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Conformational analysis of carbonic anhydrase inhibitors using ab initio molecular orbital methods. 1. Rotational isomerism in methane sulfonamide anion, CH_3-SO_2-NH^-

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Abstract Ab initio calculations have been performed on methane sulfonamide anion. Geometries have been optimized using Hartree-Fock basis sets up to 6-31+G*, and single-point calculations employing those Hartree-Fock geometries have been performed at levels up to MP2/6-311++G**. In addition, geometry optimizations for the 0°, 90°, 150°, and 180° conformers have been carried out at the MP2/6-31G*, MP2/6-31+G*, and MP2/6-311++G** levels. Vibrational frequencies have been calculated using the HF/4-31G*, MP2/6-31G*, and MP2/6-31+G* geometries. All calculations at or above the 4-31G* level agree that H—N—S—C ~90° is the global minimum. The H—N—S—C = 180° conformer is clearly higher in energy although the relative energy of this conformer varies from 0.36 to 1.03 kcal/mol for the post-HF calculations depending on basis set. The H—N—S—C = 180° conformer appears to be a very shallow local minimum. However, the potential energy surface is quite flat in this region, and the highest-level calculations, including MP2 optimizations and vibrational frequency analysis, are ambiguous on this point. The conformer with an H—N—S—C torsion of 0° is a transition state with a relative energy ~8 kcal/mol.

Key words: Inhibitors – Carbonic anhydrase – Sulfonamide – Anion – Conformational analysis

1 Introduction

The sulfonamide moiety, $R—SO_2—NR_1R_2$, is often encountered in organic and medicinal chemistry [1]. Sulfonamides, for example, are known to be potent inhibitors of the enzyme carbonic anhydrase [2, 3]. This enzyme, which occurs widely in plants, animals, and man, catalyzes the interconversion of carbonic acid and carbon dioxide [4, 5]. All known isozymes of carbonic anhydrase contain a single Zn^{2+} ion which is essential for catalytic activity. Substitution of Zn^{2+} by any other transition metal greatly reduces the turnover rate [6]. The zinc ion is located at the bottom of a deep, conical cavity, bound to three histidine residues via their imidazole nitrogens. The fourth ligand to zinc is normally hydroxyl. Sulfonamides can replace this hydroxyl, effectively inhibiting the enzyme (Figure 1). Sulfonamides bind to HCA-II in the anionic form [7–9]. Topical inhibitors of human carbonic anhydrase type II (HCA-II) provide a useful treatment for elevated intraocular pressure found in glaucoma [10–16].

The structure of HCA-II has been solved crystallographically [17, 18], and enzyme-inhibitor complexes have also been studied [11, 19–22]. As a result, it seems quite likely that computer modeling may profitably be employed to help understand enzyme inhibition. Empirical force field energy calculations (''molecular mechanics'') are commonly used to describe the interactions between ligands and receptors. In the present case we need to model the interactions between HCA-II and its inhibitors, all of which contain the anionic sulfonamide moiety (Fig. 1). There are many reports in the literature of molecular modeling on HCA-II and its inhibitors [11, 16, 23–30].

Unfortunately, there are many complicating factors. First, not much is known about rotational isomerism in sulfonamides. There is very little experimental information on the conformational preferences of sulfonamides except in the crystal phase, and these data do not provide precise information about the energy differences between the various low-energy conformers and the energy barriers that separate them. Second, as stated above, sulfonamides bind to the Zn^{2+} in the anionic form. However, there are few or no experimental data on the structures or energetic preferences of sulfonamide anions. Third, the available x-ray data on complexes of HCA-II with sulfonamide inhibitors indicate that the nitrogen of the sulfonamide group is 2.0 Å from the zinc ion. Clearly, electrostatic interactions play a major role in binding sulfonamides to CA; the atoms in the sulfonamide group, the histidines bound to zinc, and the zinc ion itself, all have large partial charges, and it is reasonable to expect that there will be significant charge transfer toward zinc from its ligands. Before reliable modeling can be performed, these issues must be addressed.

