appears at a high frequency (3446 cm^{-1}) and within the range of the free (non-hydrogen-bonded) NH band of a normal secondary amide of the *s-trans* conformation. Since the OH···O=C hydrogen-bonded conformation (I) in salicylanilide prevents NH···OH intramolecular hydrogen bonding, the NH proton chemical shift of **1** is normal. Those facts revealed that the OH···O=C hydrogen-bonded conformation (I) exists overwhelmingly in $CDCl_3$.

On the other hand, the intramolecular and inter-ring hydrogen bonds between NH and OR (R: H, CH_3, $COCH_3$), as illustrated by (II), can keep the most stable *s-trans* conformation of the amide CONH group. Even in this conformation, the aryl and the carbonyl group in the aroyl moiety are expected to be nearly coplanar if the intramolecular hydrogen bond is strong enough. The NH absorption band of *o*-methoxybenzanilide **3** appears at a considerably low frequency (3374 cm^{-1}), which suggests the presence of the NH···O-(CH_3) intramolecular hydrogen-bonded conformation (II). The participation of the NH group in hydrogen bonding was supported by its low-field ^{1}H signal (δ = 9.80). The fact that the f_{H6}(NH) is very weak and the observed f_{OCH3}(NH) clearly (2.0%) give other evidence for this conformation. After all, anilide **3** is clearly shown to take the NH···O(R) hydrogen-bonded conformation (II) overwhelmingly in $CDCl_3$, in contrast to salicylanilide **1**.

2-Acetoxybenzanilide **2** has two NH absorption bands at 3432 and 3394 cm^{-1}, assigned to the free and H-bonded

Table 1. NMR Chemical Shift (ppm) and NOE Enhancement (%) of *o*-Substituted Benzanilides ($XC_6H_4CONHC_6H_5$)

Compd			Chemical shift				NOE (NHirr)		NOE (OHirr)
No.	X	Solv.[a)]	N^{1}H	^{15}NH	^{13}CO	O^{1}H	H6	H6′	H3
1	OH	(C)	8.03	125.0	168.9	11.98	18.0	8.5	0.5
		(D)	10.41	136.1	166.6	11.81	26.7	12.5	23.0
2	$OCOCH_3$	(C)	8.09	133.7	163.7		4.1	10.7	
		(D)	10.33	140.0	164.9		13.3	13.3	
3	OCH_3	(C)	9.80	134.4	167.1		0.5	9.4	
		(D)	10.14	141.3	164.4		6.3	10.2	
4	CH_3	(C)	7.54	135.0	168.4		b)	b)	
		(D)	10.31	141.2	167.8		9.5	10.6	
5	Cl	(C)	7.99	135.9	164.8		4.8	b)	
		(D)	10.31	142.7	164.9		7.7	13.6	
6	H	(C)	7.88	127.1	165.9		7.6	8.0	
		(D)	10.27	133.9	165.4		12.7	12.5	

a) Solv. (C) $CDCl_3$, (D) DMSO-d_6. b) Signal too close to the irradiation proton.

Table 2. NMR Chemical Shift (ppm) and NOE Enhancement (%) of Substituted Salicylanilide Derivatives

