

# Conformational Analysis and Derivation of Molecular Mechanics Parameters for Esters and Thioesters

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The ab initio MP2 and DFT/B3LYP quantum chemical methods applying the 6-311++G\*\* basis set are equally useful for the conformational analysis of simple esters and thioesters. Calculated equilibrium geometric values were close to the experimental ones for the cis methyl acetate and methyl thioformate. Barriers to the O=C–X–C rotation in methyl acetate (X = O) and methyl thioacetate (X = S) were calculated at 11–13 kcal/mol with both methods. Both oxo- and thioesters favor the O=C–X–C cis, planar form. Solvent effects were estimated by using the polarizable continuum dielectric method (PCM). The cis form was found as the prevailing conformation for both the oxo- and thioesters in chloroform, acetone, acetonitrile, and water. The trans CH<sub>3</sub>–CH<sub>2</sub>–C=O structure (with cis O=C–X–C ester moiety) is a transition state both in methyl propanoate and methyl thiopropanoate, and a basically cis arrangement is preferred for both esters as revealed from B3LYP/6-311++G\*\* calculations. The potential curve for the rotation of the methyl-group of ethyl acetate shows double minima at  $\varphi = 87^\circ$  and  $\varphi = 180^\circ$ . Only the gauche methyl position ( $\varphi = 85^\circ$ ) corresponds to an energy minimum structure in ethyl thioacetate. Using the results of the conformational analyses, stretching, bending, torsion, and improper torsion (out-of-plane) parameters were derived for the –CH<sub>2</sub>–CH<sub>2</sub>–C(=O)–S–CH<sub>2</sub>–CH<sub>2</sub>– thioester moiety. In compliance with parameters in the GROMACS force field and by accepting the united CH<sub>3</sub> and CH<sub>2</sub> atom models with zero net-charge for these groups, the derived parameters are useful in molecular modeling of unusual proteins containing an acylated cysteine side chain.

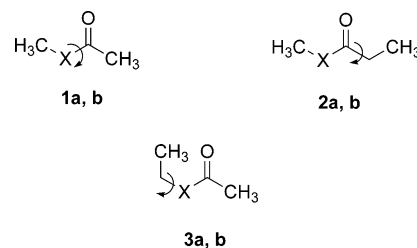
## Introduction

Generally, modeling packages using molecular mechanics force fields are parametrized for biopolymers with components of commonly appearing natural building blocks such as L-amino acids, nucleic acids, and carbohydrates. However, the occurrence of natural products with substructures not having parameters in the basic set presents a recurring problem in molecular modeling.

The M<sub>1</sub> muscarinic receptor and several of its agonist ligands were modeled in previous studies.<sup>1</sup> In the present project, a palmytoylated 435Cys residue of the M<sub>1</sub> receptor will be considered. An acylated cysteine structure, corresponding to a thioester, is unusual in natural products and appropriate parameters are not available in the GROMACS 3.1.4 modeling package<sup>2</sup> for application to receptor modeling studies. In addition to the need for the parameter derivation, thioesters are common structures in synthetic organic chemistry,<sup>3</sup> and it is interesting to compare structural features and reactivities with their oxoester counterparts.<sup>4</sup>

Structures of simple oxoesters have been studied both experimentally and theoretically in detail, while much less is known about thioesters. Methyl formate is the simplest oxoester,

## SCHEME 1<sup>a</sup>



<sup>a</sup> Key: **1a** (X = O), methyl acetate; **1b** (X = S), methyl thioacetate; **2a** (X = O), methyl propanoate; **2b** (X = S), methyl thiopropanoate; **3a** (X = O), ethyl acetate; **3b** (X = S), ethyl thioacetate. Structures correspond to the cis conformers with  $\varphi = 0^\circ$  in Figures 1–4.

