A Proton Magnetic Resonance Study of N^1-Substituent Effects on Sulfanilamides

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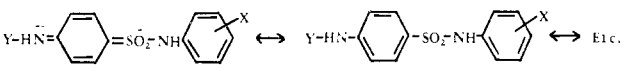
The pmr spectra for a congeneric series of substituted N^1-phenylsulfanilamides and their N^4-acetyl derivatives have been determined and qualitatively analyzed. Transmission of N^1-substituent effects through the SO_2 group could not be detected in this study. Dispersion in a plot of the chemical shifts of the sulfanilyl ring protons *vs.* the Hammett or Taft substituent constants for the anilines from which the sulfanilamides were derived is explained in terms of the ring current originating from the substituted anilyl moiety.

The sulfonamides constitute a class of biologically important compounds on which an extensive literature has developed.[2] Still, however, the electronic features of these compounds which may contribute to their action are only partially understood. Dipole measurements on benzenesulfonamides[3] and diaryl sulfones[4] indicate that there is conjugation between the sulfone group and a *p*-amino group. This has been substantiated by a number of uv spectral studies,[5] all of which suggest a considerable contribution from a structure such as I. On the other hand, it is not clear whether



I II

Y = $COCH_3$, H

the contribution of canonical structure I varies with the nature of the sulfonamide. Thermochemical measurements[6] and uv studies[5] are in apparent support of the view[7] that the nature of the sulfonamide will determine the contribution of I, but recent infrared[8] and pK_a'[9] studies contradict this view. Because of these conflicting reports and since no systematic study of the pmr spectra of biologically important sulfonamides appears to have been reported, we felt it worthwhile to pursue this approach for the insight that such a study could provide into the electronic nature of sulfonamides.

Experimental Section

The substituted N^4-acetyl-N^1-phenylsulfanilamides used in this study were prepared following well-established procedures.[2a] Hydrolysis to remove the N^4-acetyl group of these compounds was best accomplished following the methods given by Goldschmidt.[10] All of the compounds were crystallized from EtOH following decolorization with activated charcoal. Final purification of the compounds was facilitated by concentrating the material to be crystallized by refluxing the crystallizing solvent through a Soxhlet thimble which contained some of the compound.

All data were determined with a Varian Model A-60 nmr spectrometer at the normal operating temperature.[11] Except where stated otherwise, all pmr spectra were determined using Fischer Certified THF as solvent, which was used as received, and TMS as an internal standard. For convenience, the data are presented relative to the ring-proton absorbance of N^4-acetylsulfanilamide (singlet, τ 2.30). Chemical shifts upfield from this signal are assigned a positive value, and those that appear downfield are assigned a negative value.

Since all of the compounds in this study possess potentially acidic hydrogens, a dilution study was conducted using N^4-acetyl-N^1-(*p*-chlorophenyl)sulfanilamide. Both aromatic absorbances for this compound occur as a singlet. No significant variation in the chemical shift of either of these absorbances was noted (Table I). All chemical shifts which are subsequently reported were determined with the compounds in 2–5% (w/v) solution.

TABLE I

CHEMICAL SHIFTS OF THE RING PROTON ABSORBANCES OF N^4-ACETYL-N^1-(*p*-CHLOROPHENYL)SULFANILAMIDE AS A FUNCTION OF CONCENTRATION

Concn, % (w/v)	Chemical shift ν, cps[a] Sulfanilyl ring	*p*-Chlorophenyl ring
2.0	2.0	33.0
6.6	1.5	32.7
10	1.2	33.0
20	0.5	32.2

[a] The estimated uncertainty in these determinations is ±0.5 cps.

Results and Discussion

The N^1-phenylsulfanilamides (I, II, Y = H) provide spectra that are in general agreement with what is expected. The sulfanilyl ring (S ring) protons are coupled and lead to an $A'_2B'_2$ pattern,[12] while the anilyl ring (A ring) protons couple to produce patterns consistent with the type of substitution. The coupling constant for the vicinal protons on the S ring (Table II) is $J_{obsd} = 8.8 \pm 0.1$ cps.

