Published in final edited form as:

J Phys Chem A. 2016 May 26; 120(20): 3677–3682. doi:10.1021/acs.jpca.6b02757.

Anomeric Effects in Sulfamides

Eric Hansen[†], Elaine Limé[‡], Per-Ola Norrby[‡], and Olaf Wiest^{†,§,*}

[†]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States

[‡]Pharmaceutical Technology and Development, AstraZeneca, Pepparedsleden 1, SE-431 83 Mölndal, Sweden

[§]Lab of Computational Chemistry and Drug Design, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China

Abstract

Sulfamides, together with their simpler sulfonamide analogs, are common functional groups in a significant number of biologically active compounds. This is partly due to their unique electronic structure and conformational behavior, which mimics the tetrahedral intermediate involved in many proteases, esterases, and related enzymes. Here, the origin of these unique structural elements are analyzed in the context of a coupled, double anomeric effect using DFT calculations, including conformational scans, and NBO analysis. It is shown that these coupled interactions can be implicitly parametrized in MM3* type force fields using the quantum-guided molecular mechanics (Q2MM) method, yielding accurate force field parameters for molecular mechanics studies of sulfamides and sulfonamides.

Graphical abstract

*Corresponding Author: O. Wiest. Tel: +574 631 5876., owiest@nd.edu.

Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.6b02757. All energies (electronic, free energies, ZPE), single imaginary frequencies, and Cartesian coordinates for all species discussed, along with the second-order perturbation theory analysis of the Fock matrix in the NBO basis, MM3* parameters, weights used in the Q2MM optimization, and ending penalty function scores (PDF)

INTRODUCTION

Sulfonamides **1** and sulfamides (also referred to as diaminosulfones) **2**, shown in Scheme 1, are common structural elements in a large number of drugs starting with Prontosil, the first widely used antibiotic discovered in 1932 by Domagk.¹ Today, derivatives of **1** and **2** are used in virtually every therapeutic area,² including antimicrobial, antiviral, anticancer, and CNS drugs. Even the parent sulfamide (**2**, $R^{1-4} = H$) was shown to be a potent inhibitor of carbonic anhydrase,³ a target of interest in anticancer therapy.^{4,5} The ZINC database widely used in virtual screening for potential binders against biological targets currently lists 4781 and 4704 commercially available derivatives of **1** and **2**, respectively.⁶ There are a number of reasons that make **1** and **2** uniquely suited as building blocks for drugs. Their geometric and electronic structure resembles the tetrahedral intermediate involved in many acyl substitution reactions and stabilized by proteases and esterases, as indicated by the fact that they bind to the metals in many metalloproteases. At the same time, their polarity improves the physicochemical and pharmacodynamic properties of drugs, especially their solubility in water without being subject to the large desolvation penalty of fully charged functional groups. Finally, they are conformationally surprisingly rigid, decreasing the entropic penalty upon binding to a constrained active site.

Despite the biomedical importance and widespread use of **1** and **2**, the origins of these unique properties are not well understood and there are surprisingly few investigations into the electronic structure of sulfonamides and sulfamides. Previous investigations of **1**⁷⁻⁹ and its derivatives are mostly at lower level of theory and/or small basis sets despite the finding that accurate calculations of the S–O bond often require triple- ζ type basis sets.^{10,11} In 2008, Petrov and co-workers studied the conformations of *ortho*- and *para*-methylbenzenesulfonamides using electron diffraction and MP2/6-311+G** and found the eclipsed conformations to dominate, but with some staggered conformations also present.¹² To enable force field calculations, Nicholas and co-workers parametrized MM2 for sulfones based off of RHF/6-31G* calculations.⁸ Allinger and Fan developed MM3 parameters for sulfones using experimental data from electron diffraction, microwave spectroscopy, vibrational spectroscopy, and the heats of formation of several sulfones as well as HF/6-31G torsional scans.⁷ More recently, Yu and co-workers developed CHARMM parameters for sulfones using MP2/6-31G(d) calculations.⁹ However, there are few electronic structure or force field studies of **2** available.¹³

Here, we use high level electronic structure methods to study the potential energy surface of **1** and **2** and to analyze the conformational preferences and relative energies. This will provide the basis for an understanding of the electronic structure, specifically the orbital interactions responsible for these preferences. Finally, we will investigate if these inherently nonpairwise interactions can be adequately reproduced using force fields, which will be important for the molecular mechanics (MM)-type approaches commonly used in the study of enzyme–drug complexes.

