Substituent Shift Constants for the Aromatic Protons of Benzene Derivatives in Dimethyl Sulfoxide Solution

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An empirical set of substituent shift constants for 27 commonly encountered substituents, applicable to dimethyl sulfoxide solutions, for use in predicting the chemical shifts of aromatic protons has been derived. These constants differ from previously published constants determined from chemical shift measurements in relatively nonpolar solvents and yield more accurate predicted chemical shifts when the polar solvent, dimethyl sulfoxide, is required for nmr measurements of materials difficultly soluble in nonpolar solvents. Thus structural assignments can be made on these materials with increased confidence when the polar solvent is used.

A number of studies, summarized by Jackman and Sternhell,[1] have shown that the chemical shifts of ring protons in the nmr spectra of benzene derivatives can be predicted by the relationship

$$\delta = \delta_B - \sum_i S_i \quad (1)$$

The parameters, S, are substituent shift constants whose values depend mainly on the nature of the substituent and its orientation with respect to the ring proton in a given solvent system. δ_B is the chemical shift of benzene in the same system. Both δ_B and the values of S vary with the solvent employed for the nmr measurement.[2] Most of the values of S reported in the literature have been derived from measurements in nonpolar solvents, *e.g.*, carbon tetrachloride, hexane, cyclohexane, etc. A compilation of these is given in the monograph by Jackman and Sternhell. Smith listed S_o and S_m values for a wider variety of substituents from measurements on 1,4-disubstituted benzenes in both nonpolar and polar solvents, no S_p values being given. A fairly restricted set of substituent constants applicable to chloroform solutions is available.[3]

Benzene derivatives with multiple polar substituents are often poorly soluble in nonpolar solvents and nmr measurements on these compounds require polar solvents. Dimethyl sulfoxide-d_6 (DMSO-d_6) is a useful solvent not only for its high solvent power but because it is readily available at a relatively low cost. However, when predicted chemical shifts for ring protons calculated from eq 1 and the shift constants listed by Jackman and Sternhell are compared with the experimental shifts from measurements in DMSO-d_6 solution, large differences are observed in many cases.

In this laboratory, chemical shifts for the protons in several hundred benzene derivatives measured in dilute DMSO-d_6 solutions have been accumulated. These data were analyzed by a multiple regression procedure to obtain substituent shift constants for use in DMSO-d_6 solutions. With these constants it is possible to calculate predicted chemical shifts using eq 1 which closely approximate the observed chemical shifts. In addition, shift constants were derived for several frequently encountered substituents for which constants were not previously available.

(1) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," International Series of Monographs in Organic Chemistry, Vol. 5, 2nd ed, Pergamon Press, Oxford, 1969, p 202.

(2) G. W. Smith, *J. Mol. Spectrosc.*, **12**, 146 (1964).

(3) J. A. Ballantine and C. T. Pillinger, *Tetrahedron*, **23**, 1691 (1967).

Results and Discussion

The substituent constants derived in this work are listed in Table I. With these constants predicted chemical shifts for aromatic protons in a wide variety of benzene derivatives can be calculated using eq 1 and a value of 7.38 for δ_B. The standard deviation of these constants is usually less than δ 0.025. The largest standard deviations are δ 0.05 for S_p of the –NRR group and S_p for the phenyl group; only four chemical shifts involving the para orientation of these substituents were available for the calculation. The standard error

TABLE I

SUBSTITUENT SHIFT CONSTANTS FOR DMSO SOLUTIONS[a]