The S-ring absorbance for all of the N^4-acetyl-N^1-phenylsulfanilamides (I, II, Y = CH_3CO), except that derived from *o*-toluidine is a singlet (Table III). The S-ring absorbance of N^4-acetylsulfanilamide is also a singlet. The occurrence of a singlet for the S-ring absorbance in so many of these compounds strongly

(1) Trainee, National Institutes of Health Training Grant 5-T1-GM-484, 1965-1967; National Institutes of Health Predoctoral Fellow, 1967-.

(2) For still pertinent reviews see (a) E. H. Northey, "Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948; (b) J. K. Seydel, E. Krüger-Thiemer, and E. Wempe, *Jahrb. Borstel.*, **5**, 652 (1961).

(3) W. D. Kumler and I. F. Halverstadt, *J. Am. Chem. Soc.*, **63**, 2182 (1941).

(4) J. A. Singer, W. P. Purcell, and C. C. Thompson, *J. Med. Chem.*, **10**, 528 (1967).

(5) P. Grammaticakis, *Bull. Soc. Chim. France*, **21**, 92 (1954); (b) S. F. Quan, T. C. Daniels, and W. D. Kumler, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 321 (1954); (c) S. Yamabe, *Japan J. Pharm. Chem.*, **22**, 23 (1950); (d) J. M. Vandenbelt and L. Doub, *J. Am. Chem. Soc.*, **66**, 1633 (1944).

(6) (a) Z. V. Pushkareva and Z. Yu. Kokoshko, *J. Gen. Chem. USSR*, **16**, 1269 (1946); (b) B. G. Boldyrev and I. Ya. Postovsky, *Soviet Pharm. Res.*, **3**, 1 (1952).

(7) W. D. Kumler and T. C. Daniels, *J. Am. Chem. Soc.*, **65**, 2190 (1943).

(8) J. Brandmüller and M. Wahl, *Arzneimittel-Forsch.*, **17**, 392 (1967).

(9) M. Yoshioka, K. Hamamoto, and T. Kubota, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **84**, 412 (1963).

(10) S. Goldschmidt, Dutch Patent 60,705 (March 15, 1948); *Chem. Abstr.*, **42**, 4201 (1949).

(11) We are extremely grateful to A. H. Robins Co., Richmond, Va., for allowing us to make use of their instrument, and to Mr. Ashby Johnson who determined these spectra for us.

(12) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965.

TABLE II

PROPERTIES OF N¹-PHENYLSULFANILAMIDES

Anilyl ring substituent	σ[a]	Mp (lit.), °C[b,c]	Nature[d]	Sulfanilyl ring ν, cps[e]	Sulfanilyl ring J_{obsd}, cps
4-CH_3O	−0.27	200–201 (198[f])	Q	46.1	8.8
4-C_2H_5O	−0.25	198.5–199 (197[g])	Q	45.5	8.8
4-CH_3	−0.17	188–189 (188–189[h])	Q	45.3	8.7
H	0.00	193–194 (195[f])	Q	44.0	8.8
4-Cl	+0.23	195–196 (194–195[i])	Q	43.7	8.7
4-Br	+0.23	201–202.5 (200–201.5[i])	Q	43.1	8.9
4-I	+0.28	205.5–206.5 (204[j])	Q	43.4	8.9
4-$COCH_3$	+0.50	209–210 (211[h])	Q	39.8	8.9
4-NO_2	+0.78	166–167 (165[h])	Q	38.2	8.7
3-CH_3O	+0.12	162–162.5 (162[j])	Q	42.7	8.9
3-I	+0.35	131.5–132 (132–134[f])	Q	42.3	8.9
3-Cl	+0.37	133–133.5 (129–135[f])	Q	41.6	8.8
3-Br	+0.39	141–142 (142[j])	Q	40.7	8.9
3-NO_2	+0.71	177–178 (180[f])	Q	40.0	8.8
2-CH_3O	−0.39	198–199 (203–206[f])	Q	45.8	8.8
2-CH_3	−0.17	154–154.5 (155.5[h])	Q	46.7	9.0
2-Cl	+0.20	169.5–170 (169–172[k])	Q	44.2	8.9
2-Br	+0.21	166–167	Q	44.8	8.8
2-I	+0.25[l]	158.5–159.5	Q	44.0	8.9
2-NO_2	+0.80	177–178 (179[f,h])	Q	39.5	9.0
Sulfanilamide		163–164 (163[m])	Q	38.6	8.8