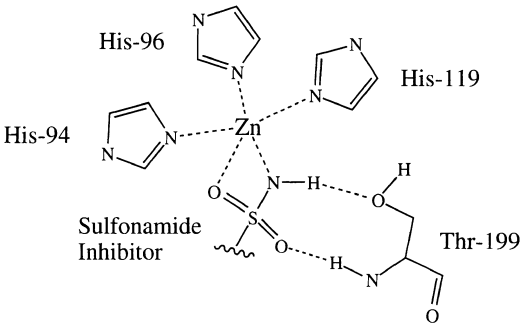

Fig. 1. Schematic diagram showing the active site of carbonic anhydrase inhibited by a sulfonamide. The Zn^{2+} ion is ligated by three histidine residues and the sulfonamide nitrogen. Hydrogen bonds and coulombic interactions are shown with *dashed lines*

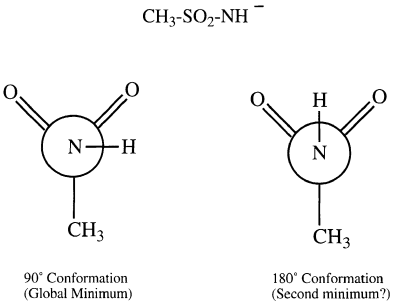

Fig. 2. The chemical structure of methane sulfonamide anion, $CH_3SO_2NH^-$ and Newman projections of the 90° and 180° conformers. The 90° conformation is the global minimum; the 180° conformer may not be a local minimum. See text for details

One way to help resolve these difficulties is to perform ab initio molecular orbital calculations on model systems. Such calculations, if taken to suitably high levels, may yield accurate relative energies for isolated gas-phase sulfonamides. These data, in turn, may be used to derive the necessary force field parameters [29–32].

Calculations on several different neutral sulfonamides have been reported. Methane sulfonamide is the most widely studied [33–35]. Bindal also looked at N-methyl methane sulfonamide [34]. Benzene sulfonamide derivatives have been studied using AM1 [28]. Liang and Lipscomb have used ab initio methods up to the 4-31G level to study the binding of sulfonamides and acetamides to the active site of HCA-II [36]. Beryllium dication was used to mimic the divalent zinc. Anions of methane sulfonamide were used in some of the calculations, but only in coordination with Be^{2+}, and no conformational analysis was performed.

Our preliminary efforts in this area focus on methane sulfonamide anion, $CH_3—SO_2—NH^-$ (Fig. 2). We have chosen to concentrate on the anion rather than the neutral molecule because it is the anion which is bound to the enzyme active site, and because much less is known experimentally or theoretically about its conformational preferences.

2 Computational procedures

The dihedral angle H—N—S—C was fixed at values of 0°, 30°, 60°, 90°, 120°, 150°, and 180°, and all other internal coordinates were fully relaxed. We initially optimized the geometries using the STO-3G*, 3-21G, and 3-21G* basis sets. We then proceeded to progressively larger basis sets for the optimization of each structure, including 4-31G*, 6-31G*, and ultimately the 6-31 + G* basis set which is double zeta on all atoms and includes polarization and diffuse functions on all non-hydrogen atoms [37, 38]. Table I summarizes the key geometric parameters at various optimization levels.

Using the HF/6-31G* optimized structures, electron correlation was estimated at the MP3/6-31G* level. Next, using the HF/6-31 + G* optimized geometries, electron correlation was estimated with the MP2/6-31 + G* and MP2/6-311 + + G** basis sets. Then, for the 0°, 90°, 150°, and 180° conformers, MP2/6-31G*, MP2/6-31 + G*, and MP2/6-311 + + G** geometry optimizations were performed. Energies are given in Table 2.