Compd						Chemical shift				NOE (NH irr)			NOE (OH irr)
No.	3	5	2′	5′(4′)	Solv.[a)]	N^1H	^{15}NH	^{13}CO	O^1H	H6	H6′	Me	H3
(a) Salicylanilides **7**—**21**													
7	H	Cl	H	H	(C)	7.86			11.86	21.2	7.8		1.4
					(D)	9.58	136.8	165.0	11.03	28.1	9.8		21.7
8	H	H	H	Cl	(C)	7.94			11.79	14.3	6.0		1.7
					(D)	10.47	135.9	166.8	11.58	22.4	17.2		24.1
9	H	H	Me	H	(C)	7.82			11.99	17.2	4.3	3.3	1.5
					(D)	10.45	132.9	165.1	12.06	21.9	4.8	11.0	23.8
10	H	Cl	Me	H	(C)	7.76			11.94	21.6	b)	5.0	2.5
					(D)	10.32	133.9	163.9	12.24	27.2	4.3	9.5	29.5
11	H	H	Me	Cl	(C)	7.80			11.86	22.6	b)	9.4	1.5
					(D)	10.45	133.7	165.1	11.96	18.6	6.9	13.5	24.5
12	H	Cl	Me	Cl	(D)	10.40	134.5	163.2	12.15	25.1	8.3	13.7	27.2
13	H	I	Me	Cl	(D)	10.39	134.2	163.2	12.14	22.6	8.6	13.5	25.2
14	H	Br	Me	(I)	(D)	10.39	134.2	163.4	12.14	25.3	4.2	11.0	22.8
15	Cl	Cl	Me	Cl	(C)	8.01			12(br)	22.4	5.6	7.9	
					(D)	12(br)	135.0	165.8	12.35	29.8	8.0	20.0	
16	Cl	Cl	Me	(Br)	(D)	12(br)	133.8	165.8	12.70	24.0	9.0	22.4	
17	H	H	F	(F)	(C)	8.06			11.43	21.3	b)		
					(D)	10.6	122.2	165.1	11.93	17.5	4.7		
18	Cl	Cl	F	(F)	(C)	8.20			11(br)	12.1	b)		
					(D)	8.47	123.0	166.4	11.46	25.8	b)		
19	Br	Br	F	(F)	(C)	8.15			11(br)	11.9	b)		
					(D)	8.55	124.0	165.7	12.17	21.3	b)		
20	Cl	Cl	Cl	Cl	(C)	8.65			11.49	32.9	16.6		
					(D)	11.05			12(br)	36.2	16.4		
21	Cl	Cl	NO_2	(Cl)	(C)	11.63			11.92	41.7	—		
					(D)	11.48			12(br)	39.6	—		
(b) 2-Acetoxybenzanilide **22**—**29**													
22	H	F	Me	Cl	(D)	9.66	134.1	163.9	15.1	12.8	8.6		
23	H	Cl	Me	Cl	(C)	7.73			b)	4.6	9		
					(D)	10.02	133.3	162.2	21.8	10.3	8.2		
24	H	Br	Me	Cl	(C)	7.73			b)	5.4	10.6		
					(D)	10.06	134.3	163.2	22.6	11.8	7.7		
25	H	I	Me	Cl	(C)	7.77			5.6	3.0	9.6		
					(D)	10.03	134.2	163.2	22.6	11.1	11.6		
26	H	Cl	Me	Br	(D)	9.99	133.1	163.5	25.4	6.5	7.4		
27	H	I	Me	Br	(C)	7.85			b)	3.2	5.6		
					(D)	9.96	133.0	163.5	22	5.8	4.3		
28	H	H	F	(F)	(C)	8.58	117.6	164.6	3.1	b)			
					(D)	10.08	124.7	162.9	13.1	7.1			
29	H	Cl	Cl	(Cl)	(C)	8.71			4.9	3.5			
					(D)	10.22			26.9	5.3			

a) Solv. (C) $CDCl_3$, (D) DMSO-d_6. b) Signal too close to the irradiation proton.

NH groups of the *s-trans* conformations, respectively. This fact suggests that **2** takes the NH···O($COCH_3$) intramolecularly hydrogen-bonded conformation (II) appreciably; the amount of this conformation is estimated to be about 35% from ratio of the area of the two NH bonds. The anilide **2** showed a stronger f_{H6}(NH) than that of **3**, but was considerably weaker than that of **1**. The NH proton signal of **2** appeared at a slightly lower field than that of **1**. All of these facts suggest that a rapid equilibrium between the inter-ring hydrogen bonded (IIa) and the free (III) conformations of **2** is present in inert solvents (Chart 2). The free species is expected to have a less rigid framework, and the aroyl ring can be twisted from the amide plane due to a steric hindrance effect by the 2-acetoxy group.