[a] K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964. [b] All melting points are uncorrected. [c] Considerable variations in melting points are noted depending on the crystallizing solvent. This no doubt reflects their polymorphic nature. [d] Q designates an $A'_2B'_2$ quartet, S a singlet. [e] Chemical shift measured to the center of the pattern relative to N⁴-acetylsulfanilamide. [f] Reference 12b. [g] E. Plazek and J. Richter, *Roczniki Chem.*, **21**, 148 (1947); *Chem. Abstr.*, **42**, 5436*d* (1948). [h] C. Marchant, *et al.*, *Can. J. Res.*, **20B**, 5 (1942). [i] Y. Osawa, *Nippon Kagaku Zasshi*, **84**, 137 (1963); *Chem. Abstr.*, **59**, 13863*a* (1963). [j] R. Benisch, *Chem. Ber.*, **81**, 297 (1948). [k] H. Stevenson, *et al.*, British Patent 840,122 (July 6, 1960); *Chem. Abstr.*, **55**, 7437*e* (1961). [l] Estimated value. [m] C. D. Hodgman, Ed., "Handbook of Chemistry and Physics," 42nd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1960–1961.

TABLE III

PROPERTIES OF N⁴-ACETYL-N¹-PHENYLSULFANILAMIDES

Anilyl ring substituent	σ[a]	Mp (lit.), °C[b,c]	Nature[d]	Sulfanilyl ring ν, cps[e]
4-CH_3O	−0.27	200–201 (200–201[f])	S	5.7
4-C_2H_5O	−0.25	207–207.5 (206[g])	S	5.7
4-CH_3	−0.17	205–206 (208[h])	S	5.0
H	0.00	209–210 (210[i])	S	4.0
4-Cl	+0.23	202–203 (203–205[j])	S	2.5
4-Br	+0.23	206–207 (208[h])	S	2.0
4-I	+0.28	208.5–209.5 (202[k])	S	2.0
4-CH_3CO	+0.50	243.5–244.5 (254[h])	S	0.0
4-NO_2	+0.78	254 dec (258[h])	S	−3.0
3-CH_3O	+0.12	191.5–192.5 (192[k])	S	2.0
3-I	+0.35	217–217.5	S	1.0
3-Cl	+0.37	198.5–199.5 (197[k])	S	1.0
3-Br	+0.39	208.5–209.5 (201[k])	S	1.0
3-NO_2	+0.71	236–238 (236–237[l])	S	−0.5
2-CH_3O	−0.39	209–209.5 (212–213[f])	S	6.0
2-CH_3	−0.17	241–242 (244[h])	Q	7.0[m]
2-Cl	+0.20	237.5–238.5	S	4.0
2-Br	+0.21	235.5–237	S	3.7
2-I	+0.25[n]	219.5–220.5	S	3.5
2-NO_2	+0.80	203–204.5 (200–201[h,l])	S	−1.0
Sulfanilamide	...	215–216 (218[o])	S	(0.0)

[a–e] See corresponding footnotes in Table II. [f] R. G. Sheperd, *J. Org. Chem.*, **12**, 275 (1947). [g–h] See corresponding footnotes in Table II. [i] A. Mangini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **4**, 127 (1940); *Chem. Abstr.*, **34**, 7286[6] (1940). [j] G.Speroni, *Chim. Ind* (Milan), **34**, 391 (1952); *Chem. Abstr.*, **47**, 2924*b* (1953). [k] Footnote *j*, Table II. [l] G. L. Webster and L. D. Powers, *J. Am. Chem. Soc.*, **60**, 1553 (1938). [m] J_{obsd} = 9.2 cps; determined with dimethyl sulfoxide-d_6 as solvent. [n] Footnote *l*, Table II. [o] Footnote *m*, Table II.

suggests that resonance between the S ring and the A ring is minimal. If appreciable resonance did exist it would be expected[13,14] that many, probably most, of the S-ring absorbances should be either a complete or a partially resolved $A'_2B'_2$ quartet.

