Ab Initio Calculations on *N*-Methylmethanesulfonamide and Methyl Methanesulfonate for the Development of Force Field Torsional Parameters and Their Use in the Conformational Analysis of Some Novel Estrogens†

Rajeshwar D. Bindal,‡,§ Joseph T. Golab,⊥ and John A. Katzenellenbogen*,‡

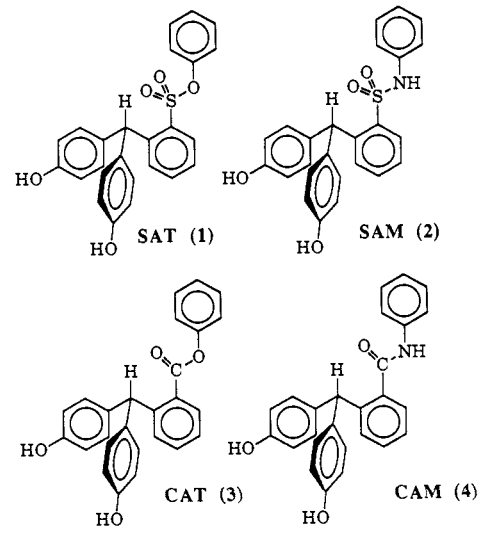
Contribution from the Department of Chemistry and National Center for Supercomputing Applications, University of Illinois, Urbana, Illinois 61801. *Received February 12, 1990*

Abstract: We recently reported the isolation and structure determination of a novel estrogen (**1**), the phenyl ester of an ortho-substituted tritylsulfonic acid, isolated from commercial preparations of phenol red. The relative binding affinity of the sulfonate **1** and of three analogues (the corresponding sulfonamide **2**, carboxylate **3**, and carboxamide **4**) for estrogen receptor suggests that the spatial disposition of the pendant phenyl ring is a critical factor in determining their affinity. Ab initio calculations on two model compounds, methyl methanesulfonate (**5**) and *N*-methylmethanesulfonamide (**6a**), reveal in the case of **5** a single-fold torsional barrier of 10.1 kcal/mol, an energy minimum at the torsion angle (C-S-O-C) = 180°, and 2.2-kcal/mol shoulders at the torsion angles ±120°. By contrast, the sulfonamide **6a** shows a 2-fold torsional barrier (9.2 kcal/mol when both methyl groups are eclipsed and 7.5 kcal/mol when the N-H eclipses the S-CH_3 bond); the two energy minima are at the torsional angles (C-S-N-C) = -98.7° and +71.7°, respectively, the latter being 1.5 to 1.9 kcal/mol higher in energy. However, the two conformers may be interconverted by nitrogen inversion, with a hindrance of 2.2 kcal/mol. Torsional force-field parameters for the modeling program CHARMm were developed by a least-squares fit to a truncated Fourier series. For appropriate minimization of conformations of the sulfonamide, we adopted a strategy to allow for nitrogen inversion, by setting the improper torsional angles around nitrogen to zero. Conformational analysis of compounds **1-4** reveal that minimum energy conformers of the low affinity compounds **3** and **4** project the pendant phenyl ring into a tight half-torus, over and around the 1,2-disubstituted ring of the trityl system, while in the highest affinity compound (**1**, sulfonate) the pendant phenyl ring is disposed on the opposite side of the torus. The sulfonamide **2**, which has intermediate binding affinity, has some higher energy conformations where the pendant phenyl group shares space with that of the sulfonate **1**. The relative energies of the various conformational minima of the systems **1-2** are within the range of computational and experimental determinations.

Introduction

Recently, we reported the isolation and structure determination of a novel estrogen, bis(4-hydroxyphenyl)[2-(phenoxysulfonyl)-phenyl]methane (**1**), from commercial preparations of phenol red, a pH indicator dye used almost universally in cell culture media.[1] In order to study the structural correlations for estrogen receptor binding in this unusual system, we have synthesized various analogues of **1** and determined their relative binding affinity (RBA) for the estrogen receptor.[2] A comparison of **1** with some other characteristic nonsteroidal estrogens and antiestrogens (cyclofenil, triarylethene, and triarylethane) by molecular modeling revealed that the phenyl sulfonate (or pendant) ring in **1** is important for optimal binding.[2] Moreover, the comparison of the RBA of compound **1** with that of related sulfonic and carboxylic amides and esters (compounds **2-4**, Table I)[3] suggests that it is the spatial orientation of the pendant phenyl ring that is a critically important determinant of receptor binding.

We were limited in our efforts to do conformational analysis of **1** and **2** because most molecular modeling packages like MacroModel[4] and SYBYL[5] lack certain essential force field parameters, particularly for the sulfonate and sulfonamide functions. Moreover, the development of force field parameters for the sulfonamide group is especially needed because this functional group is involved in many pharmacologically active substances (cardiovascular, antimicrobial). The QUANTA/CHARMm[6] molecular modeling package of Polygen has bond-stretching and angle-bending force constants for the sulfonamide function, derived from IR spectral analysis of C- and N-deuterated *N*-methylmethanesulfonamides.[7] However, the lowest energy conformations of *N*-methylmethanesulfonamide[7] and phenyl benzenesulfonate[8] were based on presumptions, supported only in part by experimental data, some of it of questionable relevance (see Results and Discussion). This uncertainty makes the sulfonamide torsional



† This paper is dedicated to the late Roger Adams on the occasion of the 100th anniversary of his birth, January, 1889.

‡ Department of Chemistry.

§ Present address: Center for Molecular Design, Washington University, St. Louis, MO.

⊥ National Center for Supercomputing Applications.

(1) Bindal, R. D.; Katzenellenbogen, J. A. *J. Med. Chem.* **1988**, *31*, 1978.

(2) Bindal, R. D.; Katzenellenbogen, J. A. *J. Med. Chem.* Manuscript in preparation.

(3) A simplified nomenclature system is adopted to assist in the discussion of the four trityl systems: SAT (*sulfonate*, **1**), SAM (*sulfonamide*, **2**), CAT (*carboxylate*, **3**), and CAM (*carboxamide*, **4**).

(4) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Change, G.; Henderickson, T.; Still, W. C. *J. Comput. Chem.*, in press.

(5) The force field in SYBYL is based on the COSMIC force field: Vinter, J. G.; Davis, A.; Saunders, M. R. *J. Comput.-Aided Mol. Design* **1987**, *1*, 31.

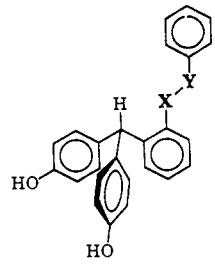
(6) Brooks, B. R.; Bruccolesi, R. E.; Olafsen, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1987**, *4*, 137-217.

(7) Noguchi, A.; Hanai, K.; Okudu, T. *Spectrochim. Acta* **1980**, *30A*, 829.

(8) Butenko, G. G.; Vereshchagin, A. N.; Remizov, A. B.; Nurullina, R. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, *8*, 1763.

