Ab initio study of the methylsulfonate and phenylsulfonate anions

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Owing to the importance of the sulfonate group in organic and pharmaceutical chemistry a theoretical study at an *ab initio* level has been carried out for this ionic group. The geometric, electronic and energy properties of the methyl- and phenyl-sulfonate anions have been calculated by optimizing with the Hartree–Fock (HF) 6-31G* and 6-31 + G* basis sets and including correlation effects at the second-order Moller–Plesset (MP2) level. In addition, the harmonic vibrational frequencies and the zero-point vibrational energy of the different conformers of these compounds have been evaluated.

The results show that the inclusion of diffuse functions does not affect the geometrical description of the sulfonate group. However, both optimizations provide a flatter pyramidal disposition for this hypervalent sulfur atom when compared with the experimental values. It has been found that the inclusion of correlation effects seems to be necessary for a good electronic description of these anions. In the case of methylsulfonate a minimum and a transition structure were located and the rotational barrier evaluated. Phenylsulfonate has a flatter rotational profile and only two structures were fully optimized and characterized. Using the assumption that there is a relation between the population of conformers in the crystalline phase and that in the gas phase, a rotational barrier for the phenylsulfonate anion is suggested.

Alzheimer's dementia is a devastating neurodegenerative disease for which no effective therapy exists. This disease affects more than 15% of the population greater than age 85 years. The deposition of a neurotoxic amyloid peptide is central to the pathology of Alzheimer's disease. Recent data from a variety of groups[1] suggest a role for sulfated proteoglycans in amyloid deposition. These data raise the possibility that sulfated (or sulfonated) compounds could interfere with amyloid formation, thus representing potential therapeutics. Since molecular modelling is central to modern rational drug design, understanding the theoretical chemistry of sulfonate derivatives and compounds containing hypervalent sulfur atoms is a neuropharmacological priority.

Theoretical investigation of the interactions of these sulfonate derivatives with their biological receptors (proteins, enzymes) requires the use of molecular mechanic approaches owing to the complexity of the systems. However, for an effective application of molecular mechanic force fields, an adequate set of parameters is needed. Most molecular modelling packages do not include parameters suitable for hypervalent S atoms (–SO–, $-SO_2-$, $-SO_3^-$, $-OSO_3^-$).[2] In this line, parameters for MM2, AMBER and CHARMm force fields have been recently developed to described the sulfate and sulfamate anions,[3] but, to our knowledge, little has been done regarding the sulfonate group.

Owing to the importance of these functional groups, we have performed *ab initio* calculations on methylsulfonate and phenylsulfonate anions to obtain accurate geometric and electronic data which can be useful in understanding structure and for providing a better description of these anions in a future molecular mechanics parametrization. Different rotamers of both anions (**1a**, **1b**, **2a** and **2b**, see Fig. 1) were analysed to evaluate the rotational barrier in each case.

This study evaluates the influence of the basis set upon the geometric, electronic and torsional properties of methylsulfonate and phenylsulfonate

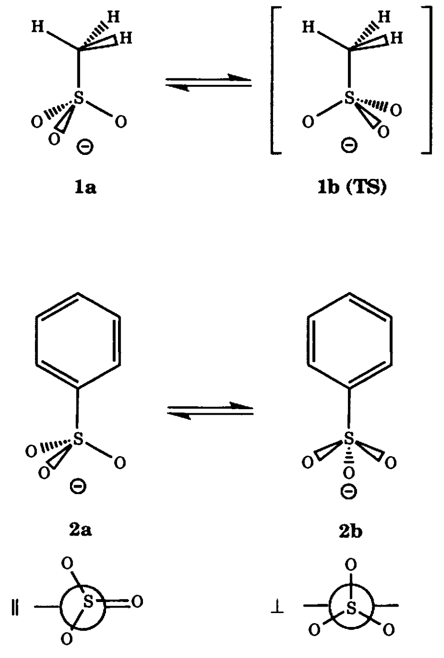

Fig. 1 Representation of the stationary structures found for the rotational equilibria of the methylsulfonate **1** and phenylsulfonate **2** anions

Computational methods

For an adequate description of hypervalent S atoms, supplementary d functions are needed.[4] Large split-valence basis sets with polarization functions provide a highly accurate description of these compounds. For this reason, the 6-31G* basis set[5] was used for a full geometry optimization of the methyl- and phenyl-sulfonate anions **1a**, **1b**, **2a** and **2b** (Fig. 1).