(13) (a) H. M. McConnell, *J. Mol. Spectry.*, **1**, 11 (1957); (b) P. F Cox, *J. Am. Chem. Soc.*, **85**, 380 (1963).

(14) M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960).

The minimal nature of the resonance, if indeed there is resonance, between the S ring and the A ring is further exemplified by a comparison of the chemical shifts for the S-ring and A-ring protons in the N⁴-acetylated and nonacetylated series. Removal of the acetyl group causes the S-ring absorbances to move roughly 40 cps upfield (Tables II and III), whereas the absorbances for the A-ring protons remain essentially un-

TABLE IV
PMR SPECTRAL PROPERTIES OF THE *para*-SUBSTITUTED ANILYL RING

Ring substituent	Nature[a]	N^1-Phenylsulfanilamides ν, cps[b]	N^1-Phenylsulfanilamides $J_{A(B)}$, cps	N^4-Acetyl derivatives ν, cps[b]	N^4-Acetyl derivatives $J_{A(B)}$, cps
4-CH_3O	Q	49.9	9.2	50.9	9.2
4-C_2H_5O	Q	51.2	8.9	51.4	9.2
4-CH_3	S	44.6	----	43.6	----
H	S	37.0	----	35.8	----
4-Cl	S	34.8	----	33.6	----
4-Br	Q	32.0	9.1	30.9	9.0
4-I	Q	29.8	9.0	29.2	8.8
4-$COCH_3$	Q	11.7	8.8	12.2	8.7
4-NO_2	Q	2.0	9.1	1.0	9.1

[a] Q designates an $A'_2B'_2$ quartet, S a singlet. [b] Chemical shift measured to the center of the pattern relative to N^4-acetylsulfanilamide.

changed in position (Table IV). Thus, while the S ring has had its electron density increased by the removal of the acetyl group, it does not appear that any significant amount of this increased electron density finds its way to the A ring.

In each of the Tables II and III, the chemical shifts of the S-ring protons are found to vary over a range of 8–9 cps. In light of the above observations, and since throughout each series only the substituent attached to the A-ring is varied while the rest of the molecule and the solvent remain unchanged, it appears that the variations in chemical shift noted for the S-ring protons must be attributed primarily to field effects originating from the A ring. Consistent with this view, it is found that a plot of the chemical shifts for the S-ring protons of the N^4-acetylated sulfanilamides[15] *vs.* the Hammett or Taft σ values for the substituents on the anilines from which they were derived (Figure 1) affords a series of three lines, each of which differs in slope and each of which can be identified with a single mode of substitution. The equations corresponding to these lines, as determined by least-squares analysis, are given by

para substituted $\quad \nu = -8.00\sigma + 3.84 \quad (r = 0.992)$
ortho substituted $\quad \nu = -8.23\sigma + 5.56 \quad (r = 0.999)$
meta substituted $\quad \nu = -4.23\sigma + 2.54 \quad (r = 0.997)$

where r is the correlation coefficient for the fit cited. The point corresponding to the *o*-methyl compound was measured relative to the center of the observed coupling pattern (THF). The point corresponding to the *o*-methoxy member was deleted in arriving at the equation for the series since inspection of Figure 1 indicates this compound to be more electronegative than usual. This may be attributed to a weak hydrogen bonding between the sulfonamido hydrogen and the methoxy oxygen, which would simultaneously diminish the delocalization of electron density from the methoxy oxygen into the aromatic ring to which it is attached and impart a partially positive charge on the methoxy oxygen.