0002-7863/90/1512-7861$02.50/0

Table I. Relative Binding Affinities (RBA) of the Tritylsulfonyl and Tritylcarbonyl Systems (**1–4**) for the Estrogen Receptor

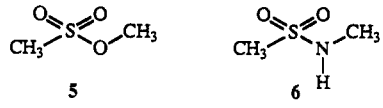


compd no. (acronym)[a]	X	Y	RBA (%) (estradiol = 100)
1 (SAT)	SO_2	O	50
2 (SAM)	SO_2	NH	12
3 (CAT)	CO	O	0.01
4 (CAM)	CO	NH	0.03

[a] See footnote 3 for a defiition of the acronyms given in parentheses.

parameters in the force field questionable. Moreover, of the three torsion angles in compounds **1–4** that determine the orientation of the pendant phenyl ring, it is the most important angle, torsion C-SO_2-Y-C (see figure with Table I), that is the least certain. The dihedral angle C-C-SO_2-Y is also involved in determining the disposition of the pendant phenyl ring (attached to Y).

In this report, we present the results of ab initio calculations on two model compounds, methyl methanesulfonate (**5**) and



5 **6**

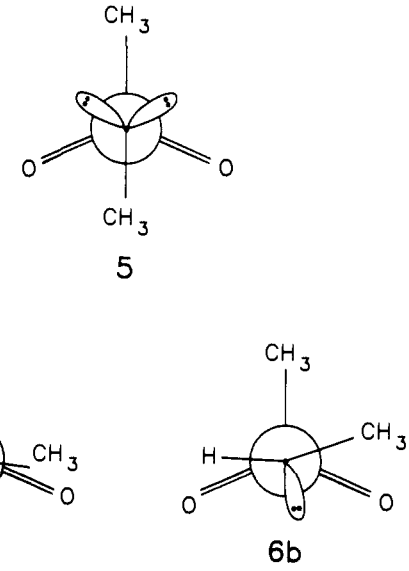
N-methylmethanesulfonamide (**6**), and use them to derive the torsional parameters for the sulfonate and sulfonamide functions. We then use these parameters in the conformational analysis of the compounds **1** and **2**. We also discuss the X-ray determined structure of the bisacetate of **1** and our attempts to define its solution conformation by high resolution NMR. Finally, we make an attempt to identify the conformational space available to **1** (and also to **2**), as compared to **3** and **4**, that appears to be responsible for their higher binding affinity to the estrogen receptor.

Experimental Section

Computational Methods. Restricted Hartree–Fock (RHF) geometry optimizations for all molecules were carried out in a 6-31G* basis set. This basis set includes a d-orbital on all nonhydrogen atoms.[9,10] Symmetry constraints were not used in the optimizations. At this level of theory, the errors in the computed bond lengths and bond angles are anticipated to be less than 0.01 Å and 1°, respectively.[11] The symbolic *Z*-matrices that define the geometry of the optimized structures are provided as supplementary material (2 pages).

These optimal geometries were then utilized in Møller–Plesset calculations (up to fourth order in perturbation theory) to better account for the effects of electron correlation.[11,12] The perturbation calculations did not include contributions from the core orbitals of nonhydrogen atoms.[11]

Ab initio analytic normal mode vibrational frequencies were calculated at the 6-31G* basis set optimized geometries.[11] The torsional barriers were calculated using the rigid rotor[11] approxiination at the HF/6-31G* level. All geometric variables were kept constant, except for the torsion angles C-S-O-C and C-S-N-C, respectively, which (along with the torsion angle C-S-N-H) were rotated in 20° increments from their respective optimized minima. The geometries of the conformations at the energy maxima for the torsional interconversion were then fully optimized as described above. The energy barrier for nitrogen inversion in the geometry-optimized minimum conformation of *N*-methylmethanesulfonamide (Figure 1, **6a**) was calculated assuming a planar transition state. This transition structure was also geometry optimized without any constraints except those needed to keep the nitrogen planar.[11,13] All computations were carried out using the Gaussian86 RevC program[14] on the NCSA Cray X-MP/48 supercomputer running under UNICOS.



5 **6a** **6b**

Figure 1. The structures of sulfonate **5** and sulfonamides **6a** and **6b**, fully optimized ab initio geometry in a 6-31G* basis set level. In each case, the sulfur atom is at the rear of the Newman projection.

Conformational analysis was done on an IRIS 4D/50G workstation (Silicon Graphics). Certain force field parameters in the molecular modeling package QUANTA 2.1A/CHARMm 21 were modified or added [see text and supplemental material (one page) for further details]. Conformation analysis for compounds **1–4** was done using the grid search routine. The torsional angles C-C-X-Y and C-X-Y-C were rotated in 30° increments. All of the conformations were then rigorously minimized, without any constraints, using several steps of steepest descent and conjugate gradient minimizers, sequentially, to an rms of 0.01 kcal/(Å·mol). This was followed by 20–25 steps of Newton–Raphson minimization to ensure the convergence of saddle point conformations to their respective stationary points.

Experimental Methods. The single-crystal X-ray structural analysis of the diacetate of **1** was done at the X-ray Crystallography Laboratory of the School of Chemical Sciences. Additional information is provided as supplementary material (15 pages).

The ^{1}H-NMR studies on compound **1** were done at the Molecular Spectroscopy Laboratory of the School of Chemical Sciences. The 500-MHz instrument (General Electric GN500) is fitted with a variable-temperature bath.

The estrogen receptor binding affinity of these compounds was evaluated in vitro by a competitive radiometric receptor binding assay, as described previously.[15]

Results and Discussion

Development of Torsional Force Parameters for Sulfonate and Sulfonamide Functional Groups. Methyl Methanesulfonate (5). The geometry optimized, computed conformation for methyl methanesulfonate (**5**) is shown in Figure 1. The computed energies are listed in Table II. Key geometrical variables are compared with single-crystal X-ray data for bis(4-acetoxy-

(9) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 203.
(10) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1983**, *77*, 3054.
(11) Hehre, W. J.; Radom, L.; Schleyer, P. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; pp 38, 82, 96, 135–186, 226–251, 261–270.
(12) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. DeFrees, D. J.; Levi, B. A.; Pollack, S. K.; Hehre, W. J.; Binkley, J. S.; Pople, J. A. *Am. Chem. Soc.* **1970**, *92*, 4085.
(13) Lehn, J. M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311.
(14) Frisch. M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; DeFrees, D. J.; Seeger, R. A.; Whiteside, D. J.; Seeger, R. A.; Fleuder, E. M.; Pople, J. A. *GAUSSIAN 86*; Carnegie-Mellon University: Pittsburgh, PA, 1984.
(15) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085.