Substituent	S_o	S_m	S_p
–H	0.00	0.00	0.00
$-CH_3$	0.17 (214)[b]	0.07 (206)	0.18 (71)
$-CH_2R$	0.13 (55)	0.07 (63)	0.15 (20)
–CHRR	0.06 (34)	0.02 (20)	0.19 (11)
–CRRR	−0.03 (50)	0.05 (18)	0.15 (24)
–CH=CH (H, R)	−0.08 (11)	0.03 (12)	0.14 (5)
–CH=CHY[c]	−0.31 (35)	−0.10 (36)	−0.03 (13)
$-C_6H_5$[d]	−0.29 (31)	−0.12 (31)	0.03 (4)
–C(=O)H	−0.52 (39)	−0.20 (35)	−0.31 (18)
–C(=O)R	−0.54 (27)	−0.11 (23)	−0.23 (16)
–C(=O)Y[c]	−0.42 (24)	−0.21 (43)	−0.19 (13)
–C(=O)O– (H, R)	−0.53 (110)	−0.12 (68)	−0.19 (53)
–C(=O)NH– (H, R)	−0.60 (23)	−0.07 (21)	−0.16 (17)
–C≡N	−0.49 (49)	−0.24 (45)	−0.32 (22)
–OH	0.53 (188)	0.14 (267)	0.58 (63)
–OR	0.41 (139)	0.04 (107)	0.37 (40)
–OC(=O)R	0.17 (31)	−0.07 (39)	0.11 (13)
$-NH_2$	0.72 (94)	0.27 (105)	0.84 (32)
–NHR	0.81 (16)	0.15 (18)	0.87 (8)
–NRR	0.67 (34)	0.17 (23)	0.80 (4)
Hindered –NHR, –NRR	0.36 (16)	0.21 (26)	0.42 (16)
$-\overset{+}{N}H_2-$ (H, R)	−0.08 (32)	−0.14 (28)	0.09 (9)
–NHC(=O)R	−0.26 (46)	0.00 (44)	0.21 (20)
–N=NY[c]	−0.53 (31)	−0.19 (37)	−0.06 (9)
$-NO_2$	−0.78 (208)	−0.27 (131)	−0.34 (70)
–Cl	−0.10 (263)	−0.07 (202)	0.03 (70)
–Br	−0.24 (108)	−0.02 (72)	−0.01 (41)
–I	−0.38 (44)	0.20 (22)	−0.05 (16)
$-SO_3-$ (H, M)[e]	−0.34 (37)	0.00 (28)	0.04 (23)
$-SO_2NH-$ (H, R)	−0.45 (28)	−0.21 (23)	−0.22 (6)

[a] A negative sign indicates a downfield shift. [b] The number of entries for this substituent orientation in the set of simultaneous equations used to calculate these constants is given in parentheses. [c] Y is an unsaturated moiety conjugated to the main group double bond. [d] This can be a substituted phenyl ring, but substituents ortho to the bond joining the rings must be absent (see text). [e] M can be an alkali metal or an ammonium ion.

of estimate for the shifts of 1629 aromatic protons included in the regression analysis is δ 0.09 and almost 98% of the predicted shifts using these shift constants are within δ ±0.20 of the experimental shifts. None of the measured shifts differed by more than δ 0.31 absolute from the predicted shift.

These new substituent shift constants for DMSO-d_6 solutions are significantly different from those compiled for use with "inert" solvents by Jackman and Sternhell. Table II compares the constants of some common substituents for the two different media. The greatest differences are usually observed for the more polar substituents. There is no consistency of direction in the change of the constant with change of solvent medium.

TABLE II
COMPARISON OF SUBSTITUENT SHIFT CONSTANTS IN DMSO AND INERT SOLVENTS

Substituent	Orientation	S (DMSO)	S (inert solvent)[a]	Δ[b]
$-CH_3$	o	0.18	0.17	0.01
	m	0.07	0.09	−0.02
	p	0.18	0.18	0.00
-CRRR	o	−0.03	−0.04	0.01
	m	0.05	0.10	−0.05
	p	0.15	0.24	−0.09
-OH	o	0.53	0.50	0.03
	m	0.14	0.14	0.00
	p	0.58	0.40	0.18
$-NH_2$	o	0.72	0.75	−0.03
	m	0.27	0.24	0.03
	p	0.84	0.63	0.21
$-NO_2$	o	−0.78	−0.95	0.17
	m	−0.27	−0.17	0.10
	p	−0.34	−0.33	−0.01
-Cl	o	−0.10	−0.02	−0.08
	m	−0.07	−0.06	−0.01
	p	0.03	0.04	−0.01
-Br	o	−0.24	−0.22	−0.02
	m	−0.02	0.13	−0.15
	p	−0.01	0.03	−0.04
$-C\equiv N$	o	−0.49	−0.27	−0.22
	m	−0.24	−0.11	−0.13
	p	−0.32	−0.30	−0.02

[a] See ref 1. [b] $\Delta = S$ (DMSO) − S (inert solvent).