The dispersion noted in Figure 1 can be said to arise because of the operation of at least two different interaction mechanisms, each of which is related to substituent effects but neither of which is simply correlated

(15) Less uncertainty is associated with the assignment of the chemical shifts for these singlet absorbances than would be associated with the assignment of chemical shifts to the center of the $A'_2B'_2$ pattern of the nonacetylated sulfanilamides.

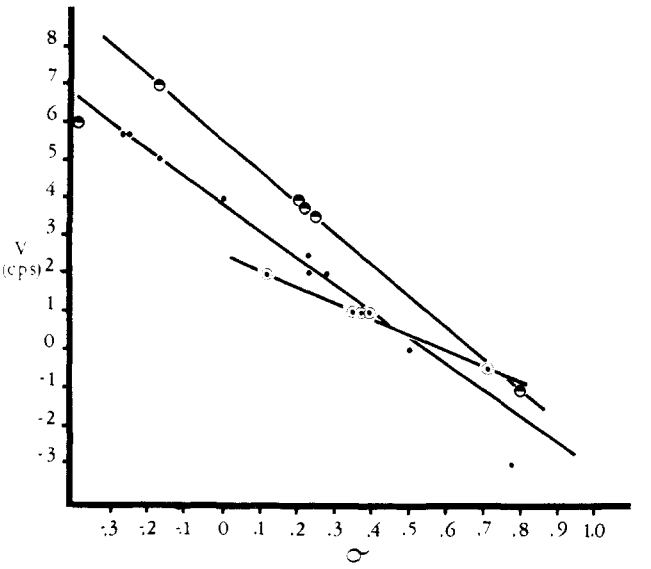


Figure 1.—Chemical shifts of the sulfanilyl ring protons of N^4-acetyl-N^1-phenylsulfanilamides plotted against the Hammett or Taft values of the substituents on the anilines from which they are derived: ◓, *ortho* substitution; ⊙, *meta* substitution; ●, *para* substitution.

with the other(s).[16] A consideration of Fisher–Hirschfelder–Taylor models of representative compounds in these series affords an indication of possible interaction mechanisms that could operate and also provide some insight into the seemingly anomalous behavior of the *o*-methyl compound. The models indicate that when rotation occurs about the SO_2–N bond the plane of the A ring will pass close to and almost parallel with the plane of the S ring. This mode of rotation appears as probable for an A ring possessing *meta* and *para* substituents as for an A ring with *ortho* substituents. Since in rotating about the SO_2–N bond the relative disposition of the aromatic rings enables each ring to pass through the field of the ring current generated by the other, the protons of each ring will be subject to a mutual shielding. By varying substituents on the A ring, the electron density within this ring will naturally be varied. Thus, an electron-donating substituent, for example, on the A ring would increase the strength of its field effect, relative to that of the unsubstituted A ring, and thereby cause the S-ring protons to appear more effectively shielded. In these terms, the dispersion represented in Figure 1 results from the effect of a substituent on both the ring current of the A ring and on the conjugative interaction of the aromatic moiety of this ring through its C–N bond. Since each of these effects is related to the nature of the substituent, then the fact that each operates within the same nucleus, but in a direction roughly perpendicular one to the other, is sufficient to account for the observed dispersion.

From a study of models, it also appears that the presence of *ortho* substituents in the A ring primarily restricts rotation about the C–N bond of this ring. Each of the *ortho* substituents employed in this study, except *o*-methyl, is capable of experiencing unfavorable steric and Coulombic interactions with the highly polar SO_2 oxygen. Seemingly, because of these inter-

(16) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

actions, an A ring with an *ortho* substituent other than methyl will be constrained to rotation about the SO_2–N bond, whereas an A ring with an *o*-methyl substituent is capable of rotation about the SO_2–N bond as well as the C–N bond of the A ring. This additional degree of rotational freedom is sufficient to change the population distribution of the various rotational isomers and thereby lead to the seemingly "anomalous" S-ring absorption for this compound.[12] Other studies[17] indicate that interaction of the methyl group with the SO_2 group changes the S–O bond character. Thus, both of the latter factors may contribute to the appearance of an "anomalous" pmr S-ring absorbance in the *o*-methyl derivative.