METHODS

All quantum mechanical (QM) calculations were performed in the gas phase using Jaguar¹⁴ at the M06/aug-cc-pVTZ level of theory using an accurate integration grid (iacc=2) unless noted otherwise. Geometries of conformations and transition structures for parent **1** and **2** were fully optimized in the gas phase and stationary points were characterized as minima or transition states using harmonic frequency calculations at the same level of theory. **2c^{ts}** was previously reported as a minimum for sulfamide with HF/STO-3G* used for the geometry optimization and HF/6-31G* with a modified d-orbital exponent used for the energies.¹³ For comparison purposes, we also performed HF/STO-3G* and unmodified HF/6-31G* calculations on conformer **2c^{ts}**, but contrary to past results, we obtained **2a** as the global minimum using both methods. Gaussian 09¹⁵ was used to calculate the single point energy of the optimized stationary points at the CCSD(T)/aug-cc-pVTZ level. Natural bond orbital (NBO) analysis was performed using NBO6.0,¹⁶ and ESP charges¹⁷ were calculated in Jaguar. All energies reported are zero-point corrected energies in units of kJ/mol. Distances are reported in Å, angles in degrees and frequencies in cm⁻¹.

The optimized geometries were used as starting points to scan the potential energy surface (PES) of each molecule at the M06/aug-cc-pVTZ level of theory. The scans were started from the *C*_{2v} symmetric structures **2c^{ts}** and **2d** for methanesulfonamide and sulfamide, respectively. For these scans, the dihedral angle around the SN and SC bonds were rotated in steps of 5° for a total of 355° with full optimization of all other parameters.

Quantum guided molecular mechanics (Q2MM) was shown to rapidly provide highly accurate, system specific force fields based upon QM reference data.^{18–24} Here, we use it to optimize a fully transferable ground state force field for **1** and **2**. The reference data include QM relative energies, geometries, RESP charges, and the Hessian matrix of energy second derivatives. The MM parameters are fit by minimizing the weighted penalty function

$$\chi^2 = \sum_i w_i^2 (x_i^\circ - x_i)^2$$

where x_i° is the QM reference data point, x_i is the corresponding MM data point, and w_i is the weight for a given data type. Weights used in the final stages of the optimization are given in the Supporting Information, as well as overall scores and scoring breakdown of the penalty function for the final force fields.

RESULTS AND DISCUSSION

Electronic Structure Calculations

Tables 1 and 2 summarize the results for the stationary points located for methanesulfonamide **1** and sulfamide **2**, respectively. The results for **1**, which has been studied previously and mainly serves as a reference compound, are in good agreement with previously reported results at lower levels of theory^{8,9} and close analogs.¹² The M06/aug-cc-pVTZ results closely track the CCSD(T)/aug-cc-pVTZ reference calculations, indicating

that the M06 method when combined with triple- ζ basis set provides reliable results for these systems.