Table II. Total Energies for Methyl Methanesulfonate and *N*-Methylmethanesulfonamide Conformers from RHF Calculations[a]

compd	$-E_e$, au 6-31G*	MP2/ 6-31G*	MP3/ 6-31G*	MP4/ 6-31G*[b]
sulfonate **5**	701.247 05	702.181 45	702.194 93	702.246 89
sulfonamide **6a**	681.416 57	682.337 31	682.357 56	682.407 91
sulfonamide **6b**[c]	681.414 25	682.334 61	682.354 85	682.404 94
ΔE,[d] kcal/mol	1.46	1.69	1.70	1.86

[a] All geometries were optimized with 6-31G* basis set. [b] The MP4 energies include single, double, triple, and quadruple substitution contributions. [c] The conformation **6b** is related to conformation **6a** by nitrogen inversion. [d] $\Delta E = E_e(\mathbf{6b}) - E_e(\mathbf{6a})$. These energies are relative, assuming zero for conformation **6a**.

Table III. Comparison of Calculated and X-ray Geometric Parameters for Methyl Methanesulfonate (**5**)[a]

geometric parameter	Ångströms or degrees ab initio	X-ray
C—S	1.761	1.766
S—O	1.579	1.589
S=O	1.427	1.414
	1.427	1.418
C—O	1.433	1.417
C—S—O	98.1	99.8
C—S=O	109.9	110.3
C—S=O	109.9	110.3
	109.9	110.3
O=S=O	119.0	117.5
O—S=O	108.9	108.6
	108.9	109.1
C—O—S	117.4	115.8
C—O—S—C	-179.9	-173.1

[a] The calculated parameters are for the 6-31G* basis set optimized geometry. The X-ray data are for the diacetate of compound **1**.

phenyl)[2-(phenoxysulfonyl)phenyl]methane (diacetate of **1**) in Table III. The bond lengths and bond angles are within the range of experimental and theoretical determinations.[11] The lowest energy conformation is that with the methyl groups on sulfur and oxygen oriented antiperiplanar. The torsional barrier (C-S-O-C), calculated by the rigid rotor approximation, is shown in Figure 2. Although it shows only a single barrier, shoulders in the energy profile are evident at $\phi = \pm 120°$. The torsional barrier height is 21.3 kcal/mol; however, geometry optimization of the transition structure, where the two methyl groups are eclipsed, results in an 11.2-kcal/mol drop in the barrier height. The steric congestion at the saddle point is relieved by opening angles C-S-O and S-O-C by 7.4° and 9.0°, respectively. The C-S and O-C bond lengths also increased by 0.01 Å, but the S-O bond length is not affected.

The calculated normal mode vibrational frequencies are compared with experimental values and are shown in Table IV. The assignments were assisted by a normal mode visualization program.[16]

***N*-Methylmethanesulfonamide (6a and 6b).** The computed conformations for *N*-methylmethanesulfonamide (**6a** and **6b**) are shown in Figure 1. The quantitative results for some of the key geometrical variables are compared with the single-crystal X-ray data for *N*-phenylmethanesulfonamide[17] in Table V. The computed total energies are summarized in Table II.

The energy difference between conformation **6a** and **6b** is in the range of 1.5 kcal/mol (RHF) to 1.9 kcal/mol (MP4) (Table II). This leads us to believe that the RHF 6-31G* basis set-optimized geometry is a good representation of the level of optimization that could be achieved by including electron correlation

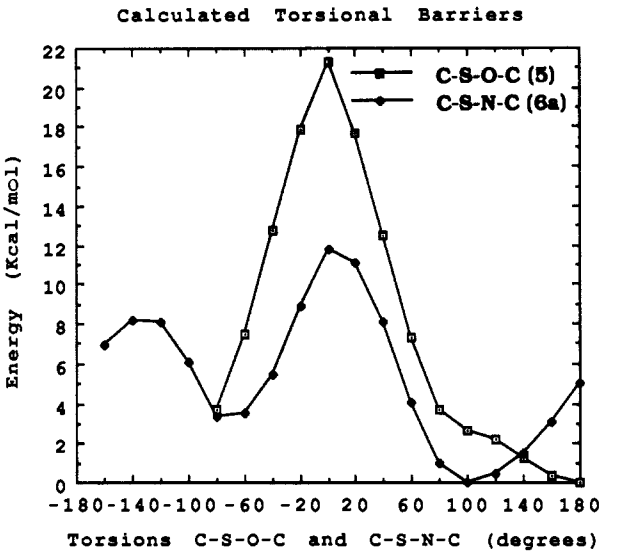


Figure 2. The single-point 6-31G* torsional barrier calculated for sulfonate **5** and sulfonamide **6a**. For actual barrier heights see text. (In deriving torsional parameters for the force field, we have scaled down the torsional curves shown here, to account for the geometry optimized 6-31G* energies of saddle point conformations. The resultant curves are provided as supplementary material.)

Table IV. Comparison of Calculated and Observed IR Frequencies of Methyl Methanesulfonate (**5**)

obsd, cm^{-1}	assignment[a]	calcd,[b] cm^{-1}	force constant mdyn/Å^2
1351	SO_2(s); C-S str	1296	18.970 8
1176	SO_2(a); (S)CH_3 bend	1128	6.822 0
1000	C-O str; S-O str	1008	3.663 4
971	(S)CH_3 scisor	971	1.298 4
810	S-O str; COS in-plane bend	792	2.677 1
719	COS out-of-plane bend	720	2.197 6

[a] Assignment of the calculated frequencies has been helped by a visualization program (ref 16). Observed frequencies of a neat liquid taken from Aldrich IR Library. [b] Calculated on 6-31G* optimized geometry. The calculated frequencies are multipled by 0.88 (ref 11).

Table V. Comparison of Calculated and X-ray Geometric Parameters[c] for *N*-Methylmethanesulfonamide Conformations **6a** and **6b**[a]

geometric parameters	ab initio **6a**	ab initio **6b**	X-ray
S—C	1.768	1.774	1.746(2)[b]
S—N	1.645	1.627	1.633(2)[b]
S=O	1.432	1.429	1.425(2)[b]
	1.432	1.429	1.443
C—N	1.460	1.453	1.438(3)[b]
O=S=O	120.7	121.8	118.6 (1)
N—S=O	106.0	106.0	105.3 (1)
	109.7	107.5	107.7
C—S=O	108.3	107.2	108.6 (1)
	107.4	106.8	108.4
C—S—N	103.4	106.8	107.5 (1)
C—N—S	119.5	122.8	120.1
C—N—H	115.0	118.5	113.1
S—N—H	109.0	113.4	108.8
C—S—N—C	98.7	71.7	-62.2
C—S—N—H	-126.2	-82.2	70.4

[a] The calculated parameters are from 6-31G(d) basis set optimized geometries. The X-ray data are for *N*-phenylmethanesulfonamide. The position of hydrogen on nitrogen is experimentally observed, (ref 17). [b] The correctionsfor rotational oscillations will increase the bond lengths by 0.005 to 0.008 Å (ref 17). [c] Distances in Å and angles in deg.

(16) Personal communications with Professor Scott Kahn at University of Illinois.

