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The Nuclear Magnetic Resonance Study of Several *o*-Disubstituted Benzenes

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The nuclear magnetic resonance spectra of six *o*-disubstituted benzenes containing a carbonyl group have been analyzed. The chemical shifts of the proton-6, adjacent to the carbonyl group, show a solvent dependence, indicating changes in the intramolecular interactions between the two *ortho* substituents.

It is known that the protons adjacent to the substituents in *o*-disubstituted benzenes often have chemical shifts differing by more than 0.1 ppm from the values estimated from a simple additive rule.[1] Interactions between the two substituents adjacent to each other must be responsible for these discrepancies. In some cases, the interactions fix the orientation of either one or both of the substituents. Fixing the substituent with a large magnetic anisotropy at one orientation markedly affects the chemical shifts of the *ortho* protons. In acetanilide, for example, the chemical shifts of the *ortho* protons depend to a great extent on whether the rotation about the bond connecting the amide nitrogen with the aromatic carbon atom is free or restricted.[2] Acetanilides, which have a substituent at the 2-position capable of forming intramolecular hydrogen bonds with the amide proton, exhibit deshielding, to a great extent, of the aromatic proton at C_6.[2]

The fixed orientation of some substituents into the plane of the ring often induces rather large long-range couplings between the substituents and particular ring protons.[3]

In this paper, the author will show that a difference in the carbonyl orientation through the intramolecular hydrogen bonding is responsible for the large difference between the chemical shifts of the proton-6 in *N*-methyl salicylamide and *N*-methyl-*o*-methoxy benzamide. Furthermore, the chemical shifts of the ring proton-6 in these compounds are very similar in dimethyl sulfoxide, which is known as a powerful solvent for disrupting the intramolecular and intermolecular hydrogen bonds of solute molecules.[4,5]

Experimental

The acids and esters used were commercial products. The amides were prepared by reacting the corresponding esters with an equimolar amount of methylamine (40% aqueous solution) in methanol at room temperature for a week. The solvent, the non-reacted ester, and the amine were distilled out under reduced pressures. The *N*-methyl salicylamide was purified by recrystallization from cyclohexane; mp 87.5—88.0°C. The *N*-methyl-*o*-methoxy benzamide was purified by distillation under reduced pressure; bp 148—150°C/4 mmHg.

The NMR spectra were obtained on a Varian A-60D spectrometer. Tetramethylsilane was used as the internal standard. A scale expansion of the recorder chart of 2 Hz/cm was used for determining the ring-proton resonances. The relative positions among the ring-proton signals were read with an accuracy of ± 0.05 Hz. The simulation of the NMR spectra was carried out by means of an electronic computer, CDC 3600, using an iterative computer program, LAOCON 3.[6] With very few exceptions, all the peaks observed were in accord with the calculated peaks within 0.1 Hz.

1) J. S. Martin and B. P. Dailey, *J. Chem. Phys.*, **39**, 1732 (1963).

2) a) M. Zanger, W. W. Simons, and A. R. Gannaro, *J. Org. Chem.*, **33**, 3672 (1968). b) R. Carter, *Acta Chem. Scand.*, **21**, 75 (1967). c) T. H. Siddall, III and W. E. Stewart, *J. Mol. Spectrosc.*, **24**, 290 (1967). d) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *Can. J. Chem.*, **46**, 2577 (1968).

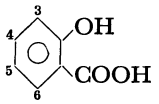
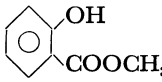
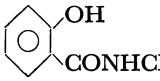
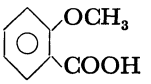
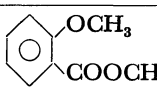
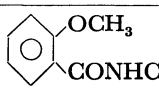
3) J. G. Karabatsos and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 3886 (1963).

4) I. D. Rae, *Austr. J. Chem.*, **46**, 2588 (1968).

5) a) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 337 (1964). b) R. H. Barker and G. J. Boudreaux, *Spectrochim. Acta* **A23** 727 (1967).

6) S. Castellano and A. A. Bothner-By *J. Chem. Phys.* **41** 3863 (1964).