Moreover, anions generally have a low ionization potential. Thus, for a proper description of an ionic molecule the use of basis sets which incorporate diffuse functions is required since these functions improved the description of long-range behaviour of molecular orbitals and the electron lone pairs.[4]

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Table 1 Geometrical parameters [bond lengths (Å), bond angles and dihedrals (°)] for the optimized stationary structures found for the methylsulfonate **1** and phenylsulfonate **2** anions at HF/6-31G*//HF/6-31G* and HF/6-31+G*//HF/6-31+G* levels of calculation and for some crystallographic structures from the CSD

	l(C–S)/Å	*l*(S–O)/Å	*a*(C–S–O)/degrees	*d*(H/C–C–S–O)/degrees
HF/6-31G*//HF/6-31G*				
1a (stagg.)	1.787	1.455	104.45	180.0
1b (eclip.)	1.808	1.455	104.72	0.0
2a ($\parallel$)	1.798	1.451	104.54	0.2
2b ($\perp$)	1.799	1.451	104.61	90.2
HF/6-31+G*//HF/6-31G*				
1a (stagg.)	1.787	1.457	104.65	179.9
1b (eclip.)	1.808	1.458	104.91	0.0
2a ($\parallel$)	1.800	1.453	104.21	0.2
2b ($\perp$)	1.800	1.453	104.60	90.0
CSD methylsulfonates				
BAKLAA	1.754	1.454	106.92	180.0
CAMSOA	1.782	1.451	106.30	171.9
CAMSUL	1.754	1.444	106.98	177.5
CEXMOH	1.793	1.452	105.24	172.7
FASJUE	1.750	1.442	106.68	180.0
TAUCYM01	1.781	1.455	106.08	167.6
Mean (30 struct.)	1.765	1.450	106.57	—
CSD phenylsulfonates				
FEYZOY	1.765	1.451	105.35	95.5
JAPCOS	1.772	1.435	106.41	6.9
JARCIO	1.778	1.451	107.05	2.5
JERNID	1.772	1.452	106.68	97.9
KERMUP	1.763	1.450	106.78	88.0
VOZZOZ	1.746	1.445	107.09	0.3
Mean (429 struct.)	1.766	1.451	106.61	—

Thus, full optimization of compounds **1a**, **1b**, **2a** and **2b** with the 6-31+G* basis set[6] were carried out and compared with the results obtained when using polarization functions exclusively.

Finally, it has been recently observed that the inclusion of correlation (at MP2 level) in *ab initio* calculations of hypervalent sulfur derivatives provides better dipole moment values when compared with the HF results.[7] To obtain a better electronic description of the sulfonate group (–SO_3^-), MP2[8] single point calculations were carried out using the optimized HF/6-31G* and HF/6-31+G* structures.

The molecular orbital *ab initio* calculations were performed using the Gaussian 92 program (DEC version).[9] The structures were optimized at the HF level using the Berny algorithm as implemented in the Gaussian 92 program. The criteria applied to terminate the geometry optimizations were those by default in the program. For all the structures studied, the calculation of the harmonic frequencies was carried out, to determine the characteristics of each stationary point and to estimate the zero-point vibrational energy. In these frequency calculations the force constants were determined analytically.

Structural features

The geometrical parameters obtained in the optimization of the different rotamers of compounds **1** and **2** at the HF/6-31G* and HF/6-31+G* levels are reported in Table 1. For comparison, the parameters of some simple X-ray structures found in the Cambridge Structural Database (CSD)[10] and the mean values for all the methyl- and phenyl-sulfonates (not substituted in both *ortho* positions) found in that Database are also included in Table 1.