The calculations indicate two unique minimum energy conformations, **1a** and **1b**. At both minima, the methyl hydrogens are staggered relative to SO₂NH₂. The amine hydrogens are eclipsed with the oxygens at the global minimum **1a**, whereas they are staggered with each hydrogen *anti* to one oxygen in **1b**, with **1b** being 7.9 kJ/mol higher in energy than **1a**. Three transition states correspond to the rotation around the S–C (**1c^{ts}** and **1d^{ts}**) and S–N bond (**1e^{ts}**), respectively. In addition, there is also a transition structure corresponding to the inversion on the nitrogen⁸ that will not be discussed in the context of the present study. The barriers for rotation around the S–C bond starting from **1a** and **1b** are 11.8 and 19.6 kJ/mol, respectively. The energy difference between the two transition structures, 7.8 kJ/mol, indicates that the barrier for rotation around the S–C bond depends strongly on the conformation around the S–N bond. The barrier to rotation around the C–N bond is higher, 27.0 kJ/mol, and largely electrostatic in nature. Considering that the other geometric parameters listed in Table 1 do not change significantly as a function of the S–C and S–N rotation, and that the nonbonded distances are too large to rationalize these findings by steric effects, the electronic effects leading to these results will be discussed in more detail below.

More complete studies of the potential energy surface (PES) indicate that rotation of the methyl leads to three symmetrically equivalent minima as expected. The 3-fold symmetry of the S–C rotation and the 2-fold symmetry of the S–N rotation leads to the highly symmetric PES shown on the left in Figure 1.

Comparison of the PES for **1** and **2** points to some interesting differences between these two molecules. Rotation of the S–N bond in **1** leads to 2-fold symmetry of the PES with the eclipsed conformation being the global minimum. In analogy, it could be expected that the global minimum of **2** to be doubly eclipsed with a C_{2v} symmetry. As shown by the PES of sulfamide in Figure 1, this is not the case and **2** is more than simply the sum of its parts. A new interaction, unique to the presence of two amines, causes the C–N rotations in the global minimum **2a** to deviate by $\sim 30^\circ$ each from the expected doubly eclipsed conformation, giving a C_2 -symmetric structure. As a result, the two S–N–N_N planes are rotated by $\sim 60^\circ$ relative to each other. The doubly eclipsed conformation **2c^{ts}** is calculated to be a transition structure 6.1 kJ/mol higher in energy. The alternative conformation **2b**, where one set of hydrogens is eclipsed and the other one staggered with the oxygens in a C_s -symmetric structure, is calculated to be 2.7 kJ/mol above **2a** in energy at the CCSD(T) level of theory. The corresponding minimum **2d** where both sets of hydrogens are staggered (also C_s) is calculated to be 9.9 kJ/mol higher in energy at the same level of theory. The rotation around the S–N bond starting from the eclipsed and staggered conformations via transition structures **2e^{ts}** and **2f^{ts}** has barriers of 15.7 and 26.4 kJ/mol relative to **2a**, respectively. Detailed geometric and energetic results for **2** are summarized in Table 2.

The surprising dependence of the dihedral angles around the two S–N bonds on each other, as well as the high barriers to rotation, are crucial for the properties of **1** and **2** in biologically active compounds but are poorly understood and not in agreement with simple, localized analyses. Previously, partial hydrogen bonding or simply electrostatic attraction

between N–H···O was used to explain the preference for the eclipsed conformation over the gauche conformation in sulfonamides,¹² but this reasoning is not consistent with the skewed conformation **2a**. Mó et al. explained that the global minimum they observed **2b** was due largely to the reduced steric hindrance between the amine hydrogens when one was eclipsed and the other was staggered.¹³ However, the N–S–N angle is even smaller in **2a** than in **2b**, which would not be predicted solely based upon sterics, as the amine hydrogens are more crowded in **2a** than in **2b**.

To elucidate the origin of the conformational preferences of **2**, we calculated second-order perturbative interaction energies in the NBO basis, which has previously been used to describe the conformational preferences of various sulfone groups in 1,3-dioxane rings.²⁵ For all conformers besides **2a**, the $n_N \rightarrow \sigma_{S-N}^*$ interaction, the lone pair of an amine donating to the adjacent empty σ^* S–N orbital, is the dominant interaction involving the amine lone pair (for full listing see the Supporting Information). For example, the $n_N \rightarrow \sigma_{S-N}^*$ interaction energy for the staggered amine in **2b** is calculated to be ~22 kJ/mol larger than the eclipsed amine. In **2c^{ts}**, both $n_N \rightarrow \sigma_{S-N}^*$ interactions are similar in magnitude, and about the same as the interaction energy of the eclipsed amine in **2b**.

