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Infrared Spectra and Intramolecular Hydrogen Bonding of Some Salicylanilides of Pharmaceutical Interest

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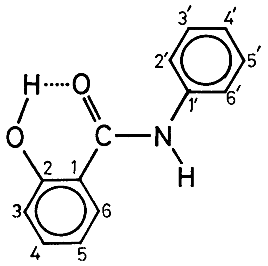
Intramolecular hydrogen bonding of the title compounds was investigated by measuring their infrared spectra in the OH, NH, and C=O stretching regions. The results showed that the intramolecular hydrogen bonding in the salicyloyl moiety plays an important role in the antibacterial activities of these salicylanilides.

As a part of a series of investigations to correlate the biological and pharmaceutical activities to their structures and physical properties, the intramolecular hydrogen bonding and the conformations of salicylanilides (**1**) were studied by infrared spectroscopy.



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Intramolecular hydrogen bonds affect remarkably the associative properties and the solubilities of these compounds, thereby influencing on their biological activities in different ways. These anilides have coplanar chelate rings made up of very strong OH···O=C intramolecular hydrogen bonds of hexagonal arrangement. In turn, the amide moiety of the anilide usually takes a planar *s-trans* conformation as illustrated by **1**. In this connection, it is interesting to examine how the hydrogen bonding and the conformations of these anilides are affected with the steric effect caused by the substituents located ortho to either or both of amide and salicyloyl groups. For this purpose, the OH, NH, and C=O stretching absorptions of these anilides were measured and discussed.

Experimental

Preparation of the materials were reported elsewhere.[1)] Infrared spectra were obtained in carbon tetrachloride solutions using a Hitachi 225 infrared spectrophotometer. The concentration of the solution was kept below 3×10^{-3} mol/l (usually at about 1×10^{-3} mol/l) in order to prevent the effect of the associated species.

Results and Discussion

Infrared spectra of the anilides are given in Table 1. In general, the *s-trans* conformer is known to be 4—8 kJ/mol more stable than the *cis*. Thus the salicylanilides without ortho (3, 6, 2', and 6') substituents absorb at about 3450 cm^{-1} in the NH stretching region, which was assigned to the *s-trans* conformation by Suzuki and co-workers.[2)] Besides this band, they have absorption bands at *ca.* 1660 cm^{-1} in the carbonyl stretching region and broad bands around 3000 cm^{-1} due to chelated OH group, both of them suggesting the presence of intramolecularly hydrogen-bonded chelate rings. These facts support the *s-trans* conformation with chelated salicyloyl group as illustrated in **1**.

Effect of 2- (and 6-) Substituents on the Conformation and the Hydrogen Bonding. The substituent at the positions ortho to the amide group (on the anilino ring) may affect considerably the conformations of the amide groups of the salicylanilides. The effect can be classified as i) that from steric hindrance and ii) that from hydrogen bond formation. Since the planar conformation of the amide group is rather rigid, the bulky group at the ortho positions causes almost exclusively a torsion around the C_{Ar}–N bond. However, the effect on the NH frequency is not predominant. In short, the steric effect by the 2'- (and 6'-)substituent does not perturb the conformation of the amide group considerably.

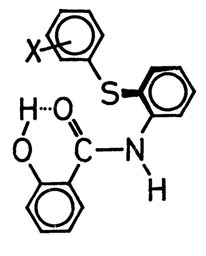
The substituents capable of forming hydrogen bonds with the NH group investigated are aryloxyl, halo, and arylthio groups, all of them behaving as hydrogen acceptors in hydrogen bonding. With three anilides (**9**—**11**) carrying 2'-aryloxyl groups, their NH stretching absorptions tend to shift towards lower frequencies only slightly. The very small but definite low frequency shifts suggest the existence of very weak hydrogen bonding. The absorptions in the carbonyl and hydroxyl stretching regions also coincide with those of the parent salicylanilide (**1**), showing no indication for the substituent effect. The 2'-chloro substituted anilides **6** and **7** absorb at 3433 and 3432 cm^{-1} in the NH stretching region, which are somewhat 20 cm^{-1} lower than those of the parent anilide (**1**). Infrared spectral shifts due to intramolecular hydrogen bonding ($\Delta\nu_{NH}=\nu_f-\nu_b$) are again rather small. However, Welti[3)] has measured the infrared spectra of some halogenated salicylanilides and concluded the existence of intramolecular hydrogen bonding from the $\Delta\nu_{NH}$ values of similar magnitudes for 2'-chlorinated derivatives and from considerably larger $\Delta\nu_{NH}$ values for 2'-brominated derivatives. The absorption due to chelated salicyloyl group is again similar to the parent salicylanilide (**1**).