The molecules of DMSO have a pyramidal structure with the sulfur atom at one apex[4] and there is a large charge separation along the oxygen–sulfur bond giving this molecule a large permanent dipole moment.[5] Consequently, when benzene derivatives are dissolved in DMSO-d_6 strong collision complexes are formed, possibly by a dipole–dipole interaction, with polarizable substituents[6] or the π electrons of the ring. As a result the electronic configuration of the solute is modified and the inductive, resonance, and through-space (field) effects of the substituents differ from those observed for the same solutes in nonpolar solvents. In addition, the effective size of a substituent is increased in such complexes and thus any steric interactions between the substituent and the remainder of the molecule are changed. It has been shown that in dilute DMSO solutions of phenol and aniline derivatives intermolecular solute–solute hydrogen bonding is absent and intramolecular bonding is markedly decreased,[7] since the –OH and –NH groups of the solute are almost exclusively bonded to the DMSO molecules. In view of these considerations, it is hardly surprising that the previously published substituent constants, derived from measurements in relatively nonpolar solvents where strong solute–solvent complex formation is less likely, yield predicted chemical shifts with large deviations from the experimental chemical shifts measured in DMSO-d_6 solutions.

In the calculation of the substituent constants listed in Table I, it was assumed that the effect of each substituent on a ring proton was independent of all other substituents and that the actual chemical shift was solely an additive function of the nature and orientation of all the ring substituents. These are the same assumptions made for the derivation of the substituent constants quoted by Jackman and Sternhell. This is a simplistic view which ignores possible steric interactions between substituents, particularly adjacent substituents. Additional phenomena, such as residual intramolecular hydrogen bonding, resonance interaction between substituents through the π-bond network, changes in solute–solvent ratio in the complexed species, etc., can also increase or decrease the chemical shifts of ring protons. In a given compound several of these may be operating simultaneously. Their net effect is usually small and no attempt has been made, except as noted below, to correct the constants listed in Table I for these phenomena. Application of such corrections would require prior knowledge of the structure of the compound, and a major purpose of this work was to obtain substituent shift constants which would aid in the identification of unknown structures. The relatively small standard error of estimate for predicted chemical shifts calculated from the substituent shift constants of Table I justifies this approach.

Preliminary calculations of the shift constants showed that two steric effects on ring proton shifts in multiply substituted benzene derivatives were too great to be ignored. The first of these was observed in biphenyl compounds; the second, in *N*-alkyl- and *N*,*N*-dialkylaniline derivatives.

When biphenyls have one or more substituents ortho to the bond joining the rings, the two rings may no longer be coplanar. In twisted biphenyls the resonance interaction between the rings is decreased and the protons of one ring are more shielded by the field effect of the ring current of the other ring. The magnitude of these changes is a function of the dihedral angle between the two rings and the largest changes are noted for ring protons ortho to the bond joining the rings. Therefore chemical shift data from biphenyl derivatives with substituents ortho to the bond joining the rings were not included in the computation of the substituent constants of Table I. The listed constants should be applied with caution in making structural determinations for unknown biphenyl derivatives.

Ring protons ortho and para to the amino group in *N*,*N*-dialkylanilines having a second substituent adjacent to the amino group are significantly deshielded as compared to *N*,*N*-dialkylanilines without an ortho substituent. Similar deshielding is also observed for

(4) Y. A. Kolesnick and V. V. Kozlow, *Russ. Chem. Rev.*, **37**, 519 (1968).
(5) D. Martin, A. Weise, and H. Niclas, *Angew. Chem., Int. Ed. Engl.*, **6**, 318 (1967).
(6) P. Weiner and E. Malinowski, *J. Phys. Chem.*, **75**, 3971 (1971).
(7) G. Gribble and F. Bousquet, *Tetrahedron*, **27**, 3785 (1971).

protons para to the alkylamino group in *N*-alkylanilines with substituents in both the 2 and 6 positions. In these derivatives substituent crowding forces the alkylamino groups out of the plane of the ring and the resonance contribution of the alkylamino group to the shielding of ortho and para protons is decreased. Shielding of protons meta to these alkylamino groups is not greatly altered. The chemical shift data from compounds containing these hindered alkylamino groups was segregated and used to compute the substituent constants for "hindered –NHR, NRR" given in Table I.