2a is markedly different from all other conformers of **2**. It has two significant $n_N \rightarrow \sigma_{S-O}^*$ interactions, where the amine lone pair donates to an empty σ^* S–O orbital. This interaction is akin to the anomeric effect, e.g., in carbohydrates, where a free electron pair donates into a properly aligned σ^* orbital. The orbital overlap is best when the amine rotates by ~30°, such that the amine lone pair and σ^* orbitals align, as shown in Figure 2 (left). The N–S–O angle, which is roughly the same for all conformers except **2a**, maximizes this favorable orbital overlap, as shown in Table 2. Importantly, the second order perturbative interaction energies indicate that each amine donates to a different σ^* orbital. These interactions are mutually exclusive; i.e., each σ^* S–O orbital can only stabilize the free electron pair of one nitrogen. As a result, the two S–N– n_N planes in the calculated structure of **2a** are rotated by ~60° rather than a coplanar structure where both amines are skewed in the same direction, as would be expected from simple extrapolation from **1**. Each $n_N \rightarrow \sigma_{S-O}^*$ interaction is predicted to provide 37 kJ/mol of stabilization. For all other stationary points, the σ_{S-O}^* orbital is stabilized predominantly by $n_O \rightarrow \sigma_{S-O}^*$ interactions. This is exemplified in **2c^{ts}**, the coplanar structure that is 6.1 kJ/mol higher in energy. Overall, the stabilization of **2a** by the two mutually exclusive $n_N \rightarrow \sigma_{S-O}^*$ interactions can be thought of as a coupled, dual anomeric effect.

Force Field Parametrization

The development of force field parameters for **1** and **2** is highly desirable given the importance their derivatives in medicinal and industrial chemistry, where virtual screening and molecular dynamics calculations require the accurate description of ligand conformations and their relative energies. CHARMM parameters for **1** are available⁹ and several other generalized force fields include parameters for **1**, but the equally important derivatives of **2** are less widely studied. This is unfortunate because, in addition to the possible applications of these parameters, it also raises the more fundamental question if the

coupled, dual anomeric effect found to be essential for the lowest-energy conformation can be represented by an appropriately parametrized force field.

To study this question, we used the Q2MM method described elsewhere^{20,21,23,24,26–28} to optimize MM3* parameters for **2**. For comparison purposes, we also parametrized **1**. The functional form of the MM3* force field was chosen because of its long history in modeling small, druglike organic compounds. The MM3* force field is closely related to MM3 from the Allinger group,²⁹ with some modifications to the electrostatics and the way parameters are assigned.³⁰ It has previously been shown to have a flexible enough functional form to allow a close fit to the reference QM data used for parametrization.²⁴

The global minimum **2a** is obtained when each nitrogen lone pair donates to distinct S–O σ^* orbitals. The parameters related to one $n_N \rightarrow \sigma_{S-O}^*$ anomeric interaction must depend on the opposite anomeric interaction, such that the geometry shifts when they begin to overlap with the same S–O σ^* orbital. This interaction is only present in **2a** whereas in **2b**, **2c^{ts}**, and **2d**, the amine lone pair instead donates to the S–N σ^* orbitals and the lone pairs of one oxygen stabilize the other S–O σ^* orbital. Although anomeric interactions could be modeled using dummy atoms for the lone pair and S–O σ^* orbital and dihedrals, this would limit the applicability of the force field to systems including dummy atoms, and it does not account for the coupling between anomeric interactions. A dihedraldihedral cross term may be able to account for interactions between the two anomeric effects, but unfortunately such cross terms are lacking in the MM3* force field.