TABLE 1. THE CHEMICAL SHIFTS OF SOME *o*-DISUBSTITUTED BENZENES

		Solvent	Chemical shift			
			H(3)	H(4)	H(5)	H(6)
I		$CDCl_3$	423.18	453.52	418.32	478.20
		DMSO-d_6	419.02	451.95	417.05	470.98
II		$CDCl_3$	420.92	448.56	414.35	471.83
		DMSO-d_6	420.65	452.64	417.85	468.64
		C_6D_6	418.51	425.77	395.65	463.52
III		$CDCl_3$	419.22	443.30	410.33	444.73
		DMSO-d_6	415.95	444.68	414.17	470.57
		C_6D_6	421.24	425.70	394.11	411.79
IV		$CDCl_3$	424.27	454.01	426.95	488.62
		DMSO-d_6	429.39	452.09	422.67	461.92
		C_6D_6	383.61	424.56	404.42	494.11
V		$CDCl_3$	419.19	448.02	419.04	468.07
		DMSO-d_6	429.62	452.71	421.97	459.92
		C_6D_6	392.38	426.71	404.50	470.18
VI		$CDCl_3$	418.32	445.65	424.03	492.97
		DMSO-d_6	427.87	447.67	422.21	468.10
		C_6D_6	390.67	426.36	412.27	514.37

Results and Discussion

The chemical shifts of the ring protons are summarized in Table 1. The chemical shifts reported for methyl salicylate in carbon tetrachloride[7] are almost uniformly located at fields higher by about 10 Hz than the present results. This is a general tendency when comparing the spectra of aromatic compounds dissolved in carbon tetrachloride and chloroform.

Dimethyl Sulfoxide Solutions. Interestingly, in dimethyl sulfoxide the chemical shifts of the ring protons at any given position are very similar for all the compounds studied. This is reasonable since, supposedly, the substituent variation in the present case has only a minor influence on the ring protons' electronic environment, provided that there are no special interactions between the two *ortho* substituents. In dimethyl sulfoxide, as is well known, the intermolecular interactions between solute and solvent molecules are preferred to intramolecular hydrogen bonds. Therefore, no special intramolecular interactions can be expected between the two substituents. Dimethyl sulfoxide molecules may interact with the hydroxyl or amide protons through the formation of intermolecular hydrogen bonds.[5] This kind of interaction shifts these resonances to lower fields. This expectation was actually realized (not listed in Table 1). The disruption of the intramolecular hydrogen bonds results in an increased freedom of movement of the substituents, probably a free rotation around the C_{ring}–CO bond, which would result in an averaing of the shielding effects of the carbonyl group on the ring proton-6. This may be the reason why the proton-6 chemical shift in all the compounds is nearly the same in dimethyl sulfoxide.

Consistent with this is the disruption of the intramolecular hydrogen bonds for methyl salicylate and other *ortho*-substituted phenols dissolved in dimethyl sulfoxide, as is suggested by the fact that the relative chemical shifts of OH in *ortho*-substituted phenols in dimethyl sulfoxide solutions are linearly-related to those for *para*-substituted phenols.[8]

Chloroform Solutions. In chloroform, on the other hand, the intramolecular interactions through hydrogen bonding may be expected to take place in some of the compounds studied, but not in others.

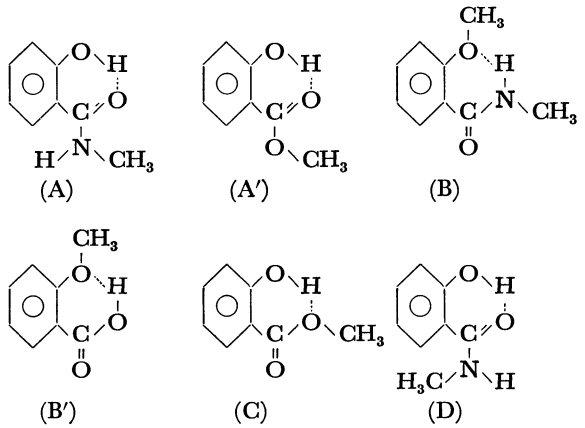
The proton chemical shifts of the compounds V, for which there is no possibility of intramolecular hydrogen bonding even in a chloroform solution, are very similar in both solvents, chloroform and dimethyl sulfoxide.

From the arguments given above, it appears that the chemical shift of the proton-6 is about 470 Hz from TMS when there are no special interactions between the two *ortho* substituents. From this point of view, the chemical shift of the ring proton-6 of *N*-methyl salicylamide in chloroform is considered to be strongly shielded. This suggests a certain interaction between the two substituents. The present author ascribes this remarkable shielding effect to the orientation fixing of the amide group through the intramolecular hydrogen bonding between phenolic hydroxyl proton and the carbonyl oxygen in the amide group, as is shown in A. A low-field resonance of the phenolic hydroxyl proton (744 Hz) is consistent with the argument described above. It is known that the resonance of phenolic hydroxyl protons is observed at about 270 Hz

7) R. Freeman and N. S. Bhacca, and C. A. Reilly, *J. Chem. Phys.*, **38**, 293 (1963).

8) M. T. Tribble and J. G. Traynham, *J. Amer. Chem. Soc.*, **91**, 379 (1969).

when they are free[9] and is shifted to lower fields when intramolecular hydrogen bonds are formed.[10,11] The phenolic hydroxyl protons of salicylaldehyde[11] and methyl salicylate[7] were observed at 665.5 and 641.7 Hz respectively. Unfortunately, however, no long-range coupling was observed between the phenolic hydroxyl proton and the ring proton-4 in *N*-methyl salicyalmide.