and its structure was determined by Curl from microwave spectroscopic investigations.<sup>5</sup> Methyl formate, however, might not be the best model for esters of aliphatic carboxylic acid. Aliphatic acids typically have a C–C(=O)–O substructure, whereas the corresponding structure in methyl formate is H–C(=O)–O. Instead, methyl acetate may be considered as the prototype of the oxoesters. The structure of methyl acetate was determined by a joint analysis of electron diffraction, microwave and infrared spectroscopy by Pyckhout et al.<sup>6a</sup> In the determined stable conformation of both methyl formate and methyl acetate, the C=O and the O–CH<sub>3</sub> groups are in cis (syn or Z) position (Scheme 1). Thus, the H–C instead of C–C bond does not affect the conformational character of the stable oxoester species. Relative energies, however, differ considerably. The trans form is less stable than the cis conformer by 3.6–5.0

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and  $8.5 \pm 1$  kcal/mol for methyl formate and methyl acetate, respectively.<sup>6b</sup>

Theoretical studies support the adoption of *cis* conformations by simple oxoesters. Calculations up to the *ab initio* MP3/6-311++G\*\*//HF/6-31G\* and B3LYP/aug-cc-pVDZ levels find the *cis* methyl acetate form more stable than the *trans* (*anti* or *E*) by 6–9 kcal/mol.<sup>7</sup> The rotational barrier corresponding to the O=C–O–C torsion angle of about 90° was calculated at 13 kcal/mol.<sup>7a,c</sup> In theoretical calculations for higher ester homologues, the *cis*-ester moiety was accepted. The CCC=O torsional potential was studied for methyl propanoate at the *ab initio* 4-21G level by Klimkowski et al.<sup>8</sup> A double-minimum profile was obtained with global and local minima at CCC=O = 0° and 122°, respectively, with a relative energy of 1.07 kcal/mol for the latter. Conformations of ethyl acetate were studied by Manning et al.<sup>9</sup> using the 4-21G basis set. The global minimum for the CCOC torsion potential (O is the ether oxygen) was calculated at 81°. The second lowest energy conformation corresponds to CCOC = 180° with relative energy of 0.2 kcal/mol. The two minima are separated by a barrier of 0.7 kcal/mol at CCOC = 120°.

Structural information from microwave spectroscopy are available for methyl thioformate,<sup>10</sup> ethyl thioformate, ethyl fluoro-, chloro-, and cyanothioformates,<sup>11</sup> and the preference of the *cis*-O=C–S–C structure has been found. However, the thioester “prototype”, methyl thioacetate, has not been determined experimentally. Thus, a starting point in structural analysis would be that thioesters in general are most stable in the OCSC *cis* conformation as evidenced by the structural information transferability from formates to other oxoesters. *Ab initio* studies<sup>12a</sup> up to the MP2/6-31++G\*\* level and DFT/B3LYP/6-31+G\* as well as MP2/6-31+G\* studies<sup>12b</sup> have confirmed that the *cis* form of methyl thioacetate is more stable than the *trans* form by about 5 kcal/mol. In MP2 and B3LYP theoretical analyses for the CSCC potential curve for ethyl thioformate and ethyl fluorothioformate, Bohn and Wiberg already set the O=CSC moiety to its preferable *cis* form.<sup>13</sup>

Two goals were identified for the present study. First, a consistent conformational analysis was performed for methyl acetate, methyl propanoate, ethyl acetate, and their thio analogues at the B3LYP/6-311++G\*\* level. The analyses included estimation of torsion barriers in the gas phase. For methyl acetate and methyl thioacetate, in-solution *cis*–*trans* energy differences and barriers were calculated with different dielectric constants. The second goal was to derive molecular mechanics parameters for thioesters usefully applicable in the GROMACS force field.