(17) Klug, H. P. *Acta Crystallogr.* **1968**, *B24*, 729.

using a higher order theory such as configuration interactions. Conformation **6a**, with the nitrogen lone pair synperiplanar to the C-S bond, is more stable because of the avoidance of electron-

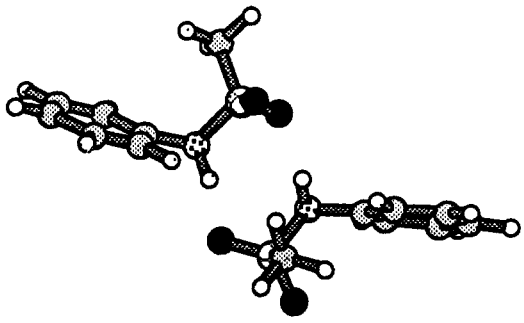


Figure 3. A sketch of a symmetrical dimer of *N*-phenylmethanesulfonamide, as determined by X-ray crystallography (see ref 17).

electron repulsion between the lone pair on nitrogen and the oxygens of the S=O bond. Apparently, the electron-electron repulsions in conformation **6a** outweigh negative hyperconjugation[18] stabilizing effects (wherein the lone pair on nitrogen is antiperiplanar to the C-S bond as in **6b**). The asymmetric nature of the torsional curve (see below and Figure 2), both on the energy and torsional axes, originates from the presence of an asymmetric nitrogen; similar behavior has been observed for *N*-fluorohydroxylamine.[19]

The bond lengths for both of the conformations fall within the range of uncertainty of experimental and theoretical determinations (Table V).[11] The geometric variables closely reflect the bonding behavior as postulated for tetramethylsulfamide by X-ray[20] and gas-phase electron diffraction.[21] The torsional angles C-S-N-C and C-S-N-H differ significantly from the X-ray determined values (Table V). However, it is known that crystal lattice forces[22] and the presence of functional groups which might be involved in intermolecular interactions (e.g., hydrogen bonding) can play a significant role in determining torsional angles. In the present case, it is well-documented that *N*-methylmethanesulfonamide exists as a dimer, both in the crystalline state[17] and in solution.[23] Figure 3 shows a sketch of such a dimer, based on an experimental report,[17] showing an H—(H)---O distance of 3.03 Å and C—N---O and N—H---O bond angles of 119.5° and 167.7°, respectively. The enthalpy of dimerization was determined to be 4.8 ± 0.4 kcal/mol by variable-temperature and concentration studies (IR).[23]

(18) Laube, T.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 5511; Rahman, M. M.; Lemal, D. M.; Dailey, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 1964; von Raguĕ Schlayer, P.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

(19) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371.

(20) Jordan, T.; Smith, H. W.; Lohr, L. L.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1963**, *85*, 946.

(21) Hargittai, I.; Vazda, E.; Szöke, A. *J. Mol. Struct.* **1973**, *18*, 381.

(22) DeRanter, C. N. *X-Ray Crystallography and Drug Action*; Clarendon: Oxford, 1984. Murray-Rust, P. *Molecular Structures and Biological Activity*; Elsevier: New York, 1982.

(23) (a) Malewski, G.; Køkig, R. *Spectrochim. Acta* **1964**, *20*, 565. (b) One of the referees suggested energy minimization of the X-ray determined dimer structure (Figure 3) of *N*-phenylmethanesulfonamide to explain the discrepancy between the ab initio calculated dihedrals (C-S-N-C and C-S-N-H) and the corresponding X-ray determined values (Table V). We have not done the energy minimization of the dimer; however, the energetics of the system show internal consistency. It is apparent that each molecule of the dimer is trapped (with respect to the dihedral C-S-N-C) in a conformation that is close to that of **6b**, which itself is higher in energy (by 1.5 to 1.9 kcal/mol) than the global minimum **6a** (Table II). A further distortion of the dihedral angle by about 10° from the geometry corresponding to **6b** to reach the X-ray dihedral will contribute another kcal/mol of strain energy to each molecule in the dimer (approximated from the scaled torsional curve provided in the supplementary material). Therefore, the calculated torsional strain in the dimer is approximated to be 5.0 to 5.8 kcal/mol. This value is compensated by the enthalpy of dimerization (4.8 ± 0.4 kcal/mol for two hydrogen bond formation), as experimentally determined for *N*-methylmethanesulfonamide (ref 23a), although it is not known whether the dimer formed in solution corresponds to **6a** or **6b**. Thus, although the lattice packing forces and symmetry requirements dictate individual molecules to be a strained conformation, the overall system is at its energy minimum.

Table VI. Comparison of Observed and Calculated Fundamental Frequencies (cm^{-1}) of *N*-Methylmethanesulfonamide (**6a**)[a]

observed[b]		calculated		force constant
cm^{-1}	assignment	cm^{-1}	assignment	mdyne/Å^2
1410	N-H bend	1428	N-H bend	1.8798
1310	SO_2(a)	1316	SO_2 wag; NH bend	12.3790
1153	SO_2(s)	1131	SO_2(a); N-CH_3 twist	2.6315
1133	N-CH_3 rock	1124	N-CH_3 twist; NH bend	1.7982
1070	C-N stretch	1059	SN str; CN str	2.7792
973	S-CH_3 rock	994	S-CH_3 bend	1.0279
839	S-N stretch	846	CNS out-of-plane bend	1.5994
762	C-S stretch			
640(b)	N-H bend	596	N-H bend	0.5165
523	SO_2 bend	515	SNC rock	1.1261
457	SO_2 bend	418	NH bend; SO_2(a)	0.4149

[a] The frequencies were calculated analytically at the 6-31G* basis set optimized geometries. [b] Observed IR and principal assignments are from ref 7. [c] The calculated frequencies are multiplied by 0.90 (ref 11). Assignment of the calculated values has been helped by a visualization program (ref 16).

The calculated normal mode vibrations for *N*-methylmethanesulfonamide are compared with the observed frequencies, and the assignments are shown in Table VI. Most of the vibrational modes are highly coupled, however, and the assignments, particularly at the lower frequency region, differ significantly from the experimental assignments.[7] Since the IR spectrum of methylmethanesulfonamide was taken as a neat liquid,[7] where the sulfonamide exists as a dimer (Figure 3), assignments of the observed frequencies do not reflect the ideal situation for force field parameterization. Moreover, the extensive coupling between various normal modes render even the principal assignments subjective. Because of these ambiguities, the normal mode calculations at the MP2 level of theory (which would have been computationally expensive) were not attempted.