Instead, we tested two different approaches. In the first, leading to force field A (**FFA**), we investigated the question whether the dual anomeric effect can be implicitly parametrized using standard, pairwise force field parameters. As an alternative approach, we also parametrized a force field B (**FFB**) that adds an additional skipped atom dihedral between the H–N $\cdots$ N–H bonds, which implicitly accounts for the coupling between the two interacting anomeric effects.

Parameters for **FFA** and **FFB** were optimized using the Q2MM method and used to calculate the relative energies of the stationary points for **1** and **2**. Table 3 shows the comparison of the relative energies obtained by **FFA** and **FFB** at the fixed, QM optimized geometries and the FF optimized minima for **1** and **2** compared to the relative energies from the M06/aug-cc-pVTZ calculations discussed earlier. Figure 3 shows the PES for scans around the S–C and S–N bonds in analogy to the scans in Figure 1. Overall, there is good to excellent agreement between the reference data and force field results for both the single point energies and the optimized geometries of the minima, with the results of **FFB** being marginally better than the ones from **FFA**. Similarly, the PESs in Figure 3 are essentially identical to the PESs from the QM calculations in Figure 1.

Next, we used the two force fields to perform Monte Carlo conformational searches of **1** and **2** in MacroModel to test their performance upon distortions away from these minima. As shown in Table 4, the use of **FFA** resulted in two false minima. Coordinates for the false minima are provided in the Supporting Information. They were confirmed as spurious by QM optimizations and frequency calculations to ensure that we did not miss any stationary

points in our initial analysis. As expected, **1f** optimized to **1a** and **2g** optimized to **2b**. One false minimum **1f** was 0.2 kJ/mol lower in energy than **1a**, the global minimum at the QM reference level. Although this energy difference is vanishingly small, it does lead to a skewed geometry of the amine in **1f**, similar to the conformation of the amines in **2a**. This indicates that **FFA** cannot adequately represent the eclipsed ground state configuration of **1a** and the skewed ground state configuration of **2b** simultaneously. In comparison, **FFB**, which contained an added skipped atom dihedral parameter to model the dual anomeric effect in sulfamide, represented both ground states accurately, as shown in Table 5.

The second spurious minimum, **2g**, is found instead of the correct minimum **2b** when using **FFA**. In **2g**, the amine that should be eclipsed instead again adopts a skewed conformation. As discussed above, this skewed configuration results from the coupled dual anomeric effect and should only be observed when both amine lone pairs donate exclusively to σ^* orbitals. However, **FFA** lacks any term describing the interdependence of the orientations of the two amines. Thus, a description of the skewed conformation vs the eclipsed conformation is not accurate, and the skewed conformation is calculated to be preferred over the eclipsed in all scenarios.

CONCLUSIONS

The unique conformational properties of sulfonamides **1** and sulfamides **2**, which are crucial for their widespread application as functional groups in medicinal chemistry, are determined to be due to an interaction of the lone pair of the nitrogen with antibonding orbitals involving sulfur. This interaction can be most easily envisioned as an anomeric effect. The fact that two such interactions are possible but mutually exclusive in **2** leads to a coupling of the two torsions and significant differences in the conformational properties of **2** compared to **1**, which can be understood in terms of a coupled, dual anomeric effect.

The generation of force field parameters that could be used to accurately describe the conformations of biologically interesting derivatives of **2** is complicated by this effect because no common force fields contain a dihedral-dihedral cross term that could explicitly describe the coupled anomeric effect of the two nitrogen lone pairs. The Q2MM method can be used to generate force field parameters that implicitly describe this coupling through a skipped bond H–N $\cdots$ N–H term, whereas attempts to emulate the dual anomeric effect without some term defining an interaction between the two amines are not successful. This demonstrates that for specific systems, it is possible to implicitly model these coupled electronic interactions using Q2MM parameter refinement and fairly simple, but well validated and flexible force field parameters. Finally, the accuracy of the results from the Q2MM force field as compared to high level QM calculation demonstrates the usefulness of rapid generation of accurate force fields.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge support of the Q2MM development effort by the National Science Foundation (CHE-1058075) and the National Institutes of Health (R01GM111645).