## Methods and Calculations

**Conformational Analysis.** Most calculations were carried out at the DFT/B3LYP level<sup>14</sup> utilizing the 6-311++G\*\* basis set.<sup>15a</sup> To explore the basis set effect on the optimized geometry, several calculations were also performed with the aug-cc-pVTZ basis set.<sup>15b,c</sup> The Gaussian 98 package<sup>16</sup> was run on a Cray SV1ex supercomputer located at the Ohio Supercomputer Center. In a study of how well hybrid density functional methods predict transition state geometries and barrier heights for some simple reactions, Lynch and Truhlar<sup>17</sup> found that calculations at the B3LYP level have an unsigned error of 3.4–4.2 kcal/mol, depending on the basis set used. To test this possible weakness of the B3LYP/6-311++G\*\* level in conformational analyses, MP2/6-311++G\*\* calculations also were performed for methyl acetate, methyl thioformate, and methyl thioacetate. The obtained values were compared with each other and the experimental data. The two sets of calculations provided similar

results (Tables 1–3). Although no experimental values are available for the barrier heights, it has been demonstrated that the B3LYP and MP2 methods using the 6-311++G\*\* basis set do not differ significantly in predicting the O=C–X–C (X = O, S) rotation potentials (Figures 1 and 2). Since calculations were about twice as fast at the B3LYP than the MP2 level for these molecules, methyl propanoate, ethyl acetate, and their thioanalogues were considered only at the B3LYP/6-311++G\*\* level.

The relative free energy,  $\Delta G$ , for the gas-phase conformers have been calculated in the ideal gas and the rigid rotator-harmonic oscillator approximations:<sup>18</sup>

$$\Delta G(\text{gas}) = \Delta E(\text{gas}) + \Delta H(T) - T\Delta S(T) \quad (1)$$

where  $E(\text{gas})$  in eq 1 is the energy of a conformer with geometry optimized in the gas phase,  $H(T)$  is the enthalpy (including the zero-point vibrational energy), and  $S(T)$  is the entropy of 1 mol of ideal gas at temperature  $T$ .  $T$  and  $p$  were set to 298.15 and 1 atm, respectively (Table 3).

Changes in the relative energies for  $\text{CH}_3\text{COXCH}_3$  (X = O, S) in solution have been studied using the polarizable continuum dielectric method (PCM)<sup>19</sup> as implemented in Gaussian 98. Mimicking chloroform, acetone, acetonitrile, and water solvents with dielectric constants of  $\epsilon = 4.7, 20.5, 35.7,$  and  $78.4$ , respectively, at  $T = 298$ ,<sup>20</sup> PCM/B3LYP/6-311++G\*\* single point calculations were carried out at the gas-phase optimized *cis*, transition state (TS), and *trans* conformations for methyl acetate and methyl thioacetate. (Table 4). By iteratively solving the Schrodinger equation for the solute in a dielectric continuum environment, the following energy terms were utilized

$$E_{\text{int}}^{\text{s}} = [\langle \Psi_{\text{s}} | H^{\circ} | \Psi_{\text{s}} \rangle] \quad (2a)$$

$${}^{1/2}E_{\text{elst}}^{\text{ss}} = [\langle \Psi_{\text{s}} | {}^{1/2}V_{\text{R}}^{\text{sol}} | \Psi_{\text{s}} \rangle] \quad (2b)$$

where  $H^{\circ}$  is the Hamiltonian of the molecule,  $V_{\text{R}}^{\text{sol}}$  is the solvent reaction field generated by the fully polarized solute in solution, and  $\Psi_{\text{s}}$  is the converged wave function of the solute obtained from an in-solution calculation. With  $E(\text{gas})$  for the total energy for a molecule optimized in the gas phase,  $E_{\text{int}}^{\text{s}} - E(\text{gas}) \equiv E_{\text{supol}}$  corresponds to the change in the solute internal energy upon polarization by the environment. For calculating free energy instead of energy changes in solution, the dispersion–repulsion,  $G_{\text{dr}}$ , and the cavity formation,  $G_{\text{c}}$ , free energy terms also are to be considered. By utilizing all these terms, the solvation free energy,  $G_{\text{solv}}$  was calculated as follows (without considering the effect of the changes in the geometry and in thermal corrections for the vibrations):

$$G_{\text{solv}} = E_{\text{supol}} + {}^{1/2}E_{\text{elst}}^{\text{ss}} + G_{\text{dr}} + G_{\text{c}} \quad (3)$$

and the relative free energy in solution is

$$\Delta G(\text{sol}) = \Delta G(\text{gas}) + \Delta G_{\text{solv}} \quad (4)$$