The 2-fold rotational barrier for the interconversion of *N*-methylmethanesulfonamide conformations **6a** and **6b**, calculated by the rigid rotor approximation, is shown in Figure 2. The reference geometry in this figure is conformation **6a**, at a C-S-N-C torsion angle of 98.7°. Conformation **6b** appears at the torsional value of -71.7° in Figure 2. (This conformation (**6b**) is related to conformation **6a** by nitrogen inversion; rotation of **6a** around the C-S-N-C dihedral angle will give the enantiomer of **6b**; see below). The energy barrier of 11.8 kcal/mol corresponds to the transition structure with the S-CH_3 and N-CH_3 bonds eclipsing, while the barrier of 8.2 kcal/mol corresponds to the saddle point conformation with the S-CH_3 bond eclipsing the N-H bond. Geometry optimization of these saddle point conformations results in the lowering of the barrier heights to 9.2 and 7.5 kcal/mol, respectively. The lowering in energy for the higher barrier (with S-CH_3 and N-CH_3 eclipsing) is effected by relieving steric congestion through opening bond angles C-S-N and C-N-S by 3° and 5°, respectively. The S-N bond length also increases by 0.01 Å, while the C-S and N-C bond lengths remain unaffected. The modest lowering of energy for the smaller rotational barrier upon geometry optimization is not reflected by any significant change in any geometric variable.

The S-N bond length of **6a** of 1.645 Å (nitrogen being pyramidal and the disposition of the nitrogen lone pair roughly in the C-S-N plane) suggests an interaction of the nitrogen lone pair with the 3d-orbitals of sulfur ((d-p)-π overlap).[20] This contention is further supported by an increase in the S-N bond length of 0.01 Å upon full geometry optimization of the transition structure wherein the two methyls are eclipsed. A comparison with the changes in bond lengths upon full geometry optimization of the corresponding transition structure for methyl methanesulfonate reveals that this increase in the S-N bond length is not the result of the steric repulsion between the methyl groups, but rather is the consequence of decreased (d-p)-π overlap at this geometry.[18] Therefore, the major electronic contributor to the rotational barrier is expected to be the varying interaction of the nitrogen lone pair with the sulfur d-orbitals. Conversely, the contribution of steric repulsions to the rotational barrier is expected to be dependent upon the bond length between the central atoms defining the torsional angle. In the case of methyl methane-

Table VII. Nitrogen Pyramidalicity in Primary, Secondary, and Tertiary Sulfonamides

	primary[a]	secondary	tertiary[b]
improver torsional angle S-N-C(H)-C(H) (deg)	126.2	132.6 (**6a**) 152.6 (**6b**)	146.8
nitrogen distance from the plane S-C(H)-C(H) (Å)	0.237	0.312 (**6a**) 0.175 (**6b**)	0.335

[a] The full geometry optimization (6-31G*, no symmetry constraints) of methylsulfonamide. The bond angles S-N-H = 111.6° and H-N-H = 112.5°. The loss of asymmetry at the nitrogen makes the torsion C-S-N-H = 116.6° for both hydrogens on nitrogen. [b] The bond angles obtained from X-ray analysis of tetramethylsulfamide (ref 18).

sulfonate, the central bond length S–O is 1.579 Å, shorter by 0.066 Å than the S–N bond in the sulfonamide (1.645 Å). Thus, the sulfonate encounters a greater repulsive steric contribution in the rotational barrier.

As a measure of the nitrogen pyramidalicity[24] in primary, secondary, and tertiary sulfonamides, the improper torsion angle (R1–N–R2–R3) and the deviation of nitrogen from planarity (the plane defined by the three substituents on nitrogen) are given in Table VII. It is apparent that the two 6-31G* basis set geometry-optimized conformations of *N*-methylmethanesulfonamide are not equally pyramidal. The nitrogen in conformation **6a** is more sp^2 hybridized than the nitrogen in conformation **6b**. Thus, the hybridization state of the nitrogen is related to the torsional angle C–S–N–C. In the case of tertiary sulfonamides, the ground state should be more pyramidal with substituents that cannot conjugate with the nitrogen lone pair. On the other hand, substituents than can conjugate (phenyl) will stabilize the planar transition structure for nitrogen inversion. If the inversion barrier is low enough, it is possible to envision a scenario where limited motion along the rotational barrier path can trigger nitrogen inversion.[25]

The interconversion of these two nonequivalent conformations (**6a** and **6b**) is assumed to take place by inversion via the planar transition structure (angle C–N–H = S–N–H = 120°).[12,24] Full geometry optimization of the assumed planar transition structure indicates a hindrance to inversion of only 2.2 kcal/mol to interconvert the two conformations. This is significantly lower than the lower barrier (8 kcal/mol) for interconversion by a torsional pathway (Figure 2).

Partial Atomical Charges for Conformational Analysis. The torsional parameters (described later) derived from the ab initio studies on *N*-methylmethanesulfonamide and methyl methanesulfonate were used to obtain lowest energy conformations of phenyl benzenesulfonate and *N*-phenylbenzenesulfonamide. Full geometry optimization of these structures by the semiempirical MNDO method gave partial atomic charges which reflected the ab initio dipole vector calculated for the model compounds (**5** and **6a–b**). These charges were specified in QUANTA/CHARMm and were used in all subsequent conformational analysis. Similarly, partial atomic charges were obtained from CAM (**3**) and CAT (**4**).[3] These charges and the dipole moments are provided as supplementary material (1 page).[26]

Torsional Parameterization. For sulfonate, **5**, the bond angles and lengths derived from molecular (QUANTA/CHARMm) were within 2.0° and 0.03 Å of the ab initio values and the X-ray determined values for the compound **1**.

The torsional energy profile from the ab initio 6-31G* rigid rotor calculations (Figure 2) was first modified to reflect the geometry optimization of the transition structure. Since geometry optimization resulted in a loss of energy of 11.23 kcal/mol for the methyl-eclipsed geometry, presumably reflecting steric interactions between the methyl groups to a large extent, the ab initio rigid rotor rotational profile was scaled down by this amount at the energy maximum ($\Theta = 0°$) and proportionally less out to ±120°, where steric effects would be minimal (see supplementary material).

The geometry implicit torsional barrier was calculated by QUANTA/CHARMm. This involved a grid search with 20° increments of the C–S–O–C torsional angle and 200 steps of conjugate gradient minimization for each conformation, keeping the torsion C–S–O–C constrained and specifying as zero the force constant value for the torsional angle C–S–O–C. The resulting torsional curve, which contains only contributions from nonbonded and electrostatic interactions, shows a maximum of 7.23 kcal/mol at $\Theta = 0°$. This curve was then subtracted from the scaled, ab initio curve. The residual torsional profile that results from this analysis has a barrier height of only 2.84 kcal/mol, and it was fit by least squares to a three-term truncated Fourier series.[16] The rms of the fit was 0.32 kcal/mol, and the values of the torsional parameters were $V_1 = 1.05$, $V_2 = -1.00$, $V_3 = 1.06$.[19] These parameters were inserted into the QUANTA/CHARMm force field, and using the modified force field, we then obtained a C–S–O–C torsional profile for methyl methanesulfonate having a barrier height of 9.3 kcal/mol (versus 10.1 kcal/mol for the scaled ab initio curve). More significantly, the curve shape of the QUANTA/CHARMm rotational profile for methyl methanesulfonate closely matched that of the scaled ab initio curve near the energy minimum ($\Theta = 180°$). For example, the energy of conformers having dihedral angles within 45° of the minimum for the force field curve and 55° for the scale ab initio curve lie within 2 kcal/mol of the minimum energy conformer.

