Folded Conformations. IV. Intramolecular Shielding and Intramolecular Charge-Transfer Interaction in Benzyl Phenyl Sulfones and Sulfoxides

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Proton magnetic resonance spectra of the title compounds (A-SO₂CHR-D) were measured and compared with the spectra of appropriate reference systems containing an alkyl substituent instead of one of the aromatic rings. The observed upfield shifts of the aromatic proton resonances in the title compounds suggest that there is a significant population of folded conformations, which possess a *gauche* orientation of the aromatic rings. This conclusion is supported by the observation of an intramolecular charge-transfer band in the u.v. spectra of the compounds containing an A ring of high electron affinity and a D ring of low ionization potential. Stabilization of the folded forms may be obtained through minimizing the $n-\pi$ repulsive forces between the sulfonyl oxygen lone pairs and the π -electron system of the D ring.

Les spectres de résonance magnétique nucléaire des composés cités (A-SO₂CHR-D) ont été enregistrés et comparés avec les spectres de référence de systèmes appropriés contenant un substituant alkyle au lieu d'un des cycles aromatiques. Les déplacements observés pour les protons aromatiques vers un champ élevé, l'aissent penser à l'existence d'une population importante en conformères plissés qui possèdent une orientation gauche pour les cycles aromatiques. Cette conclusion a été confirmée par l'observation en u.v. d'une bande de transfert de charge intramoléculaire pour les composés possédant un cycle A d'électroaffinité élevée et un cycle D à faible potentiel d'ionisation. La stabilisation des formes plissées peut être obtenue par minimisation des forces répulsives $n-\pi$ entre les doublets libres de l'oxygène du groupe sulfonyle et le système électronique π du cycle D. [Traduit par le journal]

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Introduction

During recent years it has been established that in solution a number of relatively simple molecules, possessing many degrees of internal rotational freedom, occur in preferred folded conformations (1–6). In suitably designed structures reliable probes for the detection of these folded conformations are: (*i*) intramolecular (de)shielding effects in n.m.r. spectra and (*ii*) intramolecular charge-transfer (CT) interaction between donor (D) and acceptor (A) groups which are positioned in the vicinity of each other as a result of the folding of the molecule (2, 7–13).

It has been shown by X-ray crystallography that the folded conformation of cyclo-glycyl-Ltyrosyl (14) and of ethyl *N*-methyl-*N*-*p*-tolylsulfonylmethylcarbamate (15) is retained in the solid state. In sharp contrast, 2-methyl-3-*N*methylanilinomethyl-1,4-naphthoquinone, which shows intramolecular CT interaction in solution (10), adopts an unfolded conformation in the crystal (16).

The causes of the folding of the molecules

in question have not been defined clearly. Intramolecular dipole-dipole interactions, dipoleinduced dipole interactions, and dispersion forces have all been invoked to explain the conformational preferences (3-5).

Preliminary work (2) has demonstrated the occurrence of folded conformations for benzyl phenyl sulfones (A-SO₂CH₂-D). In continuing these studies, we have now obtained new data that shed some additional light on the factors that help to stabilize the folded forms.

Results and Discussion

In Table 1 chemical shifts are presented of the aromatic protons of systems of the type A-SO₂CHR-D (R = H and $-CH_3$). In order to check for n.m.r. spectral perturbations due to intramolecular proximity effects, the selection of proper reference compounds is of crucial importance. We have used systems related as closely as possible to the compounds under study, but lacking either the A or D aromatic ring (n.m.r. data also included in Table 1). Unfortunately, for the D part of **6** no reliable reference is available at the moment because of our inability to prepare the corresponding alkane sulfonyl derivative.

