Structure and Properties of Sulfones. I. Electric Moment of 4,4'-Diaminodiphenyl Sulfone[1]

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The benzene and *p*-dioxane electric moments of 4,4'-diaminodiphenyl sulfone (DDS) and the benzene moment of 4,4'-diaminodiphenyl sulfide were determined at 25° and found to be 6.96, 7.71, and 3.44 D., respectively. The S–O bond moment was calculated to be 3.58 D. The higher moment in dioxane has been attributed to association. It was concluded that DDS as an antimalarial may compete with the zwitterion form of its competive antagonist, *p*-aminobenzoic acid.

A well-established drug used against leprosy, 4,4'-diaminodiphenyl sulfone (4,4'-sulfonyldianiline, DDS), is currently being used with some success against *Plasmodium falciparum*, which is resistant to synthetic antimalarials in common use.[2] Since it is reasonable that the activity of the drug is related to its physicochemical properties, we have initiated physicochemical characterization of the molecule and its analogs.

The nature of bonding in the sulfonyl group has been approached from the viewpoints of conjugation,[3] inductive effects,[4] and the possibility of contributions by the 3d orbitals of sulfur.[3–5] The state of the subject remains in controversy. We are directing our attention to this problem through studies in molecular structure and molecular orbital calculations.

Experimental Section

Reagents.—4,4'-Diaminodiphenyl sulfone (practical grade, Matheson Coleman and Bell) was recrystallized six times from anhydrous methanol, being once treated with decolorizing charcoal, and dried *in vacuo*, mp 178.0–178.5° (lit.[6] mp 178.5°). 4,4'-Diaminodiphenyl sulfide (K and K Laboratories) was dissolved in acetone and precipitated by addition of water; these crystals were recrystallized four times from water and decolorizing charcoal, and dried *in vacuo*, mp 108.8–109.1° (lit.[7] mp 105–107°).

Solvents.—The solvents, used without further purification, were spectroquality benzene (Matheson Coleman and Bell), spectroquality *p*-dioxane (Matheson Coleman and Bell), spectroquality cyclohexane (Matheson Coleman and Bell), SpectrAR acetone (Mallinckrodt), and analytical reagent chloroform (Mallinckrodt).

Electric Moments.—Electric moments, calculated by the Smith equation,[8] were determined as previously described,[9,10] refractive indices being determined to five places past the decimal point. Values of α (slope of dielectric constants *vs.* weight frac-

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tion) for 4,4'-diaminodiphenyl sulfone in benzene and in dioxane and for 4,4'-diaminodiphenyl sulfide in benzene were, respectively, 21.90, 30.62, and 6.497. Corresponding values for γ (slope of refractive index squared *vs.* weight fraction) were 0.6696, 0.8104, and 0.5278.

Results and Discussion

The electric moments and apparent S–O bond moments in benzene solution have recently been determined by Cumper and co-workers for several dialkyl sulfones[11] and diaryl sulfones;[12] it was found[12] that the apparent S–O bond moment of diaryl sulfones was quite sensitive to the nature of *para* substituents.

We found the electric moment of 4,4'-diaminodiphenyl sulfone in benzene at 25° (Table I) to be 6.96 ± 0.14 D. This value may be compared with values reported by Cumper, *et al.*[12] (Table I), for diphenyl sulfone, 5.05 D., 4,4'-ditolyl sulfone, 5.54 D., and 4,4'-dichlorodiphenyl sulfone, 3.30 D. The large difference in moment (1.91 D.) between 4,4'-diaminodiphenyl sulfone and diphenyl sulfone, effected by the strongly electron-releasing *p*-amino substituents, is reasonable in light of the difference (0.49 D.) between 4,4'-ditolyl sulfone and diphenyl sulfone attributed to the mildly electron-releasing *p*-methyl substituents.

We also determined in benzene at 25° the moment (Table I) of 4,4'-diaminodiphenyl sulfide (4,4'-thiodianiline), 3.44 ± 0.02 D., and used this value and that for the corresponding sulfone, according to the method of Cumper, *et al.*[11,12] (eq 1), to calculate the apparent S–O bond moment, 3.58 D., for 4,4'-diaminodiphenyl

$$\mu_{R_2SO_2} = 2\mu_{R-S} \cos \frac{1}{2}(\angle CSC) + 2\mu_{S-O} \cos \frac{1}{2}(\angle OSO) \quad (1)$$

sulfone. In eq 1 $\mu_{R_2SO_2}$ is the sulfone moment, μ_{R-S} is the group moment from the sulfide, R_2S, for which the CSC angle is assumed to be 107°; the other angles (eq 1) are 103° for <CSC and 124° for <OSO. The value, 3.58 D., may be compared (Table I) with the S–O bond moments determined by Cumper, *et al.*[12] for diphenyl sulfone, 3.65 D., 4,4'-ditolyl sulfone, 3.60 D., and 4,4'-dichlorodiphenyl sulfone, 4.27 D.

