Preferred Conformer Assignments of Diaryl Sulfoxides Employing Aromatic Solvent Induced Shifts

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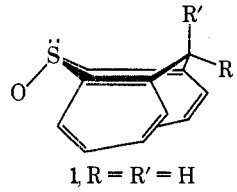
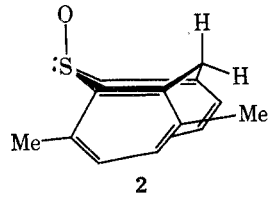
The changes in proton chemical shifts of a solute molecule on passing from a (presumably) noninteracting solvent (e.g., carbon tetrachloride or deuteriochloroform) to an aromatic solvent (e.g., benzene or toluene) are assumed to arise from long-range magnetic anisotropic effects of the solvent specifically solvated to solute molecules.[2] It is the general contention that aromatic solvent induced shifts (ASIS)[3] emanate from a number of factors including (a) solute–solvent collision complexes with time-averaged structures,[4] (b) clustering of partially oriented solvent molecules about polar sites of the solute,[5] and (c) charge-transfer interactions between solvent and solute.[2] In this manuscript we report a generalized application of ASIS to the determination of the stereochemistry of some diaryl sulfoxides.

From numerous citations[6] of aromatic anisotropic effects reflecting both steric and electronic factors of solute and/or solvent,[6a,b] we anticipated that the molecular dipoles of contrasting sulfoxides should experience different degrees of solvation (hence, shielding) in benzene solution.[6] Thus, the relative shielding effects experienced by a sensor proton might serve as a diagnostic probe for sulfoxides possessing a pseudo-axial (a′) or pseudo-equatorial (e′) sulfinyl oxygen atom conformation.

In an earlier report[7] we had shown that the preferred conformation of the sulfinyl oxygen atom in thioxanthene *S*-oxide (**1**) was 10e′ whereas that of the anancomeric 1,4-dimethylthioxanthene *S*-oxide (**2**) was 10a′. In both cases



1, R = R′ = H
cis-**3**, R = Me; R′ = H
trans-**3**, R = H; R′ = Me
4, R = R′ = Me



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the peri protons (H_4, H_5) are deshielded ($CDCl_3$) relative to the remaining aryl protons.[8] This shielding effect is considered to result from the combined inductive and anisotropic effect of the sulfinyl group.[9] However, in perdeuteriobenzene (C_6D_6)[10] the peri protons (H_4, H_5) of **1** are less shielded than the H_5 peri proton of **2**; in deuteriochloroform they are virtually identical ($\Delta\delta_{CDCl_3}$ 0.02 ppm). Hence, the observed chemical shift difference ($\Delta\delta_{C_6D_6}$ 0.40 ppm) between the peri protons of **1** and **2** in C_6D_6 clearly reflects differences in anisotropic effects of "complexed" benzene in diastereomeric environments.

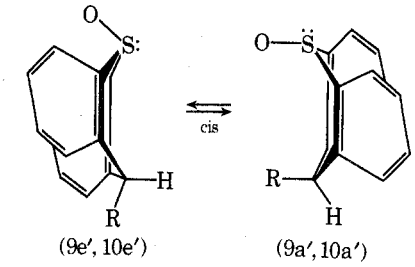
A simple analysis of the data of the aryl protons in $CDCl_3$ would not allow for a firm conclusion regarding the preferred conformation of the sulfinyl oxygen atom; however, the sign and magnitude of the ASIS value (Δ) does provide valuable insight into this problem. Since the preferred conformations of the *cis*- and *trans*-9-methylthioxanthene *S*-oxide (**3**)[7,11,12] and 9,9-dimethylthioxanthene *S*-oxide (**4**)[7,11] have already been determined, it was clear to us that the success of the ASIS technique applied to these systems (with **1** and **2** as model compounds) would be based on a corroborative prediction of sulfinyl conformational preferences which had been previously ascertained by independent schemes.

In Table I, the Δ value (−0.18) for **1** indicates less shielding of the $H_{4,5}$ protons in C_6D_6 than in $CDCl_3$ solution whereas the opposite is observed for the H_5 proton of **2** (Δ 0.20). The conclusion drawn from these data is that benzene causes a downfield shift of the proximal peri protons when solvating an e′ sulfinyl group but an upfield shift of the proximal peri protons when solvating an a′ sulfinyl group.