On the other hand, the ring proton-6 resonances of *o*-methoxy benzoic acid and *N*-methyl-*o*-methoxy benzamide were observed at very low fields, lower by about 20 Hz than the average value described in the preceding section. In these two compounds, the intramolecular hydrogen bonds give rise to planar molecules like B, where the carbonyl group is fixed in the molecular plane in quite a different way from that in A. In B, the proton-6 can be expected to be subjected to a strong electric field due to the carbonyl group and to resonate at lower fields. In the case of 2,5-dimethoxy acetanilide, where a strong effect of the carbonyl group could also be expected, the proton-6 resonance was found at 487 Hz.[2d] The amide proton resonance of *N*-methyl-*o*-methoxy benzamide was found at about 467 Hz, lower by about 60 Hz than that of *N*-methyl salicylamide, probably because of the intramolecular hydrogen bond.

Interestingly enough, the proton-6 resonates at about an average field in the case of methyl salicylate, although an intramolecular hydrogen-bond formation like A is expected to occur in this compound in chloroform; thus, the proton-6 could be expected to resonate at about the same field as that of *N*-methyl salicylamide. This unexpectedly low field resonance may be interpreted in terms of: (i) a considerable contribution by molecules of the C structure, or (ii) an electric-field deshielding exerted by the lone-pair electrons on the ester oxygen atom in A′. The IR study of methyl salicylate in carbon tetrachloride gave no evidence regarding any contribution of the C structure.[12] Therefore, the first interpretation can be ruled out.

The proton-6 of salicylaldehyde has been reported to resonate at 442.811 Hz from TMS.[11] This observation is consistent with the second explanation given above.

Ōki *et al.*[13] studied the conformations of several esters and concluded that the *s-trans* configuration is the exclusive one. Therefore, the A′ structure is considered to be the most stable one for methyl salicylate. In this geometrical arrangement, the lone-pair electron cloud of the oxygen atom in the ester group exerts a strong electric field on the proton-6, inducing a pronounced deshielding effect.

Benzene Solutions. Benzene is known as a representative solvent which has a special effect on the proton chemical shifts of compounds with a carbonyl group.[14] A similar effect has been reported for some amides.[15]

According to these results, the ring proton-6 of *N*-methyl salicylamide would be expected to shift to higher fields when dissolved in benzene if the molecular structure assumed is A. This expectation is the case, as is shown in Table 1. By contrast, for *N*-methyl-*o*-methoxy benzamide the proton-6 resonance would be expected to remain unchanged or to shift to lower fields, provided that the molecular structure assumed is B. Actually, however, the resonance signal of the proton-6 was observed at a lower fields and that of the proton-3 shifted to higher fields. These observations prove the correctness of the structural assignments given above.

Furthermore, a consideration of van der Waals' repulsion for *N*-methyl salicylamide gives preference to the A structure over D, where the amide hydrogen lies *cis* to the carbonyl group with respect to the amide bond, N–CO, because of the strong repulsion expected between the methyl group and the proton-6 in the latter structure.

On the other hand, no remarkable benzene shift was observed for the proton-6 in the II and IV compounds. In the case of the latter, the flexibility of the carbomethoxy group, *i.e.*, the free rotation around the C_{ring}–CO bond, may be an important factor in interpreting this observation. In the former compound, the lone-pair electrons on the ester oxygen atom would prevent the benzene molecules from access to the proton-6.

Spin-spin Coupling. The results are presented in Table 2. None of the coupling constants varies significantly in changing the solvent. Furthermore, no appreciable variation in any of the coupling constants is observed from compound to compound. These observations are reasonable, because the change in the substituents of these compounds seems to cause only a weak perturbation in the ring moiety.

Previous empirical efforts to interpret substituent effects on proton-proton couplings have involved a

9) L. M. Jackman "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London (1959), p. 69.

10) M. Kondo, This Bulletin, **38**, 1271 (1965).

11) D. G. de Kowalewski and S. Castellano, *Mol. Phys.*, **16**, 567 (1969).

12) N. Mori, Y. Asano, and Y. Tsuzuki, This Bulletin, **42**, 488 (1969).

13) M. Ōki and H. Nakanishi, This Bulletin, **43**, 2558 (1970).

14) a) J. D. Connolly and R. McCrindle, *Chem. Ind.* (London), **1965**, 379. b) D. H. Williams and N. S. Bhacca, *Tetrahedron* **21**, 2021 (1965). c) D. H. Williams and D. A. Wilson, *J. Chem. Soc., B*, **1966**, 144.