From an examination of the relative energies in Table 2, it appeared that the global minimum for methane sulfonamide anion would have an H—N—S—C torsion angle of approximately 90°. Starting from this point, and fully relaxing all internal coordinates, a global

Table 1. Methane sulfonamide anion: key geometric parameters, global minimum conformation, various basis sets.

	HF/ 4-31G*	HF/ 6-31G*[a]	HF/ 6-31 + G*	MP2/ 6-31G*	MP2/ 6-31 + G*	MP2/ 6-311 + + G**
C—S	1.794	1.796 (1.767)	1.796	1.816	1.815	1.815
S—N	1.541	1.549 (1.65)	1.555	1.570	1.578	1.571
S—O1	1.448	1.454 (1.43)	1.456	1.486	1.492	1.478
S—O2	1.457	1.463 (1.43)	1.466	1.497	1.506	1.490
N—H	1.005	1.005 (1.001)	1.004	1.024	1.025	1.020
N—S—O1	111.5	111.7 (107.5)	111.6	111.1	110.9	111.0
N—S—O2	114.6	114.2 (107.5)	113.9	115.0	114.4	114.6
N—S—C	107.8	108.1 (103.2)	108.2	108.2	108.5	108.1
O—S—O	115.9	115.7 (121.2)	115.6	116.6	116.5	116.4
O1—S—C	102.8	102.9 (108.0)	103.2	102.2	102.5	102.6
O2—S—C	102.7	102.9 (108.0)	103.1	102.2	102.6	102.7
S—N—H	107.2	106.9 (111.6)	107.3	105.6	106.1	104.8
C—S—N—H	88.06	90.00	90.28	89.47	91.11	90.89

Atom O2 is defined as the oxygen which is always *closer* to the sulfonamide NH proton.

[a] In the HF/6–31G* column, values in parentheses are taken from the published calculations on the neutral form of the molecule, $CH_3—SO_2—NH_2$ [33–35]

Table 2. Methane sulfonamide anion: rotation around S—N bond (C—S—N—H torsion) (relative energies in kcal/mol)

Basis set[a]	180°	150°	120°	90° (fixed)
HF/3-21G Opt	0.00	0.99	2.80	3.87
HF/STO-3G*	4.39	4.82	3.50	0.42
HF/3-21G*	0.00	0.56	1.13	0.94
HF/4-31G* Opt	1.23	1.38	1.00	0.00
HF/6-31G* Opt	0.65	0.84	0.69	0.00
MP2/6-31G*	0.46	0.61	0.57	0.00
MP3/6-31G*	0.57	0.69	0.61	0.00
HF/6-31 + G* Opt	0.80	0.92	0.65	0.00
MP2/6-31 + G*	0.54	0.61	0.54	0.04
HF/6-311 + + G**	0.73	0.88	0.65	0.00
MP2/6-311 + + G**	1.03	1.03	0.73	0.04
MP2/6-31G* Opt	0.36	0.56		
MP2/6-31 + G* Opt	0.48	0.57		
MP2/6-311 + + G** Opt	0.95	0.95		

Basis set[a]	90 (free)	60°	30°	0°	Absolute energy[b]
HF/3-21G Opt	N/C	5.32	7.93	9.50	−638.34295
HF/STO-3G*	0.00	1.03	6.44	10.33	−634.23763
HF/3-21G*	0.93	2.33	5.90	8.11	−638.62286
HF/4-31G* Opt	0.00	1.57	5.97	8.73	−641.16961
HF/6-31G* Opt	0.00	1.57	5.75	8.39	−641.80701
MP2/6-31G*	0.00	1.38	5.36	8.12	−642.60201
MP3/6-31G*	0.00	1.42	5.44	8.12	−642.61072
HF/6-31 + G* Opt	0.00	1.61	5.74	8.31	−641.82654
MP2/6-31 + G*	0.00	1.46	5.36	7.97	−642.64400
HF/6-311 + + G**	0.00	1.49	5.36	7.89	−641.91105
MP2/6-311 + + G**	0.00	1.42	5.06	7.55	−642.80491
MP2/6-31G* Opt	0.00			8.23	−642.60549
MP2/6-31 + G* Opt	0.00			8.10	−642.64821
MrP2/6-311 + + G** Opt	0.00			7.59	−642.80691