At the HF/6-31G* level of optimization, and as a result of the analysis of the vibrational frequencies, it was found that compound **1** exhibited two different stationary points: a minimum **1a** and a transition structure **1b**. The same result was obtained when both conformers were optimized at the 6-31+G* level and the frequencies calculated. For these structures, the inclusion of diffuse functions seems not to affect the C–S distance and both calculations slightly overestimate this distance in comparison with the experimental values. The bond lengths obtained for the S–O bonds at 6-31+G* are a little larger than those derived by the 6-31G* calculation, but, again, both methods slightly overestimate this bond distance. The C–S–O bond angle is a little larger when diffuse functions are included, but smaller than the X-ray experimental results (see Table 1).

For compound **2**, at both levels of calculation, two stationary points were found resembling the two idealized forms of Allinger and Tribble:[11] the 'parallel' one ($\parallel$, **2a**), in which one of the O atoms is in the plane of the aromatic ring (C–C–S–O = 0°), and the 'perpendicular' one ($\perp$, **2b**) in which one of the O atoms is perpendicular to the phenyl ring (C–C–S–O = 90°). The vibrational frequencies of both conformers **2a** and **2b** were all positive which usually characterizes the structures that are minima. These structures could, in principle, be considered as minima because in the $\parallel$ structure, even though there is a steric repulsion between the O atom and an aromatic H atom, there is a stabilization due to the conjugation between the S–O bond and the aromatic ring. Regarding the $\perp$ rotamer this conjugation is lost, but stability is gained since steric repulsion is avoided. Nevertheless, and as it will be shown later, these two stationary points cannot be properly defined as minima since they have very similar energy and no transition structure was found between them.

Regarding the geometrical features of these **2a** and **2b** structures, both C–S and S–O bond distances, are slightly larger when using diffuse functions, but, whereas C–S calculated distances are a little larger than those of the X-ray structures, the S–O theoretical distances are very similar to the experimental ones. The C–S–O angles, again, are underestimated by the theoretical calculations which provide a more planar pyramidal disposition for the SO_3^- group.

Electronic description

The Mulliken atomic charges obtained for all the structures studied at HF/6-31G*//HF/6-31G*, MP2/6-31G*//HF/6-31-G*, HF/6-31+G*//HF/6-31+G* and MP2/6-31+G*//HF/6-31+G* levels of calculation are given in Table 2. Dipole moments are not given since this magnitude has no meaning in ionic structures.

For both compounds **1** and **2**, the charges assigned to the S atom and O atoms are quite large at the 6-31G* level of calculation. Moreover, these charges increase greatly when introducing diffuse functions; the charges on the O atoms become more negative and the positive charge assigned to the S atom (+2) becomes extremely large. However, the use of correlation effects at the MP2 level corrects this overestimation, providing more reasonable atomic charges for both atoms. Thus, as suggested by Alkorta,[7] calculations at the MP2 level on compounds containing hypersulfur atoms provide a better electronic description of these atoms and their environment; this generates, in the case of neutral molecules, better dipole moment values.

Table 2 Atomic charges of the optimized stationary structures found for the methylsulfonate **1** and phenylsulfonate **2** anions at HF/6-31G*//HF/6-31G*, HF/6-31+G*//HF/6-31+G*, MP2/6-31G*//HF/6-31G* and MP2/6-31+G*//HF/6-31+G* levels of calculation

	qC^a	qS	qO
HF/6-31G*//HF/6-31G*			
1a (stagg.)	−0.69	1.51	−0.77
1b (eclip.)	−0.74	1.54	−0.77
2a (‖)	−0.26	1.57	−0.76
2b (⊥)	−0.26	1.56	−0.75
MP2/6-31G*//HF/6-31G*			
1a (stagg.)	−0.67	1.16	−0.65
1b (eclip.)	−0.71	1.18	−0.65
2a (‖)	−0.19	1.18	−0.63
2b (⊥)	−0.19	1.17	−0.63
HF/6-31+G*//HF/6-31+G*			
1a (stagg.)	−0.82	1.83	−0.87
1b (eclip.)	−0.96	2.03	−0.91
2a (‖)	−1.08	2.04	−0.82
2b (⊥)	−1.02	2.03	−0.83
MP2/6-31+G*//HF/6-31+G*			
1a (stagg.)	−0.85	1.43	−0.74
1b (eclip.)	−0.96	1.62	−0.77
2a (‖)	−1.11	1.60	−0.67
2b (⊥)	−1.08	1.61	−0.68

[a] C atom bonded to the S atom.