These parameters were then utilized to model phenyl benzenesulfonate. The grid search for the torsional angle C–S–O–C in phenyl benzenesulfonate, calculated by QUANTA/CHARMm using above torsional parameters, resulted in a second energy minima at the torsion angle C–S–O–C = ±80° from the global energy minima, 1.7 kcal/mol higher in energy than the global minimum, and having a 3.5-kcal/mol energy well. The dipole moment studies on phenyl benzenesulfonate indicate that this compound exists in 7:3 ratio of anti and gauche conformations in both gas and solution phase.[8]

The QUANTA/CHARMm force field gave bond lengths and angles for methanesulfonamide **6a** that were in very good agreement with the calculated ab initio and observed X-ray values. The geometry implicit torsional barrier (C–S–N–C) for this compound (calculated by the method that was used for the sulfonate **5**, with the additional nitrogen improper torsion angle force constant of 3 kcal/mol·deg^2) was negligible (0.7 kcal/mol). Therefore, the ab initio rigid rotor calculated torsional curve was scaled down to account for the geometry optimization of the two torsional transition structures and the second energy minima (see supplementary material, 1 page). A least-squares fit based on a 5-fold (three-term cosine plus two-term sine functions) Fourier series[16,19] gave an rms fit of 0.77 kcal/mol, with the torsional parameters $V_1 = 3.61$, $V_2 = 6.75$, $V_3 = 1.35$, $V_4 = 0.93$, $V_5 = 1.49$.[19] However, since nitrogen inversion (rather than torsional rotation) is energetically the more favorable path for interconverting the two conformations of methylmethanesulfonamide (**6a** and **6b**), we have used a much simpler torsional function with a potential constant of 3.4 kcal/mol, a periodicity of two, and a phase of 0°, to reproduce the ab initio calculated torsional barrier height.

During molecular modeling of the torsional energy profile for *N*-phenylbenzenesulfonamide, the improper dihedral constraint on nitrogen was modified. In the CHARMm force field parameter list, only one improper dihedral angle defines both the asymmetry and the planarity of nitrogen with respect to the phenyl ring bonded to it. To allow nitrogen inversion as the lowest energy hindrance for the conformational interconversion, we split the improper dihedral into its components. The value for the component responsible for maintaining the asymmetry at the nitrogen was set to zero; however, the second component responsible for

(24) Andrews, P. R.; Munro, S. L. A.; Sadek, M.; Wong, M. G. *J. Chem. Soc., Perkins Trans. 2* **1988**, 711.

(25) Raban, M.; Carlson, E. *J. Am. Chem. Soc.* **1971**, *93*, 685. Kaftory, M.; Agmon, I. *J. Am. Chem. Soc.* **1984**, *106*, 7785. Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Mol. Struct. (THEOCHEM)* **1988**, *168*, 265. von Müller, K. *Helv. Chim. Acta* **1970**, *53*, 1112.

(26) As pointed by a referee, the conclusions drawn from the present conformational analysis study are rather insensitive to the quality of partial atomic charges used. However, in studies of solute–solvent interactions or free energy perturbations, it would be imperative to make a better and more realistic estimation of partial atomic charges by electrostatic fitting of the ab initio wave function.

Table VIII. Dihedral Angles and Relative Energies of the Conformations of CAT, CAM, SAM, and SAT[a] Obtained from Grid Search and Energy Minizations[b]

compd/ conform. no.	rel energy[c] (kcal/mol)	dihedral angle[d] (deg)			
		$H-C_{sp3}-C-C(X)$	C-C-X-Y	C-X-Y-C	X-Y-C-C
SAT (1)					
1	0.0	-9	-60	-177	-3
2	0.2	-7	178	180	180
3	2.3	-10	175	-79	-166
4	2.9	-7	60	79	165
SAM (2)					
1	0.0	-4.8	-69	-141 (-84)[e]	118 (-108)[e]
2	3.5	-44	173	-141 (86)	-119 (-111)
3	4.2	-42	172	143 (-84)	63 (-67)
CAM (3)					
1	0.0	-40	-79	-178	17
2	1.4	-45	65	8	-149
3	2.0	-49	68	-169	-158
4	2.3	-36	-88	-10	158
CAT (4)					
1	0.0	-51	62	-176	-172
2	0.8	-51	-103	178	-164
3	2.4	-44	65	28	

[a] Common names given to compounds 1-4; see footnote 3. [b] See text for grid search and energy minimization procedure. [c] Energies are with respect to the global minima set to zero. [d] For further description of the dihedral angles, see figure with Table I. For SAT, X = S, Y = O; SAM, X = S, Y = N; CAT, X = C, Y = O; CAM, X = C, Y = N. [e] Angles in parentheses are for the dihedrals C-S-N-H and H-N-C-C, respectively.

keeping the nitrogen in the plane of the phenyl ring was assigned a value of 90 kcal/mol·deg^2, the value given in CHARMm for this improper torsion. Moreover, certain equilibrium values for the bond lengths and bond angles in the CHARMm force field parameter file were changed to reflect the corresponding values as observed by X-ray crystallography. The phase for the dihedral angle C-C-X-Y for SAT and SAM was also changed from 0° to 180°. The latter change furnished the X-ray crystallographically determined conformation for the sulfonate **1** as the global minimum (Table VIII and see conformational analysis for further comparison of X-ray and molecular modeling conformations of **1**). All the changes made in the CHARMm force field parameter file are provided as supplementary material (1 page).

X-ray and Solution NMR Studies on 1. The single-crystal X-ray structure of the bisacetate of **1** is shown in Figure 4. The crystal data are a = 8.391 (4), b = 12.577 (5), c = 12.308 (3) Å α = 90°, β = 100.32 (3)°, $\gamma = \alpha$. Goodness of fit is 0.042, MW 516.57, calculated density = 1.342 g/cm^3; monoclinic, space group $P2_1$ (C_2^2) and two molecules per unit cell. Some bond lengths, angles, and torsions are listed in Table III. The torsional angle H-C-C-C, describing the twist of the 1,2-disubstituted phenyl ring with respect to the axis of the triphenylmethane propeller, is 28.5 (5)°, and the torsion angle C-C-S-O is 53.2 (4)°, with the result that one of the two doubly bonded oxygens is in the plane of the phenyl ring bearing the sulfonate group. The torsion angle C-S-O-C is -173.1 (3)°, which disposes the plane of the pendant phenyl ring almost parallel to the sp^3 C-H bond. There are no noteworthy intermolecular interactions, and the intermolecular van der Waals contacts are within the expected range.