References

1. Otten H. Domagk And The Development Of The Sulphonamides. *J Antimicrob Chemother.* 1986; 17:689–690. [PubMed: 3525495]
2. Winum JY, Scozzafava A, Montero JL, Supuran CT. Therapeutic Potential Of Sulfamides As Enzyme Inhibitors. *Med Res Rev.* 2006; 26:767–792. [PubMed: 16710859]
3. Abbate F, Supuran CT, Scozzafava A, Orioli P, Stubbs MT, Klebe G. Nonaromatic Sulfonamide Group As An Ideal Anchor For Potent Human Carbonic Anhydrase Inhibitors: Role Of Hydrogen-Bonding Networks In Ligand Binding And Drug Design. *J Med Chem.* 2002; 45:3583–3587. [PubMed: 12166931]
4. Monti SM, Supuran CT, De Simone G. Anticancer Carbonic Anhydrase Inhibitors: A Patent Review (2008–2013). *Expert Opin Ther Pat.* 2013; 23:737–749. [PubMed: 23672415]
5. Supuran CT, Scozzafava A. Carbonic Anhydrases As Targets For Medicinal Chemistry. *Bioorg Med Chem.* 2007; 15:4336–4350. [PubMed: 17475500]
6. [accessed 10/23/2015] zinc.docking.org
7. Allinger NL, Fan Y. Molecular Mechanics Calculations (MM3) On Sulfones. *J Comput Chem.* 1993; 14:655–666.
8. Nicholas JB, Vance R, Martin E, Burke BJ, Hopfinger A. A Molecular Mechanics Valence Force Field For Sulfonamides Derived By Ab Initio Methods J. *J Phys Chem.* 1991; 95:9803–9811.
9. Yu W, He X, Vanommeslaeghe K, MacKerell AD. Extension Of The CHARMM General Force Field To Sulfonyl-Containing Compounds And Its Utility In Biomolecular Simulations. *J Comput Chem.* 2012; 33:2451–2468. [PubMed: 22821581]
10. Amaudrut J, Pasto DJ, Wiest O. Theoretical Studies Of The Sulfenate-Sulfoxide Rearrangement. *J Org Chem.* 1998; 63:6061–6064. [PubMed: 11672219]
11. Wolfe S, Schlegel HB. On The Constitution Of Dimethylsulfoxide. *Gaz Chim Ital.* 1990; 120:285–290.
12. Petrov VM, Girichev GV, Oberhammer H, Petrova VN, Giricheva NI, Bardina AV, Ivanov SN. Molecular Structure And Conformations Of Para-Methylbenzene Sulfonamide And Ortho-Methylbenzene Sulfonamide: A Gas Electron Diffraction And Quantum Chemical Calculations Study. *J Phys Chem A.* 2008; 112:2969–2976. [PubMed: 18302350]
13. M^o O, Paz JLGD, Yáñez M, Alkorta I, Elguero J, Goya P, Rozas I. A Molecular Orbital Study Of The Conformation (Inversion And Rotational barriers) And Electronic Properties Of Sulfamide. *Can J Chem.* 1989; 67:2227–2236.
14. Jaguar, version 83. Schrödinger, LLC; New York, NY: 2014.
15. Frisch, MJ., Trucks, GW., Schlegel, HB., Scuseria, GE., Robb, MA., Cheeseman, JR., Scalmani, G., Barone, V., Mennucci, B., Petersson, GA., Nakatsuji, H., et al. Gaussian 09: revision D.01. Gaussian Inc; Wallingford, CT: 2009.
16. Glendening, ED., Badenhoop, JK., Reed, AE., Carpenter, JE., Bohmann, JA., Morales, CM., Landis, CR., Weinhold, F. NBO 6.0. Theoretical Chemistry Institute, University of Wisconsin; Madison, WI: 2013.
17. Bayly CI, Cieplak P, Cornell W, Kollman PA. A Well-Behaved Electrostatic Potential Based Method Using Charge Restraints For Deriving Atomic Charges: The RESP Model. *J Phys Chem.* 1993; 97:10269–10280.
18. Donoghue PJ, Helquist P, Norrby PO, Wiest O. Development Of A Q2MM Force Field For The Asymmetric Rhodium Catalyzed Hydrogenation Of Enamides. *J Chem Theory Comput.* 2008; 4:1313–1323. [PubMed: 26631706]
19. Donoghue PJ, Helquist P, Norrby PO, Wiest O. Prediction Of Enantioselectivity In Rhodium Ctalized Hydrogenations. *J Am Chem Soc.* 2009; 131:410–411. [PubMed: 19140780]