Energy and rotational barriers

Table 3 shows the HF and MP2 energies calculated using the 6-31G* and 6-31+G* basis sets for the conformers of compounds **1** and **2**, the relative energy between rotamers, the energy with the zero-point vibrational energy (ZPVE) correction (estimated from 6-31G* and 6-31+G* harmonic frequencies for each molecule) and the relative energy between rotamers including that correction.

The barrier to rotation for the methylsulfonate **1** was calculated by subtracting the energy of the total minima **1a** from the energy of the saddle point **1b** with and without the ZPVE correction. Thus, when the ZPVE correction is neglected, this barrier increases slightly when introducing correlation effects at the MP2 level, over the 6-31G* or the 6-31+G* basis sets. The inclusion of diffuse functions diminishes the rotational barrier by *ca.* 0.35 kcal mol^{-1}.† Nevertheless, when the ZPVE corrected energy is considered, we obtain quite similar values for the barriers of rotation *ca.* (0.4 kcal mol^{-1} smaller) at both levels of calculation. When computing the ZPVE corrected energy for rotational barriers we have eliminated the imaginary frequency associated with the transition vector. However, since both energies [*E*(RHF) and *E*(RHF) + ZPVE] provide quite similar results for the rotational barrier, the ZPVE correction for the saddle point seems to be unimportant.

In the case of the phenylsulfonate, the difference in energy between **2a** and **2b** was evaluated using the ZPVE corrected energies. Thus, at the 6-31G* level, both the ‖ rotamer **2a** and the ⊥ rotamer **2b** were found to be equally stable, and using the

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† 1 cal = 4.184 J.

Table 3 Energy (au),^{a} relative energy (kcal mol^{-1}), energy plus the zero-point correction (au), and the relative energy (kcal mol^{-1}) for the corrected values for the stationary structures found for the methylsulfonate **1** and phenylsulfonate **2** anions at HF/6-31G*//HF/6-31G*, HF/6-31+G*//HF/6-31+G*, MP2/6-31G*//HF/6-31G* and MP2/631+G*//HF/6-31+G* levels of calculation

	E(RHF, MP2)/au	Δ*E*/kcal mol^{-1}	*E* + ZPVE/au	Δ*E*/kcal mol^{-1}
HF/6-31G*//HF/6-31G*				
1a (stagg.)min	−661.693 276 6	0.00	−661.638 335 4	0.00
1b (eclip.)ts	−661.686 864 5	4.02	−661.632 555 8	3.63
2a (‖)min	−852.203 316 8	0.05	−852.091 677 3	0.00
2b (⊥)min	−852.203 395 3	0.00	−852.091 675 2	0.00
MP2/6-31G*//HF/6-31G*				
1a (stagg.)min	−662.502 170 4	0.00	—	—
1b (eclip.)ts	−662.495 261 2	4.33	—	—
2a (‖)min	−853.639 114 0	0.11	—	—
2b (⊥)min	−853.639 292 4	0.00	—	—
HF/6-31+G*//HF/6-31+G*				
1a (stagg.)min	−661.711 066 0	0.00	−661.656 515 8	0.00
1b (eclip.)	−661.705 208 8	3.67	−661.651 187 4	3.34
2a (‖)	−852.225 665 4	0.01	−852.114 370 0	0.00
2b (⊥)	−852.225 681 4	0.00	−852.114 339 5	0.02
MP2/6-31+G*//HF/6-31+G*				
1a (stagg.)min	−662.541 951 9	0.00	—	—
1b (eclip.)	−662.535 697 8	3.92	—	—
2a (‖)	−853.688 699 3	0.13	—	—
2b (⊥)	−853.688 901 6	0.00	—	—

[a] 1 au = 4.360 × 10^{-18} J.