In order to obtain further evidence concerning the strength of the NH···O(R) intramolecular hydrogen bond, the NH chemical shifts of the anilides **1**—**6** were measured in chloroform–dimethyl sulfoxide mixtures of varying compositions (Fig. 1). Judging from the flat plots in Fig. 1, the conformation (II) of **3** is expected to persist in DMSO-d_6. This observation supports the above conclusion that the NH···O(OCH_3) intramolecular hydrogen bond in **3** is very strong. The NH···O($COCH_3$) intramolecular hydrogen bond of **2** is weaker than that of **3**, judging from its solvent dependency behavior being similar to benzanilide **6**, which suggests that the conformation (II) of **2** does not exist measurably

Table 3. Infrared NH Absorption Band (cm^{-1}) in CCl_4

Compd No.	Free	H-bonded
1	3446	
2	3432	3394
3		3374
4	3427	
5	3423	
6	3437	
7	3450	
8	3456	
10	3445	
13	3447	
15	3440	3327
16	3440	3333
17	3460	
18	3463	3399
20	3432	3362
21		3340

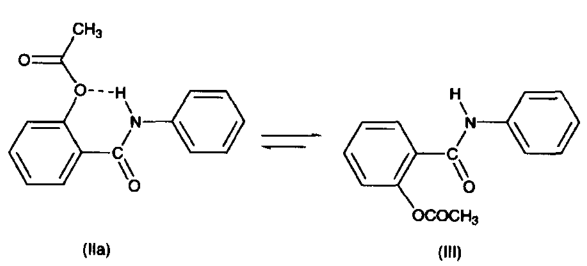


Chart 2.

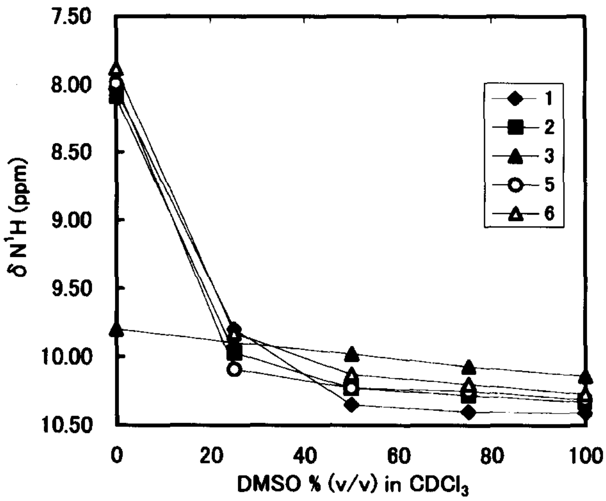


Fig. 1. Solvent-composition dependance of chemical shift of N^1H.

in DMSO-d_6.

Also, the OH···O=C intramolecular hydrogen bond of salicylanilide **1** is cleaved by the formation of an intermolecular hydrogen bond between OH and DMSO-d_6. This allows free rotation of the OH group about the C_2–O bond. In practice, a considerably large f_{H3}(OH) was observed with **1** in DMSO-d_6, but the f_{H6}(NH) is about three- or four-times stronger and ^{15}N chemical shift is about 5 ppm higher than those for *ortho*-substituted benzanilides **2**—**5**. These results suggest that the conformation (I) of salicylanilides exists considerably even in DMSO-d_6.

Effect of *ortho* Substituents of the Anilino Ring on the Conformation. We then studied the conformational change accompanied by the changes in the substituent at the *ortho* positions of the anilino ring.