[a] Indented lines indicate MP2 single-point calculations carried out using the HF-optimized geometries

[b] Absolute energy of the lowest-energy conformation at each level of theory, in Hartrees (627.51 kcal/mol equals one Hartree)

minimum structure was found, the data for which also are given in Tables 1 and 2. At all levels, it is essentially identical to the structure with torsion angle H—N—S—C fixed at 90°.

To ensure that stationary points had been identified, the H—N—S—C = 0°, H—N—S—C = 180°, and global minimum structures were used to calculate vibrational frequencies at the HF/4-31G*. The latter two conformers were minima, while the 0° conformer had a single imaginary frequency (567.8*i*). Then, vibrational frequencies were calculated for the global minimum and 180° conformers using the MP2/6-31G* and MP2/6-31 + G* optimized geometries. These results are given in Table 3.

All ab initio calculations were carried out with Gaussian-94 [39].

3 Results and discussion

In Table 1 are shown the geometries of the global minimum conformation optimized using various basis sets. There are no major differences between the HF/4-31G*, HF/6-31G*, and HF/6-31 + G* geometries. MP2

Table 3. Methane sulfonamide anion: MP2/6-31G* and MP2/6-31 + G* vibrational frequencies

MP2/6-31G* frequencies, 90°								
	273.7	292.2	298.2	386.0	490.9	503.8	527.0	
	746.7	972.1	991.4	1003.6	1148.6	1177.1	1298.4	
	1385.4	1529.4	1533.0	3104.7	3207.7	3219.9	3490.7	
MP2/6-31 + G* frequencies, 90°								
	262.5	285.9	299.2	381.7	463.4	482.7	514.9	
	736.2	950.5	982.8	991.4	1104.7	1129.7	1237.9	
	1369.5	1504.5	1507.0	3098.0	3205.8	3215.5	3489.2	
MP2/6-31G* frequencies, 180°								
A′	339.0	507.7	525.9	769.1	957.9	1011.7	1163.8	
	1174.9	1396.2	1534.6	3124.6	3231.4	3479.7		
A″	109.6	248.6	334.2	511.6	1002.6	1222.0	1524.5	3240.9
MP2/6-31 + G* frequencies, 180°								
A′	333.2	491.1	503.7	758.2	935.0	1001.3	1104.2	
	1139.4	1382.3	1512.5	3116.1	3226.4	3486.8		
A″	19.0	240.2	328.9	482.0	991.3	1150.8	1501.4	3234.3

geometries, as expected, have bond lengths ~0.02 Å longer. The H—N—S—C torsion angle of the global minimum conformer is consistently close to 90° for all HF and MP2 optimizations. For purposes of determining reasonable geometries the most economical level, HF/4-31G*, should probably be considered the basis set of choice.

It is worth noting that the valence geometry of methane sulfonamide anion, $CH_3—SO_2—NH^-$, is rather different than the neutral molecule $CH_3—SO_2—NH_2$ [35]. The differences at the HF/6-31G* level are summarized in Table I. The S—N bond lengthens from 1.55 Å in the anion to 1.65 Å in the neutral molecule, while the S = O bonds shorten from 1.46 Å in the anion to 1.43 Å in the neutral molecule. In addition, the O—S—O bond angle in the anion is 116° as opposed to 121° in the neutral species. All of these differences are consistent with an increased S=N bond character and delocalization of the negative charge in the anion.