20. Hansen E, Rosales AR, Tutkowski B, Norrby P-O, Wiest O. Prediction Of Stereochemistry Using Q2MM. *Acc Chem Res.* 2016; 49doi: 10.1021/acs.accounts.6b00037
21. Jensen F, Norrby PO. Transition States From Empirical Force Fields. *Theor Chem Acc.* 2003; 109:1–7.
22. Limé E, Lundholm MD, Forbes A, Wiest O, Helquist P, Norrby PO. Stereoselectivity In Asymmetric Catalysis: The Case Of Ruthenium-Catalyzed Ketone Hydrogenation. *J Chem Theory Comput.* 2014; 10:2427–2435. [PubMed: 26580763]
23. Limé E, Norrby PO. Improving The Q2MM Method For Transition State Force Field Modeling. *J Comput Chem.* 2015; 36:244–250. [PubMed: 25430788]
24. Lill SON, Forbes A, Donoghue P, Verdolino V, Wiest O, Rydberg P, Norrby PO. Application Of Q2MM To Stereoselective Reactions. *Curr Org Chem.* 2010; 14:1629–1645.
25. Juaristi E, Notario R. Computational Reexamination Of The Eclipsed Conformation In Cis-2-Tert-butyl-5-(Tert-Butylsulfonyl)-1:3-Dioxane. *Struct Chem.* 2013; 24:1855–1862.
26. Norrby PO. Selectivity In Asymmetric Synthesis From QM-Guided Molecular Mechanics. *J Mol Struct: THEOCHEM.* 2000; 506:9–16.
27. Norrby PO, Brandt P. Deriving Force Field parameters For Coordination Complexes. *Coord Chem Rev.* 2001; 212:79–109.
28. Norrby PO, Liljefors T. Automated Molecular Mechanics Parameterization With Simultaneous Utilization Of Experimental And Quantum Mechanical Data. *J Comput Chem.* 1998; 19:1146–1166.
29. Allinger NL, Yuh YH, Lii JH. Molecular Mechanics. The MM3 Force Field For Hydrocarbons. 1. *J Am Chem Soc.* 1989; 111:8551–8566.
30. MacroModel, version 11.0. Schrödinger, LLC; New York, NY: 2015.

Figure 1.

QM relaxed 2D PES of **1** (left) and **2** (right). For both molecules, the bonds were rotated by 355° in 5° increments starting from conformation **1a** or **2c^{ts}**, respectively. The torsions rotated for methanesulfonamide and sulfamide are listed on the axes. The nitrogen lone pair, n_N , is represented by a dummy atom constrained to lie on the plane bisecting the N–H bonds, whereas X is a dummy atom *anti* to one C–H bond and bisecting the two other.

Figure 2.

NBO orbital diagram for **2a**. NBO overlap between the nitrogen lone pair n_N and S-O antibonding orbital σ_{S-O}^* (left). Partial NBO overlap between the nitrogen lone pair n_N and S-N antibonding orbital σ_{S-N}^* in **2a** (right). The $n_N \rightarrow \sigma_{S-N}^*$ interaction is stronger in all the other sulfamide conformers, and the $n_N \rightarrow \sigma_{S-O}^*$ interaction dominates in **2a**.