The introduction of a 2′-methyl group should hinder the coplanarity of the anilino aromatic ring to the amide moiety. The $f_{H6'}$(NH) values of the 2′-methyl-substituted anilides **9**—**16** are less than the $f_{H2'}$(NH) values ($= f_{H6'}$(NH), in these case) of 2′-unsubstituted anilides **1**, **7**, **8**. This fact implies that *ortho*(6′)-H in 2′-methyl-substituted anilides **9**—**16** lies more distant from the amide NH group than the *ortho*-H in 2′-unsubstituted anilides. Simultaneously, the 2′-methyl signal was always enhanced more significantly than the 6′-hydrogen signal on the anilino ring when the amide NH was irradiated; i.e., $f_{2'-Me}$(NH) $> f_{H6'}$(NH). Thus, the NH/Me contiguous non-coplanar conformation (I_{anti}) must be more predominant than the alternative NH/H6′ contiguous non-coplanar conformation (I_{syn}) (Chart 3). In the (I_{syn}) and (I_{anti}) conformations, the OH···O=C intramolecular hydrogen bond is expected to be maintained as in 2′-unsubstituted salicylanilides, judging from the f_{H6}(NH) and OH proton chemical shift being similar to those of 2′-unsubstituted anilides **1**,**7**, and **8**.

Because the halogen atom can serve as a hydrogen-acceptor, the introduction of 2′-halo substituents stabilized the coplanar geometry of the molecule by the cooperation of an additional NH···X (X = F, Cl, I) hydrogen bond, and favors the conformation (I_b) (Chart 4). The large f_{H6}(NH) and the low NH proton chemical shift of **20** support the existence of the conformation (I_b). Thus, 2′-halo-substituents were shown to have a tendency to favor the OH···O=C coplanar conformation (I) by a comparison of the f_{H6}(NH) and OH proton chemical shifts among the relevant amides. However, the NH···F hydrogen bond must be considerably weak, judging from the small down-field shift of the NH proton in **17**—**19**. The high-field shift of the ^{15}N chemical shift (about 10 ppm) was observed with these 2′ (and/or 6′)-fluoro-substituted anilides. A similar high-field shift had been observed with 2-fluoroanilines and 2-fluoropyridines.

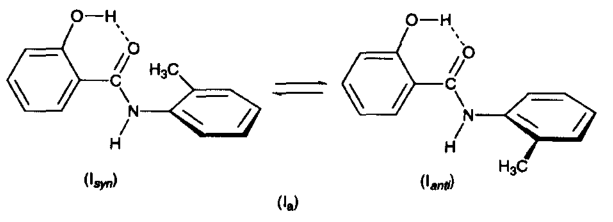


Chart 3.

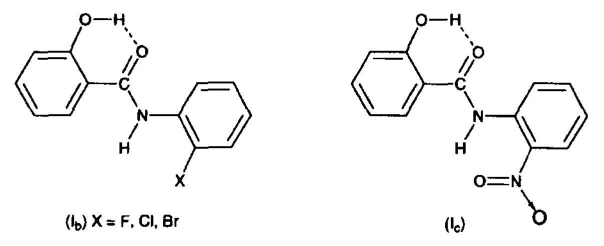


Chart 4.

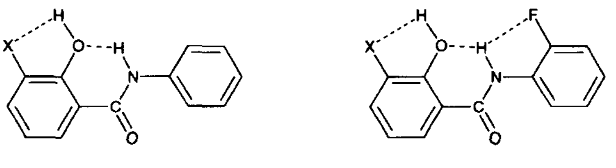
By introducing a 2′-nitro group on the anilino ring, the f_{H6}(NH) greatly increases actually, it is as large as 36% for 2′-nitroanilide **21**. Its NH proton signal appears at an extremely low field, which intimates the participation of the NH group in a strong hydrogen bond with a 2′-nitro group. The δ_{OH} of **21** falls within the range of the normal OH···O=C chelate. Thus, the stable NH···X and NH···NO_2 hydrogen bonds should suppress the participation of an alternative NH···OH hydrogen bond, and should stabilize the conformation (I_c).