All gas-phase calculations for molecules except  $\text{CH}_3\text{COSCH}_2\text{-CH}_3$  have been performed successfully at the B3LYP/6-311++G\*\* level. For ethyl thioacetate, the Gaussian program indicated an error in the orthogonal basis most of the time, and reduced the number of the basis functions considered to a value of 185–193 instead of considering 196 basis functions for the 6-311++G\*\* basis set. The error appeared at different geometries, mainly with the CSCC torsion angle of about 90° or larger. For this reason, the ethyl thioacetate rotational potential was obtained based on B3LYP/6-311+G\*\* optimized geom-

**TABLE 1: Calculated and Experimental Geometric Parameters for Methyl Acetate, cis-Methyl Thioformate, and Methyl Thioacetate,<sup>a</sup> Where Values in Parentheses Were Obtained in Geometry Optimizations Utilizing the Aug-cc-pVTZ Basis Set**

	MP2/6-311++G**	B3LYP/6-311++G**	exp <sup>b</sup>
CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub> , cis			
C-C	1.506 (1.500)	1.507 (1.505)	1.496
C=O	1.212 (1.212)	1.207 (1.205)	1.206
C-O	1.354 (1.351)	1.353 (1.351)	1.357
O-CH <sub>3</sub>	1.436 (1.436)	1.440 (1.438)	1.438
C-C=O	126.1 (126.0)	125.8 (125.6)	
O=C-O	123.3 (123.3)	123.3 (123.3)	123.0
C-O-CH <sub>3</sub>	114.3 (114.0)	116.0 (115.9)	116.4
CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub> , trans			
C-C	1.515	1.515	
C=O	1.207	1.201	
C-O	1.362	1.362	
O-CH <sub>3</sub>	1.429	1.432	
C-C=O	123.6	123.6	
O=C-O	118.7	118.5	
C-O-CH <sub>3</sub>	119.7	121.5	
H-C(=O)-S-CH <sub>3</sub> , cis			
H-C	1.104 (1.100)	1.105 (1.102)	
C=O	1.214 (1.214)	1.204 (1.203)	1.20
C-S	1.757 (1.756)	1.776 (1.771)	1.77
S-CH <sub>3</sub>	1.804 (1.805)	1.825 (1.820)	1.80
H-C=O	123.3 (123.3)	123.5 (123.4)	
H-C-S	111.5 (111.6)	110.8 (110.6)	109.0
O=C-S	125.2 (125.1)	125.7 (125.9)	126.0
C-S-CH <sub>3</sub>	98.4 (98.2)	100.0 (100.1)	100.0
CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub> , cis			
C-C	1.513	1.513	
C=O	1.216	1.207	
C-S	1.777	1.798	
S-CH <sub>3</sub>	1.803	1.823	
C-C=O	123.5	123.7	
O=C-S	122.6	122.5	
C-S-CH <sub>3</sub>	98.5	99.7	
CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub> , trans			
C-C	1.514	1.513	
C=O	1.215	1.205	
C-S	1.785	1.809	
S-CH <sub>3</sub>	1.810	1.831	
C-C=O	122.9	123.5	
O=C-S	118.1	117.4	
C-S-CH <sub>3</sub>	104.1	105.5	

<sup>a</sup> The cis structure corresponds to a torsion angle of 0° for the O=C-X-CH<sub>3</sub> moiety. Distances are in Å and angles in deg. <sup>b</sup> Methyl acetate: ref 6. Methyl thioformate: ref 10.