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	1	ł	D	
Compound	δ _{112,6} †	$\delta_{H_{3,5}}$ †	δ _{112,6} †	δ _{113,5} †
1 p -NO ₂ C ₆ H ₄ SO ₂ CH ₂ C ₆ H ₄ N(CH ₃) ₂ - p	7.77 (23.4)	8.23 (10.8)	6.88 (21.0)	6.54 (10.8)
$2 p - NO_2C_6H_4SO_2CH_3$	8.16	8.41		
$3 C_2 H_5 SO_2 CH_2 C_6 H_4 N(CH_3)_2 - p$			7.23	6.72
4 p -NO ₂ C ₆ H ₄ SO ₂ CH(CH ₃)C ₆ H ₄ N(CH ₃) ₂ - p	7.73 (25.8)	8.20 (12.6)	6.96 (18.6)	6.57 (7.8)
5 $C_2H_5SO_2CH(CH_3)C_6H_4N(CH_3)_2-p$	`		7.27	6.70
6 $(p-NO_2C_6H_4SO_2CH_2C_6H_4-p)_3NCH_3$	7.86 (18.0)	8.27 (8.4)	7.01‡	6.86 <u></u>
7 p -ClC ₆ H ₄ SO ₂ CH ₂ C ₆ H ₄ OCH ₃ - p	7.50 (21.6)	7.37 (10.2)	6.97 (21.0)	6.77 (9.6)
8 p -ClC ₆ H ₄ SO ₂ CH ₃	7.86	7.54		
9 n -C ₄ H ₉ SO ₂ CH ₂ C ₆ H ₄ OCH ₃ - p			7.32	6.93
10 p -ClC ₆ H ₄ S(O)CH ₂ C ₆ H ₄ OCH ₃ - p	7.36 (13.2)	7.26 (8.4)	(22.8) 6.82§ (0.0)	
11 p -ClC ₆ H ₄ S(O)CH ₃	7.58	7.40	· · · ·	
12 $n-C_4H_9S(O)CH_2C_6H_4OCH_3-p$			7.20	6.82
13 p -ClC ₆ H ₄ SCH ₂ C ₆ H ₄ OCH ₃ - p	(0,6) 7.178 $(0,6)$		7.13 (3.0)	6.78 (0.6)
14 p -ClC ₆ H ₄ SCH ₃	7.18§			
15 n -C ₄ H ₉ SCH ₂ C ₆ H ₄ OCH ₃ - p		-	7.18	6.79

TABLE 1. Chemical shifts of the aromatic protons of the D and A groups of the compounds $A-SO_2CHR-D$ (R = -Hand --CH₃), A-S(O)CH₂-D, A-SCH₂-D, and of suitable reference compounds (40°)*

Chemical shifts in p.p.m. downfield from internal TMS ($\delta = 0$). Concentration 0.2 M in CDCl₃. Ring carbon attached to SO₂, S(O), S, or CHR is called C_1 . †Upfield shifts ($\Delta \delta_H$) in Hz between parentheses.

¹No suitable reference available, §Center of broad singlet.

The data given in Table 1 reveal that the aromatic proton resonances of 1, 4, 6, and 7 are shifted to higher field by ca. 0.15-0.40 p.p.m. (" $\Delta \delta_{\rm H}$ -values"). Since the effect of dilution (0.1– 1.0 M) on the chemical shifts is negligible (<0.05 p.p.m.), significant shifts due to intermolecular shielding can be excluded. Therefore, the upfield shifts suggest that these compounds possess significant populations of conformations in which the aromatic rings experience each other's magnetic anisotropy effect.

In the benzyl sulfones a conformation with eclipsed aryl rings will be sterically unfavorable owing to $\pi - \pi$ repulsion. Conformations with S=O eclipsed with the D ring will be destabilized by $n-\pi$ repulsion. However, two gauche conformations, which permit mutual shielding of the aromatic ring protons, are easily attainable (Fig. 1). The observed upfield shifts are only slightly smaller than those found for the phenyl



FIG. 1. Newman projections of stable rotamers, that result from rotation about the SO2-CHR bond in A-SO₂CHR-D.

TABLE 2. Position (λ_{max}) and molar absorptivity (ε_{max}) of the intramolecular CT band of some sulfonyl systems (in CHCl₃)

Compound	Color	λ _{max} (nm)	ε _{max} (I mol ⁻¹ cm ⁻¹)
1	Orange	364	526
4	Orange	367	590
6	Red	365 (sh)	1740

absorptions of 1,8-diphenylnaphthalene (17) where the phenyl rings assume a preferred faceto-face arrangement.

Additional evidence for folding of the sulfonyl systems is provided by u.v. spectroscopy. Those compounds that contain an A ring of high electron affinity together with a D ring of low ionization potential are colored and they exhibit a broad and structureless long-wavelength absorption band which cannot be attributed to either of the separate chromophores (Table 2 and Fig. 2). The new band obeys Beer's law in the concentration range between at least 10^{-5} - 10^{-3} M. This strongly suggests that the band should be attributed to intramolecular CT interaction. Since it is reasonable to suppose that the σ and π electrons of the SO₂—CHR bridge are involved to only a minor extent in the CT interaction (18), the transition will be mainly

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FIG. 2. U.v. spectra of 10^{-3} *M* solutions of 4 (—), 2 (…), and *p*-CH₃C₆H₄CH₂C₆H₄N(CH₃)₂-*p* (---) in CHCl₃.