Conclusion.—The persistence of a singlet absorption for the S ring in the N^4-acetylated series (I, II, Y = CH_3CO) and the essentially constant chemical shift for the A-ring protons in the members of the N^4-acetylated and the nonacetylated series strongly suggests that at least for nonacidic or nonionized acidic sulfanilamides, substituted phenyl substituents placed on the sulfonamido nitrogen have extremely little, or none, of their effect transmitted through the SO_2 group. This conclusion is not in agreement with the uv[5] and thermochemical results[6] previously cited.

It appears most likely that the discrepancy between the conclusions of this pmr study and the uv studies has its origin in the changing nature of the photoexcited states of these compounds. In this study only ground-state properties are being measured, while in the latter studies the electronic transition between the ground state and some photoexcited state is being determined. Assuming the electronic ground state to be the same in both instances, the spectral variations observed in the uv studies appear to reflect differences in the excited state properties of the various sulfanilamides. The uv studies could be indicating resonance conjugation in the excited state, the mixing of excited molecular orbitals between the S ring and the A ring when the planes of the latter are situated one above the other, or a combination of these factors. The discrepancy between this study and the thermochemical studies most probably is due to the polymorphic nature of crystalline sulfanilamides. Since the combustion experiments in the latter instance were performed using crystalline sulfanilamides of doubtful crystal structure, it must be inferred that these experiments were reflecting differences in the crystal nature of the compounds rather than fundamental electronic differences.

In conclusion, this study indicates that attempts to correlate the spectral properties of sulfanilamides with their observed bacteriostatic activities will be frustrated by the free rotation allowed about the SO_2–N bond when these compounds are in solution. Quests for such correlations apparently will require that model systems be constructed in which rotation about this bond is prohibited. These compounds, while no doubt biologically inactive or poorly so, should provide a more realistic approximation to the bound form of a sulfanilamide. Comparison of the spectral properties of these model systems with the biological activities of their unrestricted counterparts may thus prove more profitable in seeking correlations and in investigations of the electronic character of bound sulfanilamides.

(17) An ir analysis of these compounds has been completed and will be reported in detail at a later date. In solution, the S–O band positions for these N^1-phenylsulfanilamides is a function of their concentration. Extrapolation to zero concentration affords absorption values for the S–O bond which may be considered as independent of intermolecular association effects. The force constants for the S–O bond of the *ortho*-substituted compounds whose S-ring pmr absorbance appears as a singlet are relatively invariant. However, the *o*-methyl compounds studied have significantly lower values for their S–O force constant.

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Researches in the Indole Series. XX.[1] Quantum Mechanical Calculations and Charge-Transfer Complexes of Substituted Indoles

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Quantum mechanical as well as charge-transfer complex properties have been determined for a number of indole derivatives. Good agreement has been found between these two ways of evaluating the electron-donor ability. Methyl lysergate does not display exceptional donor ability.

The problem of correlating the "psychotropic" properties of molecules with some of their electronic properties has attracted much interest since the proposition of the "submolecular" hypothesis for the action of these drugs.[2] Chlorpromazine was found to be a very potent donor; Karreman, Isenberg, and Szent-Györgyi[2a] suggested that its tranquilizing activity might be related to an electron-donating action. These papers pointed out the remarkable ability of indole compounds to act as electron donors in the formation of charge-transfer complexes (CTC) with various donors, for instance, flavine mononucleotide (FMN).

The electron-donating ability of a compound can be estimated experimentally from the wavelength of the absorption maximum of the CTC formed with appropriate donors. With a given acceptor these wavelengths are inversely proportional to the ionization

(1) M. Julia, H. Sliwa, and P. Caubere, *Bull. Soc. Chim. France*, 3359 (1966), paper XIX in this series.

(2) (a) G. Karreman, I. Isenberg, and A. Szent-Györgyi, *Science*, **130**, 1191 (1959); (b) A. Szent-Györgyi, "Introduction to Submolecular Biology," Academic Press Inc., New York and London, 1960.