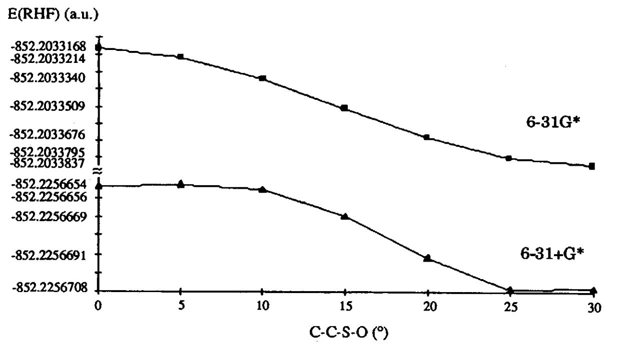

Fig. 2 Cross-section of the conformational surface, calculated at 6-31G* and 6-31 + G* levels, along the C–C–S–O dihedral angle which is fixed from 0 to 30° in steps of 5°

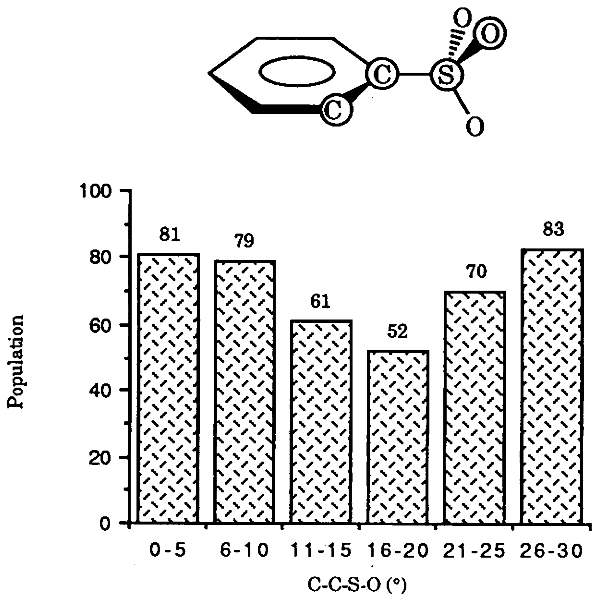

Fig. 3 Histogram of the population of the X-ray structures found for phenylsulfonate derivatives (not substituted in *ortho* position) according to the dihedral angle C–C–S–O. The number at the top of each column represents the population of structures corresponding to that range of the dihedral angle.

6-31 + G* basis set conformer **2a** was only 0.02 kcal mol^{-1} more unstable than the ⊥ structure. However, for this sulfonate it was not possible to localize the transition structure between both conformers **2a** and **2b**. Fig. 2 shows a cross-section of the conformational surface, calculated at 6-31G* and 6-31 + G* levels, by optimizing all the variables except the dihedral angle C–C–S–O which is fixed from 0 to 30° in steps of 5°. It can be observed that, at both levels of calculation, the energy diminishes uniformly from one minimum to the other without finding a maximum in between. Besides, frequency calculations were carried out for each one of these points and positive frequencies were always found for every structure. This fact seems to be more in agreement with a flat surface for the phenylsulfonate rotation.

By analysing the vibrational frequencies obtained for the totally optimized rotamers **2a** and **2b** it is observed that the three first frequencies are smaller than 200 cm^{-1} for both structures and at both levels of calculation (see Table 4). This means that **2a** and **2b** are quite relaxed structures, and, since they are close in the conformational space and the surface around these points is planar, the rotational barrier between them should be rather small. All these reasons could justify why it was not possible to locate the transition structure by using traditional approaches since probably what we have for compound **2** is the free rotation of the sulfonate group with respect to the phenyl ring.

Table 4 First three vibrational frequencies (cm^{-1}) obtained for the **2a** and **2b** conformers of the phenylsulfonate anion at HF/6-31G*//HF/6-31G* and HF/6-31 + G*//HF/6-31 + G* levels of calculation

	$\tilde{\nu}$/cm^{-1}	
	HF/6-31G*	HF/6-31 + G*
2a(‖)	13.8710 137.9856 199.4598	17.9065 134.3991 197.5975
2b(⊥)	30.6067 137.0079 203.1244	25.8562 132.8724 199.5070