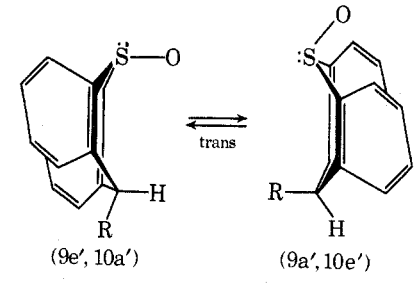
Both **4** and *cis*- and *trans*-**3** exist in preferred conformations with 10e′ sulfinyl oxygen atoms and it is evident from Table I that the Δ values correlate well with these previously established sulfinyl oxygen orientations. In the *cis*- and *trans*-9-ethylthioxanthene *S*-oxide (**5**) series, the Δ value for the trans isomer is characteristic of an e′ sulfinyl oxygen atom conformation while the Δ value for the cis isomer is similar to that found for a diaryl sulfoxide with an a′ sulfinyl oxygen, e.g., 1,4-dimethylthioxanthene *S*-oxide (Δ +0.21). A similar trend is observed for the cis and trans forms of 9-isopropylthioxanthene sulfoxide (**6**). The results indicate that the sulfinyl group occupies the a′ conformation in the cis forms and the e′ conformation in the trans forms of **5** and **6**. This conclusion is to be contrasted to that obtained for the diastereomers of **3**, where both diastereomers exist with the sulfinyl oxygen in the e′ conformation.[7]

In a previous report[13] we noted that alkyl groups larger than methyl at C-9 overwhelmingly prefer the 9a′ conformation in the sulfide and from these results we suggest that the preferred conformations of the diastereomers of **5** and **6** are *cis*-(9a′,10a′) and *trans*-(9a′,10e′).[14,15]

These conclusions are in harmony with those arrived at by Michaelis et al.[16] regarding the cis and trans *S*-oxides of 9-[(*N*-methyl-3′-piperidyl)methyl]thioxanthene. Employing ir, uv, and ^1H NMR spectroscopy, Michaelis et al.[16] assigned the dipseudo-axial conformation (9a′,10a′) to the cis form and the 9a′,10e′ conformation to the trans diastereoisomer.



(9e′, 10e′) (9a′, 10a′)



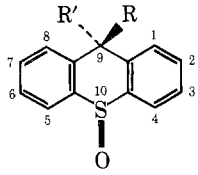
(9e′, 10a′) (9a′, 10e′)

Experimental Section[17]

The preparations of the sulfides and thioxanthene *S*-oxide, 1,4-dimethylthioxanthene *S*-oxide, *cis*- and *trans*-9-methylthioxanthene *S*-oxide, and 9,9-dimethylthioxanthene *S*-oxide have been described elsewhere.[7,14]

***cis*- and *trans*-9-Ethylthioxanthene *S*-Oxides (5).** A solution of *m*-chloroperoxybenzoic acid (7.68 g, 44.6 mmol) in CH_2Cl_2 (125

Table I
Proton Magnetic Resonance Parameters[a] of Substituted Thioxanthene *S*-Oxides



Compd	Solvent	$C_{1,2,3,6,7,8}$ H[b]	$C_{4,5}$ H[c]	Δ[d]
Thioxanthene *S*-oxide (**1**)	$CDCl_3$	7.35	7.86	−0.18
R = R' = H	C_6D_6	6.96	8.04	
1,4-Dimethylthioxanthene *S*-oxide (**2**)	$CDCl_3$	7.46	7.84	+0.20
R = R' = H	C_6D_6	6.96	7.64	
cis-9-Methylthioxanthene *S*-oxide	$CDCl_3$	7.40	7.88	−0.15
(*cis*-**3**) R = Me; R' = H	C_6D_6	6.96	8.03	
trans-9-Methylthioxanthene *S*-oxide	$CDCl_3$	7.42	7.96	−0.16
(*trans*-**3**) R = H'; R' = Me	C_6D_6	6.94	8.12	
9,9-Dimethylthioxanthene *S*-oxide (**4**)	$CDCl_3$	7.44	7.98	−0.22
R = R' = Me	C_6D_6	7.06	8.20	
cis-9-Ethylthioxanthene *S*-oxide	$CDCl_3$	7.43	7.88	+0.21
(*cis*-**5**) R = Et; R' = H	C_6D_6	6.94	7.67	
trans-9-Ethylthioxanthene *S*-oxide	$CDCl_3$	7.35	7.96	−0.15
(*trans*-**5**) R = H; R' = Et	C_6D_6	6.99	8.11	
cis-9-Isopropylthioxanthene *S*-oxide	$CDCl_3$	7.38	7.80	+0.25
(*cis*-**6**) R = *i*-Pr; R' = H	C_6D_6	6.94	7.55	
trans-9-Isopropylthioxanthene *S*-oxide	$CDCl_3$	7.34	7.97	−0.15
(*trans*-**6**) R = H; R' = *i*-Pr	C_6D_6	7.00	8.12	
9,9-Dimethylthioxanthene[e]	$CDCl_3$	7.15	7.43	+0.31
	C_6D_6	6.97	7.12	