All attempts to identify any conformational bias of compound **1** in solution, by measuring NOE, difference spectroscopy, or 2D ^{1}H NOE experiments with variable mixing times, failed (500 MHz). The experiments were attempted at two temperatures (22 and -30 °C). Therefore, since no NOE was observed, it appears that the pendant phenyl ring is preferably disposed in a fully extended orientation (anti). A variable-temperature study (down to -90 °C), to slow down or freeze one-ring or two-ring concerted rotation of the two phenyl rings with C_2 symmetry axis in the triphenylmethane[27] portion of the molecule, was also unsuccessful. Since the para-substituted phenyl rings appear as AA'BB' spin systems[1] (rather than ABCD), even down to -90 °C, these rings must be rotating rapidly on the NMR time scale.

(27) Brocas, J.; Gielen, M.; Willem, R. *The Permutation Approach to Dynamic Stereochemistry*; McGraw-Hill: Cambridge, 1983; pp 472-499. Mislow, K.; Gust, D.; Finocchiaro, P.; Boettcherr, J. *Top. Curr. Chem.* **1974**, *47*, 1.

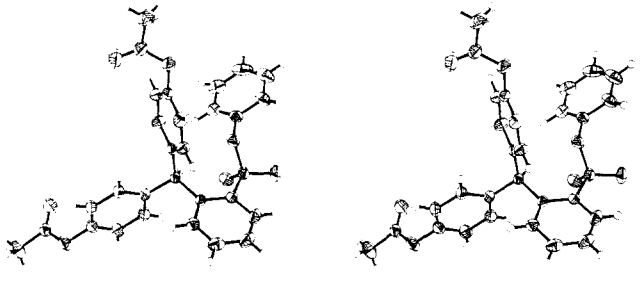


Figure 4. A relaxed stereoview of the sulfonate **1**, as determined by single-crystal X-ray crystallography. See text and supplementary material for further details.

The proton chemical shifts of the 1,2-disubstituted phenyl ring show solvent dependence. In case of **1**, there appears to be some intermolecular interaction of the free phenol with the oxygens of the sulfonate group. This is noted by an upfield chemical shift of 0.2 ppm for the proton on the phenyl ring ortho to the sulfonate group upon changing the solvent from acetone-d_6 to methylene-d_2 chloride; the addition of methanol-d_4, in the latter case, reverts the chemical shift to its original position. This effect was not noted in NMR studies of the diacetate of compound **1**.

Conformational Analysis of Compounds 1-4. Trityl systems of the type studied here (two phenyl rings with C_2 axes) will adopt two enantiomeric helical conformations. Although these would be in rapid equilibrium, care was taken to maintain a single, consistent helical sense of the molecules during molecular modeling. The conformational analysis of compounds **1-4** was done as described in computational details (Experimental Section) and under torsional parameterization (preceding section). See Table VIII for a list of relative energies and dihedral angles for all the minimum energy conformations for SAT, SAM, CAT, and CAM.[3]

All of the minimum energy conformations produced from each of the four compounds were first compared among themselves, and then the selected, unique conformations for all of the compounds were compared by superimposing the trityl portion of the molecules. For all the conformations of SAT, the bond lengths and the bond angles were found to be in agreement with the X-ray determined values. The lowest minimum energy conformation of SAM has a torsion angle for C-S-N-C that differs by 10–15° from that of the ab initio calculated value for **6a**. In all of the conformations of SAT, the trityl ring bearing the sulfonate substituent has a more vertical disposition with respect to the C_{sp^3}-H bond than any of the conformations of SAM, CAT, and CAM;

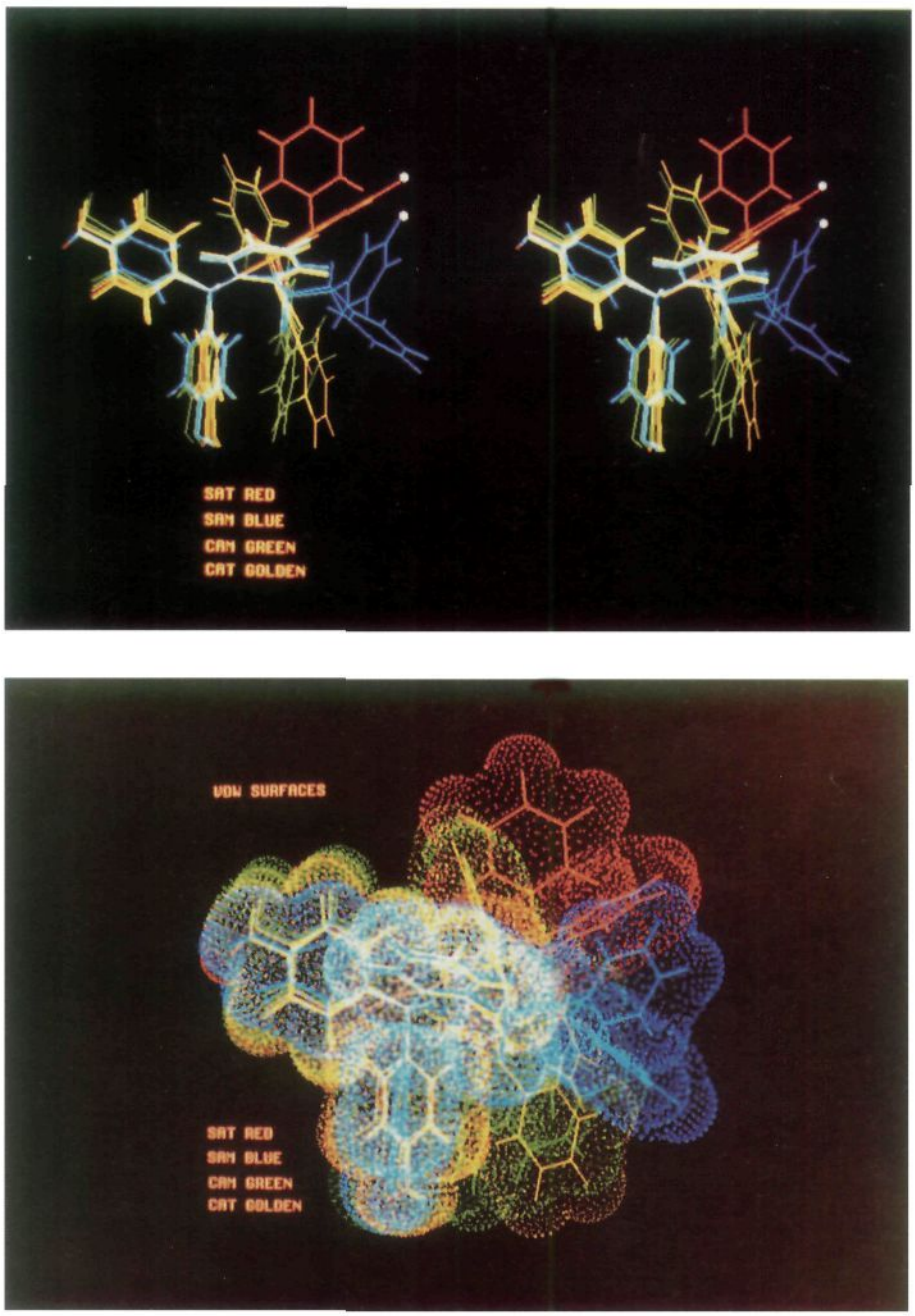


Figure 5. The superimposition of various conformations of SAT, SAM, CAT, and CAM through the trityl potion of the conformations: (top) relaxed stereoview of skeletal models of the conformations; (bottom) van der Waals surfaces of the conformations.

this C–H bond is flanked by two oxygens from the sulfonate function. In case of CAT (**3**) and CAM (**4**), all of the minimum energy conformations are within 2.4 kcal/mol of the global minima (Table VIII).