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the result of excitation of an electron from the highest occupied molecular orbital of the D ring to the lowest vacant orbital of the A ring in a folded conformation. However, there is a considerable difference in orientation of the A and D ring in the folded form of 1 as compared with that in the *inter*molecular complex between N,N-dimethyl-p-toluidine and methyl p-nitrophenyl sulfone because in the latter case a CT band is observed at much longer wavelength (2). It is of interest to note that sulfone **6**, which contains two potential donor-acceptor systems, shows a much larger ε_{max} (at 365 nm) than 1. Apparently both benzyl phenyl sulfone systems are partially folded in solution.

For 1, 4, and 7 (and the corresponding reference compounds) the temperature dependence of the n.m.r. and u.v. spectra was examined in the hope of obtaining sufficiently large effects to allow the calculation of the thermodynamic parameters for the equilibrium between folded and unfolded forms. Although at higher temperatures deshielding of the aromatic proton resonances was observed, indicating partial unfolding, the differences were distressingly small (*i.e.* <3 Hz over the range -60 to $+60^{\circ}$ in CDCl₃ or +40 to $+180^{\circ}$ in DMSO- d_6).

However, the temperature effect suggests that there exists a (small) preference for the folded gauche conformations. This is in contrast to the situation for (substituted) 1,2-diphenylethanes where the *trans*-form is definitely favored, presumably owing to the repulsive π - π interaction in the gauche forms (19).

For 1 an increase in temperature is accompanied by a small hypsochromic shift of the CT maximum (17.8°, λ_{max} 368 nm, ε_{max} 526 l mol⁻¹ cm⁻¹; 47.8°, λ_{max} 360 nm, ε_{max} 536 l mol⁻¹ cm⁻¹), most likely attributable to a solventeffect. The limited data presented in Table 3 also suggest that solute-solvent interactions play a role in determining the equilibrium between folded and unfolded forms. More polarizable solvents seem to destabilize the folded conformations of 7 in contrast to the minor effect of solvent polarizability on the folding tendency of some cyclic peptides (4).

The data obtained thus far do not allow definite conclusions regarding all possible mechanisms which may produce the folding tendency of the molecules. It is clear however, that CT interaction does not contribute significantly to the ground state stabilization as demonstrated by the approximately equal $\Delta\delta_{\rm H}$ values for **1** and **7**.

In order to investigate whether dipolar interactions involving the strongly polarized sulfuroxygen bonds of the sulfonyl function are effective in producing folded gauche conformations, we have prepared the sulfoxide and sulfide analogs of 7. The data in Table 1 reveal that intramolecular shielding is decreased in the sulfoxide 10 and is negligible in the sulfide 13, as compared with 7. These results may be rationalized by assuming that the repulsive interaction between the lone pairs on the sulfonyl oxygen(s) and the π -electron cloud of the D ring (Fig. 1) will at least partially determine the favored dihedral angle defined by the bonds C_1^{A} —S—CHR— C_1^{D} and therefore the folding tendency. The known preference (20) of aryl sulfones to adopt conformations in which the ring C_1^A 2p-orbital is staggered between the two sulfonyl oxygen atoms ("case II conjugation")

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D Α $\Delta \delta_{\text{II}_{2,6}}$ $\Delta \delta_{\mathfrak{H}_{3,5}}$ $\Delta \delta_{H_{216}}$ $\Delta \delta_{H_{3,5}}$ Compound Solvent 7 CDCl₃ 21.6 10.2 21.0 9.6 7 CF₃COOH $\sim 20^{+}$ ~ 3 18.6 8.4 7 ~ 2 15.6 DMSO-d₆ $\sim 16^{+}$ 5.4

TABLE 3. Solvent effects on the upfield shifts, $\Delta \delta_{H}^{*}$, of the aromatic protons of 7 (40°)

* $\Delta\delta_{\rm H}$ in Hz. Concentration of solute: 0.2 *M*. †Less accurate values because of the broad resonances.

TABLE 4. Chemical shifts of alkyl groups in some sulfones, sulfoxides, and sulfides

		Chemical shift* of			
Compound	CH ₃	CH ₃ CH ₂ SO ₂ —	-CH ₂ AI		
I6 CH ₂ SO ₂ CH ₂ C ₆ H ₆	2.74		4.26		
$17 \text{ CH}_3\text{SO}_3\text{CH}_3$	2.99				
18 C ₂ H ₅ SO ₂ CH ₂ C ₆ H ₅	1.29	2.83	4.18		
19 C ₂ H ₅ SO ₂ C ₂ H ₅	1.40	3.02			
20 $C_{7}H_{5}SO_{2}C_{6}H_{4}CH_{3}-p$	1.25	3.09			
21 CH ₃ SOCH ₂ C ₆ H ₅	2.45		4.03		
22 CH ₃ SOCH ₃	2.62				
23 $CH_3SCH_2C_6H_5$	1.96		3.64		
$24 \text{ CH}_{3}\text{SCH}_{3}$	2.06				

*Chemical shifts in p.p.m. downfield from internal TMS ($\delta = 0$). Concentration 0.2 M in CDCl₃.

will help to orient the A and D ring parallel to each other.