[a] Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane and were obtained at 60 and/or 100 MHz. [b] Only the center of the absorption resulting from these protons is reported and these data are included in this table to show the consistent upfield shifting effect of C_6D_6 on protons removed from the sulfinyl environment. [c] The chemical shifts reported here represent the arithmetic mean of the $C_{4,5}$ H multiplet. [d] ASIS = $\Delta_{C_{4,5}H} = \delta_{CDCl_3} - \delta_{C_6D_6}$ at ambient temperature. [e] This derivative is included to show that all protons are shielded in C_6D_6 solution.

ml) was added dropwise to a cold (ice bath) solution of 9-ethylthioxanthene (8.10 g, 35.7 mmol) in 150 ml of CH_2Cl_2. The resulting solution was stirred at 0–5° for 6 hr, allowed to warm to room temperature, treated with a saturated solution of $NaHCO_3$ (4 × 100 ml), and washed with water (100 ml). Drying ($MgSO_4$) and evaporation of the solvent (N_2 gas) gave 8.58 g of crude *S*-oxides. TLC indicated only a trace of 9-ethylthioxanthene.

***cis*-9-Ethylthioxanthene *S*-Oxide (*cis*-5).** The yellow solid (diastereoisomeric sulfoxides) was dissolved in *n*-hexane and slow evaporation of the solvent gave colorless needles of *cis*-9-ethylthioxanthene *S*-oxide. The mother liquor was decanted, concentrated, and seeded with crystals of *cis*-**5** to afford more colorless crystals. This process was repeated several times and two recrystallizations of the combined solids from ethyl acetate gave 910 mg (3.76 mmol, 10.5% yield) of pure *cis*-**5**: mp 111.0–112.0°; ir (Nujol) 8.44, 9.33, 9.74, and 9.68 μm. Anal. Calcd for $C_{15}H_{14}OS$: C, 73.34; H, 5.82; S, 13.23. Found: C, 74.41; H, 6.03; S, 13.19.

***trans*-9-Ethylthioxanthene *S*-Oxide (*trans*-5).** The hexane mother liquor resulting from the separation of *cis*-**5** was evaporated to dryness (N_2 gas stream), the crystals were redissolved in 95% ethanol, and the solution was allowed to evaporate slowly. This process gave ca. 3.6 g of an inhomogeneous material which was recrystallized from ethyl acetate to afford 1.07 g (4.43 mmol, 12.3% yield) of pure *trans*-**5**: mp 119.0–120.0°; ir (Nujol) 9.65 and 9.17 μm. Anal. Found: C, 74.66; H, 5.93; S, 13.28.

***cis*- and *trans*-9-Isopropylthioxanthene *S*-Oxides (6).** A solution of *m*-chloroperoxybenzoic acid (7.68 g, 44.6 mmol) in CH_2Cl_2 (150 ml) was added dropwise to a cold solution (ice bath) of 9-isopropylthioxanthene (10.0 g, 40.7 mmol) in CH_2Cl_2 (200 ml). The resulting solution was stirred at 0–5° for 48 hr, washed with a saturated solution of $NaHCO_3$ (4 × 100 ml) and water (2 × 100 ml), dried ($MgSO_4$), and concentrated to dryness (N_2 gas) to give 11.2 g of crude material. This material was dissolved in *n*-hexane and as the solvent slowly evaporated two distinct crystalline forms crystallized in the flask. Manual separation gave two batches of crystals.

***cis*-9-Isopropylthioxanthene *S*-Oxide (*cis*-6).** The batch of needles was recrystallized from hexane to afford 1.36 g (5.32 mmol, 12.7%) of colorless, pure *cis*-**6**: mp 101.0–102.5°; ir (Nujol) 9.86, 9.71, 9.63, and 9.91 μm. Anal. Calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29; S, 12.50. Found: C, 74.92; H, 6.32; S, 12.61.

***trans*-9-Isopropylthioxanthene *S*-Oxide (*trans*-6).** The batch of rectangular blocks was recrystallized from hexane to yield 2.87 g (11.2 mmol, 26.8%) of homogeneous *trans*-**6**: mp 166.0–166.5°; ir (Nujol) 9.67 and 9.26 μm. Anal. Found: C, 74.94; H, 6.24; S, 12.30.

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Registry No.—**1**, 1011-81-0; **2**, 51517-43-2; *cis*-**3**, 19018-80-5; *trans*-**3**, 19018-81-6; **4**, 19019-06-8; *cis*-**5**, 56195-77-8; *trans*-**5**, 56195-78-9; *cis*-**6**, 55235-94-4; *trans*-**6**, 56195-79-0; 9,9-dimethyl-T, 19019-10-4; *m*-chloroperoxybenzoic acid, 937-14-4; 9-ethyl-T, 28612-38-6; 9-isopropyl-T, 28612-39-7.