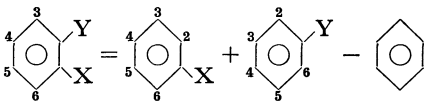
15) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960); *ibid.*, **5**, 139 (1962) and many other papers published later.

TABLE 2. COUPLING CONSTANTS

		J_{34}	J_{35}	J_{36}	J_{45}	J_{46}	J_{56}
I	$CDCl_3$	8.49	1.07	0.46	7.15	1.77	7.95
	DMSO-d_6	8.42	1.12	0.43	7.31	1.83	7.90
II	$CDCl_3$	8.31	1.08	0.42	7.17	1.78	7.83
	DMSO-d_6	8.39	1.17	0.41	7.35	1.73	8.08
	C_6D_6	8.51	1.14	0.45	7.25	1.75	7.98
III	$CDCl_3$	8.32	1.21	0.47	7.28	1.59	7.96
	DMSO-d_6	8.30	1.13	0.55	7.18	1.70	7.98
	C_6D_6	8.27	1.14	0.42	7.42	1.55	8.01
IV	$CDCl_3$	8.52	0.97	0.49	7.36	1.86	7.88
	DMSO-d_6	8.40	1.00	0.38	7.43	1.84	7.75
	C_6D_6	8.40	1.00	0.24	7.39	1.87	7.78
V	$CDCl_3$	8.38	1.02	0.35	7.45	1.83	7.69
	DMSO-d_6	8.46	0.98	0.36	7.45	1.86	7.67
	C_6D_6	8.51	1.08	0.34	7.41	1.84	7.59
VI	$CDCl_3$	8.31	1.01	0.34	7.36	1.90	7.79
	DMSO-d_6	8.24	1.05	0.34	7.35	1.85	7.69
	C_6D_6	8.33	1.00	0.23	7.33	1.92	7.67

correlation with the substituent electronegativity, E_x. Castellano and Sun[16] observed a definite trend of coupling values with E_x in a study of a number of monosubstituted benzenes. J_{23} and J_{26} were found to increase, and J_{24} and J_{25} to decrease, with E_x, and it was suggested that the inductive effect of the substituent was the principal factor involved. Fraser,[17] on the other hand, from a consideration of the J_{ortho} values in a series of monosubstituted derivatives, concluded that the π-contributions to J were at least as important as the inductive effect. Some other studies have been done in establishing a qualitative correlation between J and E_x for disubstituted benzenes.[18-22]

If a simple additivity rule can be applied to the H–H coupling constants, the following equations can give estimates for the coupling constants of *o*-disubstituted benzenes.



$$J_{34}(XY) = J_{34}(X) + J_{23}(Y) - J_o$$
$$J_{35}(XY) = J_{35}(X) + J_{24}(Y) - J_m$$
$$J_{36}(XY) = J_{36}(X) + J_{25}(Y) - J_p$$
$$J_{45}(XY) = J_{45}(X) + J_{34}(Y) - J_o$$
$$J_{46}(XY) = J_{46}(X) + J_{35}(Y) - J_m$$
$$J_{56}(XY) = J_{56}(X) + J_{45}(Y) - J_o$$

where J_o, J_m, and J_p stand for the *ortho*-, *meta*-, and *para*-coupling respectively between two ring protons of unsubstituted benzene.

From the above equations, one can calculate the 51 J_o's, 34 J_m's, and 17 J_p's, using the coupling constants of the present compounds and monosubstituted benzenes.[23,24] The averaged values are 7.46, 1.30, and 0.67 for J_o, J_m, and J_p respectively. These values are in good agreement with the experimental values.[25]

16) S. Castellano and C. Sun, *J. Amer. Chem. Soc.*, **88**, 4741 (1966).
17) R. R. Fraser, *Can. J. Chem.*, **44** 2737 (1966).
18) P. F. Cox, *J. Amer. Chem. Soc.*, **85**, 380 (1963).
19) J. E. Loemker, J. M. Read, Jr., and J. H. Goldstein, *J. Phys. Chem.*, **72**, 991 (1968).
20) A. R. Tarpley, H. B. Evans, and J. H. Goldstein, *Anal. Chem.*, **41**, 402 (1969).
21) H. B. Evans, Jr., A. R. Tarpley, and J. H. Goldstein, *J. Phys. Chem.*, **72**, 2552 (1968).
22) S. Castellano and R. Kostelnik, *Tetrahedron Lett.*, **1967**, 5211.
23) S. Castellano, C. Sun, and R. Kostelnik, *ibid.*, **1967**, 5205.
24) K. Hayamizu and O. Yamamoto, *J. Mol. Spectrosc.*, **25**, 422 (1968).
25) J. M. Read, Jr., R. E. Mayo, and J. H. Goldstein, *J. Mol. Spectrosc.*, **21**, 235 (1966).