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# Sulfur–Aromatic Interactions: A Computational Study of the Dimethyl Sulfide–Benzene Complex

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To investigate sulfur–aromatic interactions, intermolecular interaction energies between dimethyl sulfide and benzene were computed using ab initio molecular orbital calculations. Inclusion of electron correlation at the MP2 level predicted significantly more stable complexes compared to Hartree–Fock calculations, whereas density functional theory with the B3LYP functional shows no improvement over Hartree–Fock calculations. The molecular mechanics force fields AMBER95 and OPLS-AA were successful in reproducing the MP2 results. 

## INTRODUCTION

Many different types of interactions contribute to the process of protein folding, including electrostatic, hydrogen bonding, and hydrophobic interactions (*1*). Among these are interactions involving aromatic side chains of phenylalanine, tyrosine, and tryptophan residues. These aromatic groups can interact with each other (''$\pi$–$\pi$ interactions'') (*2*) or with positively charged side chains (''cation–$\pi$ interactions'') (*3*), both of which have been the subject of several experimental and computational investigations. Less commonly mentioned is the interaction between a sulfur-containing side chain, methionine or cysteine, with an aromatic group (*4*).

My interest in sulfur–aromatic interactions arose when it was brought to my attention that a computational study, using molecular dynamics, predicted a 1.6 kcal/mol increase in stability brought about by a leucine-for-methionine mutation (M32L) in staphylococcal nuclease (*5*). This was an unusual result, because most mutant proteins are less stable than the wild type. But molecular dynamics simulations on other mutants of staphylococcal nuclease have provided correct results, compared to experimental studies (*5–7*). The particular mutant, M32L, was subsequently made (by a colleague in this department, incidentally), and its experimentally determined stability turned out to be 0.8 kcal/mol *less* stable than that of the wild type (*8*).

This discrepancy between theory and experiment suggests that there might be something about sulfur–aromatic interactions that is worth looking into. While the present studies do not provide a definite answer as to the cause of the discrepancy, they do provide some insights that are of some relevance to any chemical or biomolecular systems in which sulfur–aromatic interactions have a role to play.



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## COMPUTATIONAL METHODS

Dimethyl sulfide (DMS) was chosen as a model molecule to represent the methionine side chain, while benzene, as usual, served as the prototypical aromatic molecule. The primary intention of these studies is to obtain a reasonable estimate of the interaction energy between these two molecules, thus allowing a judgment to be made whether this interaction is significant enough to play a role in determining protein structure. Ab initio molecular orbital calculations were used for this purpose (*9*). Ab initio calculations have developed to the point that their use is almost routine, and acceptance of their results have grown steadily. There is also increasing reliance on ab initio calculations for the development of molecular mechanics parameters for use in molecular dynamics simulations and related methodologies (*10*).

All the computations employed the 6-31G* basis set. Three different methodologies were employed: Hartree–Fock (HF), second-order Møller–Plesset perturbation theory (MP2), and density functional theory (*11*) with the B3LYP functional (*12*). HF theory is the simplest form of ab initio calculations and the one most routinely used for practical applications. However, its shortcomings have long been recognized. For the purpose of these studies, the most serious deficiency is its inability to treat dispersion interactions properly (*13*). These interactions are expected to be important when the molecules involved include benzene, with its highly polarizable $\pi$-electron density, and sulfur, also highly polarizable due to the presence of empty *d*-orbitals. Thus, HF theory is not expected to give accurate results. It is included here mainly for the purpose of comparison.

The MP2 method includes an explicit treatment of electron correlation, it is better able to deal with dispersion interactions (*13*), and its results may be considered fairly reliable. More accurate computations can be performed, by using higher orders of perturbation theory and larger, more flexible basis sets. However, such computations are significantly more expensive, and I do not consider the added expense justified for the purpose of these investigations.