The effect of 2′-substituents on 2-acetoxybenzanilides **22**—**29** are similar to the cases of salicylanilides. Because the salicyloyl OH group is absent in this series of anilides, they exclusively take the alternative NH···O hydrogen-bonded conformation (II). This conformation must be stabilized additionally by an attractive dipolar interaction between the amides and the acetoxy carbonyl groups in these anilides. A comparative study of the f_{H6}(NH) and the $f_{\mathrm{H6'}}$(NH) with those of unsubstituted 2-acetoxybenzanilide **2** showed that the NH···O($COCH_3$) intramolecular hydrogen bond in these anilides is neither interfered by the 2′-methyl group (in **22**—**27**), which enforces the non-coplanar conformation (II_{syn} or II_{anti}), nor weakened by 2′-halo (F, Cl) group, which is capable of forming a NH···X hydrogen bond (as in **28** and **29**). The presence of bridged X(F, Cl)···H(N)···OAc hydrogen bonds in **28** and **29** was deduced from their NH proton signals, which appear at a considerably lower field than those of **22**—**27**. This sort of hydrogen bonding had been shown to be present in similar anilides by infrared spectroscopy.[2]

Effect of 3-Substituents in the Salicyloyl Ring on the Conformation. We next studied the conformational changes accompanied by the introduction of various substituents (Y) at the 3-position, *ortho* to the hydroxy group in the salicyloyl ring. A hydrogen-accepting 3-substituent may cause a considerable perturbation on the OH···O=C hydrogen bond by forming an alternative OH···Y, which can affect the conformation of the whole molecule.

When chlorine or other halogen substituent was introduced at the 3-position as **15**,**16** and **18**—**21**, the NH proton chemical shift appeared at a considerably lower field compared with the 3-unsubstituted derivatives. The infrared spectra of some of these 3-halo-anilides have low-frequency ν_{NH} bands originating from hydrogen-bonded NH groups besides the high-frequency ν_{NH} bands assigned to the free NH groups (Table 3). In the cases of 3-chloro-2′-methylanilides, **15** and **16**, the absorption bands assigned to the NH···OH···X (X = halogen) hydrogen bonded species appear within the range between 3327 and 3333 cm^{-1}, in contrast to 3440 cm^{-1} for the normal *s-trans* secondary amide group. In the cases of 3-chloro-2′-fluoro-substituted anilide **18**, the absorption band assigned to the OH···NH···X(F) hydrogen bonded conformation (II_c) appear at 3399 cm^{-1} (Chart 5). The f_{H6}(NH) of **18** and **19** are smaller than that of **17** and their NH proton chemical shifts are lower than that of **17**; both facts also proved the conformation (II_c) in $CDCl_3$.

Correlation between Conformation and Antibacterial Activities. We previously already reported that the salicylanilide derivatives bearing at 3-halo, 2′-fluoro, and/or 2-*O*-acetyl substituent(s) have stronger antifungal activities than other acetanilides.[9] The most predominant conformations of these anilides are shown to be either of ($II_{a—c}$), which have a NH···O intramolecular hydrogen bond commonly. Thus, the antibacterial and antifungal activities of these anilides are expected to have some connections with the intramolecularly hydrogen-bonded conformation (II). This finding can be a guideline in searching for a possible bio-active substance. However, the conformation (II) can be expected to persist only in hydrophobic media, and further research is necessary before rationalizing the biological activities of these anilides in terms of their hydrogen-bonding properties.



(II_b) X = Cl, Br, I

(II_c) X = Cl, Br

Chart 5.

Conclusion. Salicylanilide derivatives take both or either of the conformations (I) and/or (II). These two conformations are stabilized by intramolecular hydrogen bonding and are considerably rigid. The cooperation of NH···O(R) and OH···X intramolecular hydrogen bonds or acylation of the OH group raises the hydrophobicity of the salicylanilide molecules, which can be a reason for the increase in antibacterial activity. In highly polar and solubilizing solvents, such as dimethyl sulfoxide, the intramolecular hydrogen bonds, particularly the NH···O(R) (R = H,$COCH_3$) intramolecular hydrogen bonds, are weakened or broken because of an intermolecular hydrogen bond between the solvent and the NH or OH group of the anilides. The NOE method could be applied very usefully to elucidate the steric structures and conformations of bactericidal benzanilides.

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