In an attempt to gain additional evidence for the proposed nonbonded interactions, the chemical shifts were measured of alkyl groups in some sulfones, sulfoxides, and sulfides containing either an aryl or an alkyl moiety in one of the β -positions (Table 4). In 16, 18, and 21, the methyl and ethyl groups clearly experience upfield shifts as compared with 17, 19, and 22, respectively, most likely due to the magnetic anisotropy effect of the β -aryl group.^{2, 3} Analysis of the intramolecular shielding of the methyl group in the gauche conformations of 16, 21, and 23 using Johnson and Bovey's isoshielding lines (21) and known bond angles and distances (22-24) reveals that the shielding should be approximately equal in 16 and 23 and appreciably less in 21 (Table 5).⁴ The data in Table 4 TABLE 5. Calculated and observed intramolecular shielding in the *gauche* conformations of 16, 21, and 23

	Shieldi	ng (Hz)	Mole fraction	
Compound	Calcd.	Observed	conformation*	
16	+18	+15	0.83	
21	+13	+10	0.77	
23	+18	+6	0.33	

*These values are presumably slightly too low because of the inductive effect of the $\beta\text{-aryl}$ ring (see text).

show however, that intramolecular shielding decreases in the order sulfone > sulfoxide > sulfide, as in the case of the benzyl phenyl sulfones, thereby supporting the proposed $n-\pi$ repulsive interactions.

Experimental

N.m.r. spectra were recorded on a Varian A-60 D spectrometer equipped with a Varian V 6049 variable temperature controller. The recorder was calibrated with a side band technique using a Hewlett-Packard 200 AB audiooscillator and a Hewlett-Packard 5223 L electronic counter. Chemical shifts are given relative to TMS ($\delta = 0$) as internal reference. If necessary, peak assignments were confirmed through the use of Eu(DPM)₃ as a paramagnetic shift reagent. U.v. spectra were taken with a Zeiss PMQ II spectrophotometer using 1 cm cells at

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 $^{^{2}}A$ downfield shift would be expected solely on basis of the inductive effect of the β -aryl ring.

³In 20 only the methyl part of the ethyl moiety can be positioned in the shielding region of the aromatic ring.

⁴Calculation of the intramolecular shielding in benzyl phenyl sulfones is less straightforward but it is reasonable to expect that the preference for *gauche* conformations will be decreased due to π - π repulsions.

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Table 6.	Yields and	physical	properties of	the new	compounds
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Compound	Yield (%)	M.p. (°C)	Color	Recrystallizing solvent	I.r. of SO or SO ₂ (cm ⁻¹ , KBr)
1	80	200–201	Orange	$CH_2Cl_2/MeOH$ (1:1)	1149, 1345
3	30	114.5-115.5	Colorless	EtOH (96%)	1115, 1300
4	80	166–167	Dark red	$CH_2Cl_2/MeOH$ (1:1)	1140, 1320
5	40	92–93	Colorless	EtOH (96%)	1125, 1300
6	40	207–209	Orange	$CH_2Cl_2/MeOH$ (1:1)	1140, 1305
7	70	151-153	Colorless	EtOH (96%)	1145, 1325
9	70	69-71	**	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	1120, 1300
10	70	141-143	**	"	1040
12	60	93-95	"	21	1020
13	80	71-73	**	EtOH (60%)	_
14	40	*	"		

*B.p. 119°/0.3 mm; n_D²⁰ 1.5400.

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room temperature and 2 cm cells at variable temperatures in a temperature-controlled cell holder. I.r. spectra were measured on a Perkin-Elmer model 257 or model 125.

Melting points (uncorrected) were determined with a Mettler FP 1 melting point apparatus equipped with a Mettler FP 52 microscope attachment. Elemental analyses were carried out in the Microanalytical Section of our Department (supervisor: Mr. W. M. Hazenberg) and were satisfactory for the new compounds described.

Compounds 2 (25), 8 (26), 11 (27), 14 (28), 16, 18, 20, 21, and 23 were prepared by literature procedures. The new compounds were prepared as follows: sulfones 1 and 3-6 by condensation of aromatic amine with formaldehyde (or acetaldehyde) and the appropriate sulfinic acid (29); benzyl sulfides 13 and 15 from the corresponding thiols with *p*-methoxybenzylalcohol (29, 30); and sulfoxides 10 and 12 and sulfones 7 and 9 by oxidation of 13 and 15, respectively, with 30% H₂O₂ in acetic acid (31). Yields and physical data of the new compounds are given in Table 6.

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