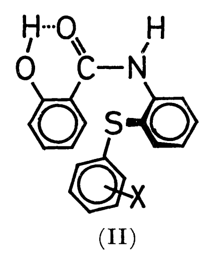
The most intense ν_{NH} bands of 2'-arylthiosalicyl-

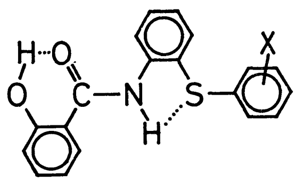
TABLE 1. INFRARED ABSORPTIONS IN THE OH, NH, AND C=O STRETCHING REGIONS OF SALICYLANILIDES

No.	Substituent on		ν_{OH}/cm^{-1}	ν_{NH}/cm^{-1}			$\nu_{C=O}$/cm^{-1}	
	Anilino moiety	Salicyloyl moiety		*s-trans*	*s-cis*	H-bonded	Amide (chelate)	Others
1	None	None		3454 (67)			1657 (373)	
2	3-Cl-4-(*p*-ClC$_6$H$_4$S)	5-Cl		3450 (110)			1663 (350)	
3	3-Cl-4-(*p*-ClC$_6$H$_4$S)	3,5-Cl$_2$	3511 (56)	3449 (104)		3398 (67)	1659 (254)	1686 (85) free
4	2-CH$_3$-4-Cl	5-Cl		3466 (40) 3442 (40)			1659 (201)	
5	2-CH$_3$-4-Cl	2-*O*-Ac-5-Cl	3538 (36)	3440 (82)	3405 (sh)			1697 (320) free 1792 (157) Ac 1768 (210) Ac
6	2,4-Cl$_2$	5-Cl		3433 (113)			1659 (325)	
7	2,4-Cl$_2$	3,5-Cl$_2$	3516 (43)	3432 (108)		3362 (42)	1660 (350)	1684 (111) free
8	2,4-Cl$_2$	2-*O*-Ac-5-Cl		3425 (sh)	3399 (148)			1692 (242) free 1792 (233) Ac 1772 (157) Ac
9	2-(*p*-FC$_6$H$_4$O)-5-Cl	5-Cl		3443 (122)			1659 (372)	
10	2-(*p*-ClC$_6$H$_4$O)-5-Cl	5-Cl		3443 (130)			1660 (281)	
11	2-(*p*-ClC$_6$H$_4$O)-5-Br	5-Cl		3444 (124)			1660 (275)	
12	2-(*p*-ClC$_6$H$_4$O)-5-Br	2-*O*-Ac-5-Cl			3406 (103)			1689 (273) free 1791 (229) Ac 1769 (167) Ac
13	2-(*p*-ClC$_6$H$_4$O)-5-CF$_3$	5-Cl		3444 (72)			1660	[1752] [1702]
14	2-(α-C$_{10}$H$_7$O)-5-Br	5-Cl		3439 (120)			1659 (277)	
15	2-(β-C$_{10}$H$_7$O)-5-Br	5-Cl		3439 (120)			1659 (293)	
16	2-(α-C$_{10}$H$_7$O)-5-CF$_3$	5-Cl		3443 (78)	3420 (sh)		1660 (248)	1686 (sh) [1753 (125)] [1705 (40)]
17	2-(β-C$_{10}$H$_7$O)-5-CF$_3$	5-Cl		3442 (93)	3419 (sh)		1659 (174)	[1757 (94)] [1702 (74)]
18	2-(α-C$_{10}$H$_7$O)-5-CF$_3$	2-*O*-Ac-5-Cl			3405 (87)			1686 (252) free 1790 (185) Ac 1765 (170) Ac [1705 (sh)]
19	2-(β-C$_{10}$H$_7$O)-5-CF$_3$	2-*O*-Ac-5-Cl		3441 (sh)	3408 (57)			1687 (200) free 1789 (121) Ac 1777 (148) Ac [1750 (200)] [1700 (220)]
20	2-(*p*-ClC$_6$H$_4$S)-5-Cl	5-Cl	3525 (14)	3434 (sh)	3406 (sh)	3353 (90)	1661 (306)	[1701 (47)]
21	2-(*p*-ClC$_6$H$_4$S)-5-Cl	3,5-Cl$_2$	3516 (22)	3434 (sh)	3406 (sh)	3353 (80)	1659 (137)	1685 (21) free
22	2-(*p*-ClC$_6$H$_4$S)-5-Br	5-Cl			3402 (sh)	3360 (82)	1663 (227)	
23	2-(*p*-ClC$_6$H$_4$S)-5-CF$_3$	5-Cl			3402 (sh)	3362 (66)	1662 (283)	[1751 (20)] [1703 (107)]