The substituent shift constants obtained in this study for DMSO solutions have proven to be very useful in identifying or confirming the structures of benzene derivatives and for making preliminary assignments of shifts in computer analyses of spectra. It must be emphasized that they reflect the average effect of a complexed substituent upon the ring protons and for a given compound calculated and observed shifts can differ. Even so, they yield closer estimations of the chemical shifts to be expected when the polar solvent DMSO-d_6 is employed for examination of compounds difficultly soluble in the usual nonpolar solvent. Comparison of scattered data in the literature on chemical shifts of benzene derivatives examined in acetone, also a highly polar solvent with some properties similar to that of DMSO, have indicated that the new substituent shift constants can sometimes yield predicted shifts which are closer to the measured values than the previously available constants for nonpolar solvents. The utility of the new values for qualitative assessment of substituent effects on chemical shifts of ring protons in condensed aromatic and heterocyclic compounds which are seldom appreciably soluble in nonpolar solvents is obvious.

Experimental Section

The compounds of known structure employed in this study were obtained by purchase from chemical supply houses or were synthesized in the laboratories of American Cyanamid Co. The samples were of high purity as evidenced by the absence of extraneous signals in their nmr spectra and were used without further purification. The spectra were obtained in DMSO-d_6 solutions containing less than 10% solute (w/v) with 1% sodium 3-trimethylsilylpropane-1-sulfonate (DSS) added as the internal standard. The deuterated DMSO (99.5% isotopic purity) was purchased from commercial suppliers and dried and stored over Linde Type 4A Molecular Sieves.

Spectra were measured on either a Varian A-60 spectrometer with the charts calibrated using a standard $CHCl_3$–TMS reference sample or on a Varian HA100-D spectrometer with calibration by means of the V-4315A frequency counter. Solution temperatures were maintained at 32–34°. A number of compounds were examined on both spectrometers; the chemical shifts abstracted from these spectra agreed within ±0.02 ppm. The observed shifts for the protons in the compounds used in this study ranged from δ 5.70 to 9.18 *vs.* DSS.

The unsubstituted benzene singlet signal determined from repetitive measurements on 5–10% (w/v) solutions in DMSO-d_6 at 34° was 737.6 ± 0.4 Hz downfield from the DSS signal. Therefore, a value of 7.38 was taken for δ_B in this work.[8]

The second-order aromatic signal patterns usually obtained were analyzed either by the algebraic methods described by Garbisch[9] or by the use of the iterative computer program LAOCOON-3.[10]

Assuming that the effect of a substituent depends only on its orientation with respect to the proton under consideration and that the effects of other protons regardless of their orientation are zero, an equation of the following type was written for each proton included in this study.

$$\delta_B - \delta_{exp} = \sum_{i,j} n_{i,j} S_{i,j} \quad (2)$$

δ_{exp} is the observed shift *vs.* DSS of an aromatic proton in DMSO-d_6 solution. The coefficients, n, could have the values of 0, 1, or 2 depending on the number of substituents of a given type in the relevant orientation. The indices, i and j, define the nature and orientation of the substituent having the shift constant S. For example, the equations written for the protons of 3-nitro-4-cyanotoluene were

$$\text{H-2}\quad 7.38 - 8.24 = -0.86 = S_{o,CH_3} + S_{o,NO_2} + S_{m,CN} \quad (3a)$$

$$\text{H-5}\quad 7.38 - 8.04 = -0.66 = S_{m,CH_3} + S_{m,NO_2} + S_{o,CN} \quad (3b)$$

$$\text{H-6}\quad 7.38 - 7.84 = -0.46 = S_{o,CH_3} + S_{p,NO_2} + S_{m,CN} \quad (3c)$$

In this manner 1629 equations involving constants for 29 different substituents were obtained. Simultaneous solution of these equations resulted in the 87 shift constants listed in Table I.

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(8) δ_B is 7.41 when TMS is used as the internal standard.
(9) E. W. Garbisch, Jr., *J. Chem. Educ.*, **45**, 311, 402 (1968).
(10) S. Castellano and A. A. Bothner-By, private communication.