It should be recognized that the calculated S–O bond moment will reflect errors from the determination of the moment of 4,4'-diaminodiphenyl sulfone. The value, however, may give a rough indication of the extent of electronic interaction in the S–O bond, which

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TABLE I

ELECTRIC MOMENTS AT 25° AND APPARENT S—O BOND
MOMENTS OF 4,4′-DIAMINODIPHENYL SULFONE
AND RELATED COMPOUNDS

Compd	Solvent	Electric moment, D.	App S-O bond moment, D.
4,4′-Diaminodiphenyl sulfone	Benzene	6.96 ± 0.14	3.58
4,4′-Diaminodiphenyl sulfone	p-Dioxane	7.71 ± 0.03	
4,4′-Diaminodiphenyl sulfide	Benzene	3.44 ± 0.02	
Diphenyl sulfone	Benzene	5.05^a	3.65^a
4,4′-Ditolyl sulfone	Benzene	5.54^a	3.60^a
4,4′-Dichlorodiphenyl sulfone	Benzene	3.30^a	4.27^a

^{a} Taken from C. W. N. Cumper, J. F. Read, and A. I. Vogel, *J. Chem. Soc.*, 5860 (1965).

is a question of current interest.[5,11] The electron attracting p-chloro substituent causes a large increase in the S–O bond moment (4.27 D.) of 4,4′-dichlorodiphenyl sulfone, compared to the S–O bond moment (3.65 D.) of diphenyl sulfone. The chloro substituent is expected to exert a large inductive and a small resonance effect, as is indicated by its relative induction and resonance substituent constants.[13] If the primary effect of the p-chloro substituents were induction of electrons from the already partially positive sulfur[14] of the S–O bond, the S–O bond moment would be expected to rise, as it does.

On the other hand, the p-amino group should exert a large resonance and a small inductive effect[13] in a net direction opposite to that of the p-chloro substituent. If electrons were donated by the p-amino group through resonance to the partially positive sulfur, and if there were negligible resonance interaction between the sulfur and oxygen of the S–O bond as has been previously suggested,[3] the S–O bond moment would be expected to decrease significantly. That this S–O bond moment is found to be not very different from the corresponding bond moment for diphenyl sulfone might indicate the resonance release of electrons has extended to the oxygen of the S–O bond. The similarity of the S–O bond moments for 4,4′-diaminodiphenyl sulfone and diphenyl sulfone might be explained by the approximate balancing of effects of the amino groups: (1) the decrease in bond moment due to lessening in positive charge of the sulfur and (2) the increase in bond moment due to increase of electron density on the oxygen.

4,4′-Diaminodiphenyl sulfone has a low solubility in benzene and, therefore, the moment is difficult to measure in this solvent. For this reason, the moment was also determined in p-dioxane. The large solvent

effect (0.75 D.) was quite surprising in view of the close agreement between the benzene and dioxane moments of phenylmethyl sulfone, 4.73 D. and 4.77 D.,[15] respectively. This solvent effect suggests complex formation, quite possibly of the charge-transfer type,[16] between 4,4′-diaminodiphenyl sulfone and p-dioxane.

Antimalarial activity of DDS is competively antagonized by p-aminobenzoic acid (PABA).[17] If the competition of DDS with PABA is influential in the antimalarial action of DDS and if the carbonyl bond of PABA plays a role in its biological interactions, the similarity of the S–O bond of DDS to the C=O bond of PABA may be of importance in the antimalarial action of DDS. Comparison of the bond moments of S–O in DDS (3.58 D.) and C=O (2.3 D.[18]), such as would be expected for the carbonyl group in PABA, shows considerable difference in the polarity of these two groups. This observation could mean that the interaction of DDS with the PABA receptor is not

DDS   PABA
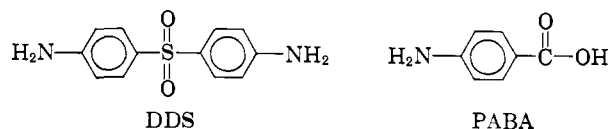
sensitive to the polarity of the S–O bond. An alternate conclusion, however, may be offered by the observation that PABA can exist in the zwitterion form (13% zwitterion in aqueous solution[19]). The C-O⁻ group of the zwitterion of PABA is considerably more polar than the neutral carbonyl group and, therefore, is more comparable to the S–O bond of DDS. The nature of the amino groups of DDS may also be more similar to the amino groups of the zwitterion of PABA than those for the uncharged species of PABA, since the strongly inductive sulfonyl group undoubtedly makes the amino groups electron deficient or relatively positively charged. Comparison of these physicochemical parameters for DDS and PABA suggests that DDS may be competitive with PABA in the zwitterion form; this possibility should not be overlooked in the design of antimalarials having a mode of action similar to that of DDS.

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