a) Broad band due to chelated OH (at *ca.* 3000 cm^{-1}) is omitted. b) Bands in brackets are assigned to the intensified overtones of CF absorptions.







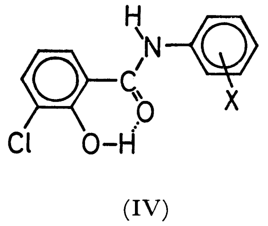
	(I)	(II)	(III)
	s-trans(free)	*s-cis*(free)	H-bonded
ν_{NH}/cm^{-1}	3434	3402	3360
Abundance	Less	Least	Most predominant

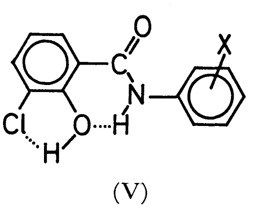
Table 2. NH and C=O stretching frequencies of some 2-substituted 5-chloroacetanilides

X	ν_{NH}/cm^{-1}	$\nu_{C=O}$/cm^{-1}
H	3440	1714
p-ClC_6H_4O	3435	1712
p-ClC_6H_4S	3366	1715 1698.5

anilides **20**—**23** are located at around 3350 cm^{-1}, which is a remarkably lower frequency than those of the other 2′-substituted derivatives discussed above. Besides this band, two additional absorption bands are observed at 3434 and 3402 cm^{-1}. The larger $\Delta\nu_{NH}$ suggests the presence of a hydrogen bond stronger than those in 2′-aryloxy and 2′-chloro derivatives (**7**—**13**). Similarly, NH···S intramolecular hydrogen bond is stronger than NH···O hydrogen bond in the series of the corresponding acetanilides given in Table 2. The other two NH bands were assigned to the free *s-trans* (I) and *s-cis* (II) conformers of the salicylanilides **20**—**23**. These 2′-arylthiosalicylanilides have weak bands at 1700 cm^{-1} of the $\nu_{C=O}$ region in addition to the strong bands at about 1660 cm^{-1}. This may be an indication of an unchelated structure for the *s-cis*(free) conformer absorbing at 3402 cm^{-1} in ν_{NH} region. If the chelated conformation (III) is assumed for the cis conformer, the molecule is expected to be considerably crowded sterically. Therefore an unchelated conformer may appear in a small amount.