Nevertheless, in a recent paper[12] rotational barriers have been estimated using crystal structures by performing crystal statistics and taking into account the hypothesis proposed by Ramachandran and co-workers.[13] This hypothesis has been criticized by some authors,[14] but supported by many others.[12,15] Assuming the Boltzmann distribution for a system with different energy states or conformers and a negligible entropic contribution for the equilibrium between conformers we can express the difference in energy between states by eqn. (1).

$$\Delta H^{\circ} = -RT\ln([\text{conformer A}]/[\text{conformer B}]) \quad (1)$$

Thus, Ramachandran and co-workers[13] proposed that the frequency distribution of a particular molecule (containing a certain fragment I) in a vacuum would be approximately identical to the frequency distribution for crystal structures in the CSD containing such a fragment I. Following this hypothesis and using eqn. (1) an approximation for the actual rotational barrier for the phenylsulfonate has been carried out.

Hence, a survey of phenylsulfonates (not substituted in the *ortho* positions which interfere with the rotation of the $-SO_3^-$ group) was performed using the CSD and a total of 429 hits were obtained. The histogram in Fig. 3 represents the different populations of phenylsulfonates according to the C–C–S–O dihedral angle. It is observed that the majority of the crystallographic structures detected correspond to the dihedral angles found for rotamers **2a** and **2b** (0 and 90°) with very similar populations of 81 and 83 structures, respectively. Thus, the minimum observed in this histogram with a total of 52 structures would correspond to the population of a possible intermediate between these two structures with a C–C–S–O dihedral angle around 16–20°. By applying eqn. (1) and using the populations of both minima at a temperature of 300 K, we determined the difference in energy between rotamer **2a** and rotamer **2b** to be 0.014 kcal mol^{-1}, *i.e.* approximately null as it was found at the 6-31G* and 6-31 + G* levels of calculation (see Table 3). Then, applying eqn. (1) at 300 K, and using the populations of the minima and that of the suggested intermediate we can propose a 'barrier' for the rotation of the sulfonate group of *ca.* 0.27 kcal mol^{-1}. This means a free rotation of the sulfonate group with respect to the phenyl ring as was expected from the theoretical calculations.

Conclusions

Regarding the influence of the basis set over the geometrical description of these sulfonate anions, it seems that the inclusion of diffuse functions has a very small influence on the C–S or S–O bond distances. In addition, both basis sets, HF/6-31G* and HF/6-31 + G*, supply a slightly flatter description of the pyramidalization of the $-SO_3^-$ group than that observed with the experimental geometries.

In general, for a good electronic description of the $-SO_3^-$ group the inclusion of correlation effects at the MP2 level is required. Polarization with or without diffuse functions is insufficient for providing good charges for the S and O atoms of sulfonate derivatives. Again, the Mulliken analysis results are dependent on the basis set used. Thus another kind of electronic descriptor, *e.g.* electronic densities or electrostatic potentials, should be considered for use in a future parametrization.

Methylsulfonate **1** has a bi-periodical conformational profile with only one energy minimum and one saddle point represented by conformers **1a** and **1b**, respectively. All the calculations performed yielded a quite similar rotational barrier of 4 kcal mol^{-1} and the inclusion of diffuse functions or correlation effects at the MP2 level seems not to affect the relative energy values obtained. Thus, for this small system, calculations at the HF/6-31G* level are enough to describe properly its stability and rotational barrier.

The phenylsulfonate anion presents a different conformational surface. Two structures were fully optimized and characterized by all positive frequencies as if both were minima. All the basis sets used provided a very similar stability for both rotamers with or without correlation effects. This was confirmed by the populations of the crystal structures found for both conformations in a search in the CSD. However, at the levels of calculation used here, it was not possible to localize a transition structure between them. The large relaxation of both conformers as reflected by the small values observed for the vibrational frequencies of **2a** and **2b**, the similar stability found for both rotamers at any level of calculation, the almost null barrier to the rotation (0.27 kcal mol^{-1}) found for the phenylsulfonate anion by using the CSD structures and the Boltzmann distribution approach and the fact that all the structures in a cross-section in the rotational surface had all positive frequencies seem to show that there is a total free rotation for the phenylsulfonate anion which would be in agreement with a flat rotational surface.

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