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(14) We are cognizant of the differences in conformation equilibrium constant of the two cis and trans forms of **5** and **6** which undoubtedly reflect the increased size of the alkyl group.
(15) Professor S. S. C. Chu of Southern Methodist University has informed us that the isomer which we have identified as *cis*-**6** (9a′,10a′) in solution has the same conformation in the solid state: S. S. C. Chu, *Acta Crystallogr., Sect. B*, **31**, 1082 (1975).
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(17) All melting points were obtained in a Mel-Temp apparatus (open capillary) and are corrected. ^{1}H NMR spectra were recorded on Varian Models HA-100 and A-60 NMR spectrometers. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Crobaugh Laboratories, Cleveland, Ohio. All compounds were shown to be homogeneous by thin layer chromatography (silica gel substrate) on glass plates using ethyl acetate or chloroform as eluents and with uv and iodine vapor for visualization. Ir spectra were recorded using a Beckman Model IR-8 spectrophotomer.

p-(Aminomethyl)phenoxymethyl Polymer for Solid Phase Synthesis of Protected Peptide Amides[1]

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We have previously[2] reported on the use of *p*-methoxybenzyl (pmb) as an amido protecting group and on the synthesis of a related *p*-alkoxybenzylamine support for the preparation of C-terminal peptide amides. Attempts to prepare peptide amides using this polymer as a substitute of the benzhydryl amino polymer[3] showed that the anchoring bond between the first amino acid and the polymer is not stable in the conditions normally associated with the removal of *N-tert*-butyloxycarbonyl (Boc). Thus, when the Boc-Ala-*p*-alkoxybenzylamine resin, Boc-Ala-NH-resin, was treated with 50% (v/v) trifluoroacetic acid in methylene chloride or 1 *N* HCl–acetic acid to remove the Boc group, alanine amide was released in 80% yield. A similar result has been obtained by the use of Boc-Val-NH-resin and Boc-Gly-NH-resin. This experimental finding led us to use this support for the preparation of small protected peptide amides suitable for conventional peptide synthesis. This approach has been already described[4] and is very important, since the two most necessary requirements for the successful synthesis of pure long peptide chains by the solid phase peptide technique, i.e., nearly 100% stepwise yields and careful choice of protecting groups, are often difficult to meet.

This paper describes the preparation of the *p*-(aminomethyl)phenoxymethyl polymer (*p*-alkoxybenzylamine polymer) and its application to the synthesis of three protected peptide amides using for amino protection the very acid labile 2-phenylisopropyloxycarbonyl group (Ppoc).[5]

Two synthetic routes to this support are outlined in Scheme I.

Initial preparation was carried out by reaction of the Merrifield resin (IV) with *p*-cyanophenol followed by reduction with $LiAlH_4$ in presence of ammonia. A second procedure involved the treatment of the *p*-alkoxybenzyl alcohol resin[6] with HBr in methylene chloride to give the *p*-alkoxybenzyl bromide polymer, which was converted to the desired amine derivative by reaction with ammonia in methylene chloride.

The first method required accurately controlled conditions because of the possible concurrent formation of the *p*-alkoxybenzyl alcohol polymer. To overcome this drawback the cyano polymer, obtained by treating the Merrifield resin with a large excess of *p*-cyanophenol for short reaction times, was reduced in a stream of dry ammonia. This difficulty did not occur in the preparation of the *p*-alkoxybenzylamine polymer starting from the *p*-alkoxybenzyl alcohol support. However, this route was discarded since the sequence of reactions, i.e., preparation of the *p*-alkoxybenzyl alcohol polymer, conversion to the corresponding bromide derivative, and final amination, was long and tedious. For this reason the synthesis of our models was carried out on the polymer prepared by the first procedure. Ppoc-amino acids were attached to the amine support via DCC. The degree of substitution was 0.4–0.5 mequiv/g; the remaining free amino groups were blocked by acylation. The Ppoc group was removed by 30-min exposure to 1% (v/v) trifluoroacetic acid in methylene chloride.[5] During this time there was hardly any free amide released from the resin, indicating that the anchoring bond was largely stable under these conditions.

The following protected peptide amides were prepared on the *p*-alkoxybenzylamine support: Z-Pro-Leu-Gly-NH_2 (I), Z-Ala-Phe-Gly-Leu-Met-NH_2 (II), and Z-Gln(Dmb)-Gly-Leu-Val-NH_2 (III). The protected peptides were released from the resin by 50% (v/v) trifluoroacetic acid in methylene chloride after 30 min and were purified by crystallization.

The products proved to be homogeneous by thin layer chromatography and gave the expected amino acid analysis after acid hydrolysis.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer IR-257 with KBr pellets. Amino acid analyses were carried out on a Beckman Model 120 B amino acid analyzer. Thin

Scheme I