Effect of Substituents on 3- and Other Positions on the Salicyloyl Residue. The 3-chloro derivatives (**3**, **7**, **21**) have two absorption bands in the ν_{NH} region; the one at a higher frequency (*ca.* 3430 cm^{-1}) may be assignable to the free *s-trans* amide group, while the other at a lower frequency (3400—3350 cm^{-1}) should arise from an intramolecularly hydrogen-bonded NH group. According to Welti,[3] these absorption bands are assigned properly to the conformer (IV) and (V), respectively. The former is estimated to be more predominant from the intensities of their characteristic absorption bands.



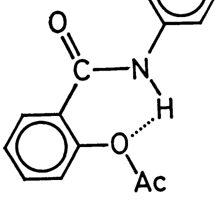


	(IV)	(V)
ν_{OH}/cm^{-1}	3000 (broad)	3516
$\nu_{C=O}$/cm^{-1}	1660	1685
ν_{NH}/cm^{-1}	3430	3400—3350
Abundance	More predominant	Less predominant

The conformations of the salicylanilides might be perturbed seriously by the acetylation of the 2-hydroxyl functional groups, since the intramolecular hydrogen bond participating in the formation of the chelate ring and keeping the carbonyl and the hydroxyl groups close is no longer persistent. The acetyl derivatives (**5**, **8**, **12**) have NH absorption bands at approximately 3400 cm^{-1}, which can be assigned to the NH···O(Ac) hydrogen bonded conformers (VI). The considerably small $\Delta\nu_{NH}$ values in these compounds are reasonable since the acetoxyl group is in general a hydrogen acceptor weaker than the hydroxyl groups.[4] The conformer (VI) become less favorable by the introduction of 2′-substituent, and the 3440 cm^{-1} band due to the free *s-trans* conformer appears. The low frequency shift of this band in **8** is ascribable to the intramolecular hydrogen bonding with 2′-chloro substituent. The acetyl derivatives usually have three absorptions at about 1690, 1770, and 1790 cm^{-1} in the $\nu_{C=O}$ region; the former band is assigned to the amide and the latter two to the acetyl group.

Table 3. Antibacterial activities of some substituted salicylanilides

Compound	Antibacterial activity (MIC: μg/ml)	
	S. aureus (A)	*B. subtilis* (B)
2	10	10
3	0.16	0.16
10	0.8	0.8
11	0.8	0.8
12	0.16	0.16
13	0.8	0.8
14	50	10
15	50	10
16	1	1
17	1	1
18	0.16	0.16
22	0.8	0.8
23	5	0.8



(VI)

5′-Trifluoromethylsalicylanilides (**13** and **23**) have two unusual absorption bands at 1750 and 1700 cm^{-1}. These bands are interpreted as the intensified overtone vibrations, by Fermi resonance, of strong C–F stretching vibrations in 850—900 cm^{-1} region, since the intensities of the carbonyl band at *ca.* 1690 cm^{-1} is remarkably reduced, and since the corresponding trifluoromethyl substituted aniline has no such bands.

Preliminary Results on the Correlation with Their Antibacterial Activities. The six-membered hydrogen bonding in salicyloyl moiety is hereby shown to be perturbed when 3-chloro or 2-*O*-acetyl substituent is introduced to the salicylanilide molecule. The antibacterial activities towards *Staphyrococcus aureus* FDA 209-P (A) and *Bacillus subtilis* PCI-219 (B) are remarkably high with the compounds carrying the above substituents (**3**, **12**, and **18**) as given in Table 3. Thus, the structural and conformational change in the salicyloyl moiety might play an important role in the biological activities of these salicylanilides. On the other hand, the activity is not affected considerably by the conformational change in the amide moiety. However, further informations on a wider range of the anilides and the bacteria is necessary in order to conclude the structure-activity relationship confidently.

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References

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2) I. Suzuki, M. Tsuboi, T. Shimanouchi, and S. Mizushima, *Spectrochim. Acta*, **16**, 471 (1960).

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4) An alternative explanation that the 3400 cm^{-1} band arises from the free *s-cis* conformer cannot be excluded.