An examination of the data in Table 2 reveals that subtle differences in relative energy remain even at the highest levels. The relative energy of the H—N—S—C = 180° conformer is 1.23 kcal/mol above the global minimum at the HF/4-31G* level, but only 0.73 kcal/mol at the HF/6-311 + + G**//HF/6-31 + G* level. Further, the MP3/6-31G*//HF/6-31G* relative energy is only 0.57 kcal/mol, while the MP2/6-311 + + G**//HF/6-31 + G* energy is 1.03 kcal/mol. With respect to the energy of the conformer with H—N—S—C = 180°, it appears that the correct answer is somewhere between 0.4 and 1.2 kcal/mol, with ~1.0 perhaps the "best" result. The energy of the H—N—S—C = 0° transition structure shows an unusually wide scatter. It appears to decrease somewhat as a function of basis set; our highest-level calculation, MP2/6-311 + + G**//6-31 + G*, gives 7.54 kcal/mol. However, because of the large spread of values in Table 2, a barrier height of anywhere between 7 and 8.5 kcal/mol cannot be ruled out.

The HF/4-31G* vibrational frequencies confirmed that the 0° structure is a transition state. Higher-level MP2/6-31G* and MP2/6-31 + G* frequency calculations (Table 3) show that the H—N—S—C = 180° conformer has a very low-frequency mode. Further, although lower-level Hartree-Fock calculations show a slight preference for the 180° conformer, the well depth is extremely shallow at all levels of theory. Indeed, our highest level MP2/6-311 + + G** calculations indicate that the 150° and 180° points have essentially the same energy. Because the potential energy curves are so flat around H—N—S—C = 180°, and because of the low-frequency mode seen in the MP2/6-31 + G* frequency calculation, we cannot unequivocally state that the 180° conformer is a local minimum. It is not likely that simply augmenting the basis set will resolve this issue.

It is worthwhile to speculate about the physical effects which give rise to the 90° global minimum. The two lone pairs on the nitrogen anion can be delocalized into the σ^* orbitals of the S—O bond. C—S—N—H torsions of either 180° and 90° will allow such anomeric stabilization. Similar effects were observed by Cramer, and coworkers for phosphorus stabilized anions [40]. In the methanesulfonamide anion, the 180° conformation should actually provide superior anomeric stabilization, because both nitrogen lone pairs are optimally situated for such delocalization. In addition, however, there are significant electrostatic and steric effects which also are operative. For example, in the 90° conformation there should be an electrostatic attraction between the amide proton and the nearly oxygen. This interaction is not present in the 180° conformation. As the C—S—N—H torsion approaches 0°, there is considerable repulsion between the anionic nitrogen lone pairs and the electron-rich S—O bonds; this, more than simple van der Waals repulsion between the proton and the methyl group, is probably responsible for the 7-8 kcal/mol barrier height.

Finally, with respect to the relative energies given in Table 2, it is clear that there is good qualitative agreement between all the basis sets at or above the HF/4-31G* level. On the other hand, the smaller basis sets, STO-3G*, 3-21G, and 3-21G*, HF/3-21G, appear to be inadequate for estimating energy differences between conformers in this system. Any calculations on sulfonamide anions which are not carried out at the HF/4-31G* level or above should be treated with caution.

4 Conclusions

High-level ab initio calculations have been carried out on methane sulfonamide anion; these calculations indicate that preferred angle of the C—S—N—H torsion is approximately 90°. The C—S—N—H = 180° conformer has an energy 0.8 ± 0.4 kcal/mol higher than the 90° form. The C—S—N—H = 180° conformer is a local minimum at the HF/4-31G* level. However, at higher levels of theory, the potential surface is very flat and there is a very low-frequency vibrational mode. For these reasons it cannot be ruled out that the 180° conformer may be a transition state. The 0° conformer is clearly a transition state with an energy 7-8.5 kcal/mol higher than the 90° global minimum. The effects of basis set on geometry are small past the HF/4-31G* level. The geometries and relative energies obtained at low levels of theory such as 3-21G* are quite different than those calculated with all of the larger basis sets and appear to be inadequate for sulfonamide anions.

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