Density functional theory (*11*) is a fundamentally different approach to the problem of electron correlation and has been recently applied successfully to a great variety of problems (*14*). The B3LYP functional (*12*) in particular has been judged roughly comparable to MP2 in performance, with a significant reduction in computational expense. To my knowledge, density functional theory has not been widely tested for the calculation of intermolecular interaction energies, although there is one study that looks at hydrogen-bonded complexes (*14f*), where the performance of B3LYP/6-31G** calculations proved unreliable. Its inclusion here is meant to be a test of its performance for this particular type of problem.

Three different structures of the DMS–benzene complex were chosen as representative configurations for the computations of the interaction energy. These are shown in Fig. 1. Complex I has the sulfur atom on the sixfold symmetry axis of the benzene ring, with the two methyl groups oriented towards the face of the benzene ring. Complex II has one of the methyl groups pointed directly toward the face of the benzene ring. Complex III has the DMS molecule on the side of the benzene ring, with the planes of the two molecules mutually perpendicular.

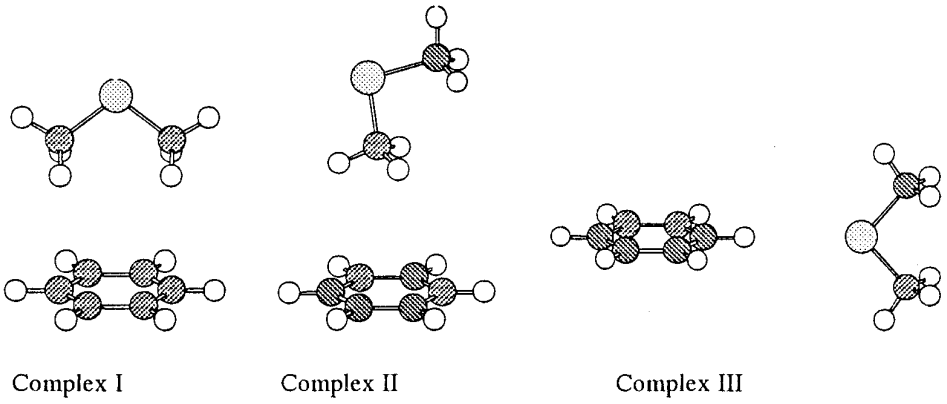


**FIG. 1.** Structures of the three dimethyl sulfide–benzene complexes.

Energies were calculated at fully optimized geometries for each complex (with one exception explained below), subject only to the symmetry contraints inherent in the point group for each structure ($C_{2v}$ for Complex I and III and $C_s$ for Complex II). Interaction energies were calculated simply by subtracting the total electronic energy of an isolated DMS molecule and an isolated benzene molecule from the total electronic energy of the complex. Of course, there are inaccuracies inherent in such a simple approach, including the neglect of basis set superposition errors (*13*) and the lack of a correction for the contributions of vibrational energies and entropies. However, it is sufficient for the present purpose.

Other structures were initially considered in survey calculations using HF/3-21G calculations. One was a structure similar to Complex I, with the DMS molecule rotated 90° around the symmetry axis. The interaction energy of this structure is only slightly greater (i.e., less negative) than that of Complex I. Another structure investigated was similar to Complex III, but with the benzene and DMS molecules coplanar. Again, this structure is slightly less stable than Complex III. Yet another is similar to Complex I, but with the methyl groups of DMS pointing away from the benzene ring. This structure was not stable; during optimization, the DMS and benzene molecules drifted farther and farther away from each other.

Another aspect I was interested in investigating is the performance of currently available molecular mechanics force fields for the calculation of sulfur–aromatic interactions. Consequently, interaction energies for Complexes I–III were calculated using several different versions of two widely available force fields. Three versions of the AMBER force field parameters include the older united-atom (*15*) and all-atom (*16*) versions (which include explicit representations of the lone pair electrons on the sulfur atom), and the newer all-atom version (which does not use lone pairs) (*17*). The other force field used was OPLS. One set of calculations used the united-atom model for DMS (*18*), another used the all-atom model (*19*). In both sets the all-atom model for benzene was used.