In case of SAT, the two lowest minimum energy conformations differ by only 0.2 kcal/mol; both have the torsion angle (C–S–O–C) at 180° (Table VIII). The lowest energy conformation SAT1 is very similar to the structure observed by X-ray crystallography of the diacetate of **1**, except that the dihedral angle S–O–C–C in the X-ray determined structure is 90° (versus −3° in SAT1). This dihedral angle difference does not alter the position of the centroid of the pendant phenyl ring. While the pendant phenyl ring of SAT1 is within the torus defined by various conformations of CAT and CAM (explained later), the pendant phenyl ring of SAT2 (red and starred in Figure 5), which is very nearly the same energy at SAT1, is away from the torus. The next conformation (SAT3) is 2.1 kcal/mol higher in energy than SAT2 and has the substituents on S and O gauche with respect to each other. A similar conformation (SAT4) is also found, 2.9 kcal/mol higher in energy than SAT1; however, the pendant ring in SAT4 projects within the torus defined by CAT and CAM.

The global minimum for SAM (SAM1, Table VIII) has the pendant phenyl ring within the torus defined by the corresponding phenyl ring of various conformations of CAT and CAM (for clarity not shown in Figure 5). However, two other minimum energy conformations, SAM2 and SAM3, were found with the energies of 3.5 and 4.2 kcal/mol higher than SAM1, respectively. The major contributors to this energy difference are repulsive van der Waals and electrostatic in origin; the energy difference between SAM2 and SAM3 is electrostatic in origin. Both of SAM2 and SAM3 have their bond angles C–N–H and S–N–H smaller by 7° and 5°, respectively, as compared to SAM1 and X-ray crystallographically determined values. Moreover, SAM2 and SAM3 are "enantiomeric" with respect to the dihedral angles C–S–N–C

and C-S-N-H. The pendant phenyl ring of SAM2 (blue and starred in Figure 5) is in close proximity to the corresponding ring of SAT2 (red and starred in Figure 5). The distance between the centroids of the phenyl rings is 2.51 Å.

The conformational situation for CAM and CAT is very different; four and three unique conformations, respectively, were found within 2.4 kcal/mol of their global minima (Table VIII). In all of these conformations, the pendant phenyl ring proscribes a torus above and partly around the 1,2-disubstituted phenyl ring of the trityl part of the molecule. These conformations are shown in Figure 5 (CAM green and CAT golden), and, for both CAT and CAM, no conformation is observed wherein the pendant phenyl ring falls outside this torus.

The van der Waals surfaces of all of the conformations of CAT, CAM, SAM (except SAM1), and SAT (except SAT1 and SAT4) show that part of the pendant phenyl ring of SAM and SAT do share a common region in space, while the pendant phenyl rings in all of the conformers of CAT and CAM are restricted to the torus above and around 1,2-disubstituted phenyl ring (Figure 5) and are thus excluded from the common space of the SAT2 and SAM2. We believe that the space nearly common to the two pendant phenyl rings of SAM2 and SAT2 should be considered as the region whose occupancy confers high binding affinity to the estrogen receptor (cf. Table I).

Conclusions

We have developed force field torsional parameters for the central bond of the sulfonate and sulfonamide functional group. In the process, we have found that the energy minima proposed for the sulfonamide in the literature are quite different from those calculated using standard ab initio methods. To implement torsional parameters in an empirical force field for the sulfonamide, where the nitrogen is asymmetric, one must use a five-term torsional potential function, containing both cosine and sine terms, in order to reproduce the torsional curve that results from the ab initio calculation. However, the situation can be simplified by reducing the nitrogen improper torsion angle force constant to allow nitrogen inversion to be the lowest energy barrier for conformer interconversion as predicted by ab initio calculations. This approach allows nitrogen hybridization to be a conformational variable, along with the dihedral angles. A survey of nitrogen-containing compounds reveals that nitrogen can exist in various hybridization states in between that of sp^2 and sp^3.[24] Therefore, the hybridization state of nitrogen should be considered a conformational variable.

Assignment of the ab initio calculated normal modes for the sulfonate did not pose any difficulty; however, with the sulfonamide, the normal modes are highly coupled, and the assignments became somewhat subjective. In addition, the experimental IR data on the sulfonamide is from a dimeric species, so that band positions and coupled motions may be different from those of a free sulfonamide. Thus, with both the calculated and the experimentally determined case, accuracy in determining the force constants for bond length and angle deviations is compromised to some extent.

The use of these new torsional parameters in the CHARMm force field for conformational analysis of compounds **1–4** has given us clues about the conformational space common to the higher affinity sulfonate and sulfonamide systems (**1** and **2**) versus that for the low affinity carboxylate and carboxamide systems (**3** and **4**). On the other hand, in a comparison of SAT, which is fairly apolar, with SAM, which is fairly polar (because of the hydrogen bonding site on the secondary sulfonamide group), it is reasonable to presume that the extent of polar solvent association for the two compounds will be quite different. As a result, the actual energy barriers for the interconversion of conformations of **2** and their relative energies may yet be somewhat different from that calculated in vacuum. However, a comparison of the relative energies of various conformations of SAT and SAM and their binding affinities toward the estrogen receptor provides a consistent picture, within the limits of accuracy of the molecular mechanics conformational analysis method. The results of this conformational analysis of these trityl sulfonyl systems provides us with new insights into the relationship between structures and binding affinity for ligands for the estrogen receptor. This information will be important in the design of new functionalized ligands for this receptor.

Acknowledgment. We are grateful for support of this work by grants from National Institute of Health (RO1 DK15556) and the National Science Foundation. R.D.B. and J.A.K. thank the National Center for Supercomputing Applications at the University of Illinois at Urbana-Champaign for the grant to use the Cray X-MP/48 and Dr. Scott R. Wilson for performing the X-ray structure on the diacetate of compound **1**. The advice of Dr. W. Clark Still for assigning partial atomic charges and Dr. Scott D. Kahn for providing Fourier fit and IR visualization programs[16] is also gratefully acknowledged.

Supplementary Material Available: *Z*-matrices for compounds **5** and **6**, an account of modifications made to force field parameters of CHARMm to carry out the molecular modeling of **1** (SAT) and **2** (SAM), unscaled and scaled torsional energy profiles for compounds **5** and **6**, partial atomic charges used for conformational analysis of SAT (**1**) and SAM (**2**), and X-ray crystallographic data on the diacetate of compound **1** (SAT) (22 pages). Ordering information is given on any current masthead page.