Figure 3. MM reproduction of the QM calculated PES (Figure 1) for **1** (left) and **2** (right) using **FFA** (top) and **FFB** (bottom). The torsions rotated for 1 and 2 are listed on the axes, respectively.

Scheme 1.

Generalized Structures of Sulfonamides 1 and Sulfamides 2

Table 1

Energies and Geometries of the Optimized Stationary Points Found on Methanesulfonamide's PES

Conformer	1a	1b	1c ^{ts}	1d ^{ts}	1e ^{ts}
E _{rel} (M06)	0.0	8.5	10.8	19.4	26.0
E _{rel} (CCSD(T))	0.0	7.9	11.8	19.6	27.0
Frequency ^a	-	-	197.2 <i>i</i>	204.7 <i>i</i>	292.6 <i>i</i>
S-N	1.67	1.66	1.68	1.66	1.69
S-C	1.77	1.78	1.79	1.80	1.78
S-O ₁	1.44	1.44	1.44	1.44	1.44
S-O ₂	1.44	1.44	1.44	1.44	1.44
N-S-C	102.8	107.4	104.1	108.5	102.4
O-S-O	121.8	122.4	121.7	122.2	119.5

^aFor the negative eigenmode of a transition state.

Table 2

Energies and Geometries of Sulfamide's Optimized Stationary Points

Conformer	2a	2b	2c ^{ts}	2d	2e ^{ts}	2f ^{ts}

E _{rel} (M06)	0.0	1.6	4.0	8.6	13.7	24.9
E _{rel} (CCSD(T))	0.0	2.7	6.1	9.9	15.7	26.4
Frequency	-	-	149.2 <i>i</i>	-	240.3 <i>i</i>	282.5 <i>i</i>
S-N ₁	1.66	1.68	1.66	1.66	1.67	1.69
S-N ₂	1.66	1.65	1.66	1.66	1.67	1.65
S-O ₁	1.43	1.43	1.44	1.43	1.44	1.43
S-O ₂	1.43	1.43	1.44	1.43	1.44	1.43
N ₁ -S-N ₂	99.9	106.8	104.5	110.9	100.7	105.7
O ₁ -S-O ₁	121.0	123.9	123.7	124.5	120.5	121.4
N ₁ -S-O ₁	112.1	105.9	106.8	105.3	— ^a	— ^a
N ₁ -S-O ₂	104.9	106.7	106.8	105.3	— ^a	— ^a

^a Nonsymmetric structures with two different values; see Supporting Information.

Table 3
Comparison of Energies for FFA (without Skipped Atom Dihedral) and FFB (with Skipped Atom Dihedral)

method	geometry	1a	1b	1c ^{ts}	1d ^{ts}	1e ^{ts}	2a	2b	2c ^{ts}	2d	2e ^{ts}	2f ^{ts}
QM		0.0	8.5	10.8	19.4	26.0	0.0	1.6	4.0	8.6	13.7	24.9
FFA	fixed	0.0	8.9	9.7	19.4	26.1	0.0	2.0	4.2	10.4	14.4	23.3
	opt.	0.0	11.2				0.0	0.7		8.5		
FFB	fixed	0.0	8.7	10.3	19.6	25.5	0.0	2.6	4.0	9.1	13.5	24.2
	fpt	0.0	8.8				0.0	1.6		8.6		

Table 4

Results from MM3* Conformational Search Using Optimized FFA

Conformer	1f	1a	
Energy (kJ/mol)	0	0.2

Conformer	2a	2g	2d	
Energy (kJ/mol)	0	0.4	8.5	

Table 5

Results from MM3* Conformational Search Using Optimized FFB

Conformer	1a
Energy (<i>kJ/mol</i>)	-

Conformer	2a		
Energy (<i>kJ/mol</i>)	0	1.6	8.6