**TABLE 2: Parameters for the  $V = V_0 + \frac{1}{2}[V_1(1 + \cos\varphi) + V_2(1 - \cos2\varphi) + V_3(1 + \cos3\varphi)]$  Potential<sup>a</sup>**

	V <sub>0</sub>	V <sub>1</sub>	V <sub>2</sub>	V <sub>3</sub>
MP2/6-311++G**				
CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub>	8.216	-7.605	8.993	-0.611
CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub>	4.781	-4.300	8.716	-0.481
B3LYP/6-311++G**				
CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub>	7.884	-7.450	9.143	-0.434
CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub>	4.632	-4.357	9.454	-0.275
CH <sub>3</sub> -CH <sub>2</sub> -C(=O)-O-CH <sub>3</sub>	1.189	-0.907	0.218	-0.282
CH <sub>3</sub> -CH <sub>2</sub> -C(=O)-S-CH <sub>3</sub>	1.112	-1.390	-0.173	0.278
CH <sub>3</sub> -C(=O)-O-CH <sub>2</sub> -CH <sub>3</sub>	-7.214	5.524	-3.205	1.690
B3LYP/6-311++G**//				
B3LYP/6-311+G**				
CH <sub>3</sub> -C(=O)-S-CH <sub>2</sub> -CH <sub>3</sub>	-5.688	4.472	-3.344	1.216

<sup>a</sup> V in kcal/mol.

eries (with 188 basis functions) and the energies were calculated from single point calculations at the B3LYP/6-311++G\*\* level. The basis set orthogonality error was not found in single point calculations except for the CCCC torsion angle of 180°, where the energy was calculated with 193 basis functions at the B3LYP/6-311+G\*\* optimized geometry. This geometry was obtained also with a slightly reduced basis set, with 185 instead

of 188 basis functions. From comparable cases (in many cases, Gaussian accepted 196 basis functions in repeated restarts at the geometry optimized with 193 or less basis functions) the energies with 193 and 196 basis functions differed by about 0.01 kcal/mol. This error was considered negligible in the present application.

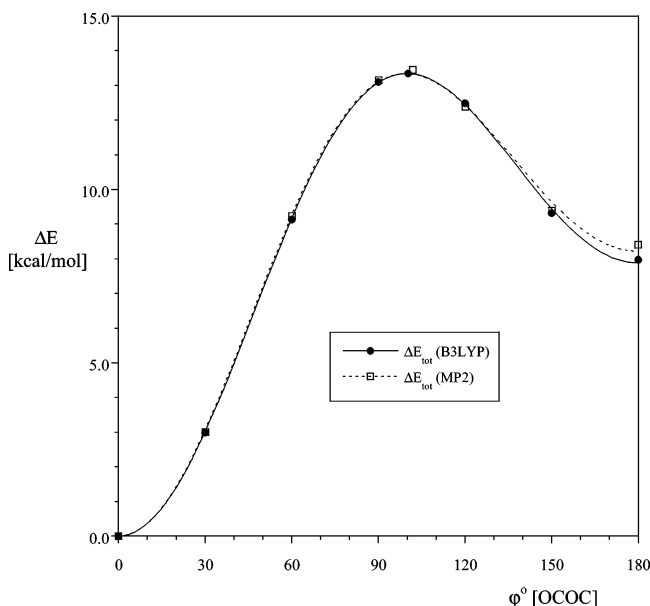
**Parameter Estimation.** When the -C(sp<sup>3</sup>)-C(sp<sup>3</sup>)-C(=O)-S-C(sp<sup>3</sup>)-C(sp<sup>3</sup>) moiety is introduced into a modeling system, new parameters are needed for the C(sp<sup>2</sup>)-S bond stretching, for the bending of the O=C-S, C(sp<sup>3</sup>)-C(sp<sup>2</sup>)-S, and C(sp<sup>2</sup>)-S-C(sp<sup>3</sup>) bond angles, for the C(sp<sup>3</sup>)-C(sp<sup>3</sup>)-C(sp<sup>2</sup>)-S, O=C(sp<sup>2</sup>)-S-C(sp<sup>3</sup>), C(sp<sup>3</sup>)-C(sp<sup>2</sup>)-S-C(sp<sup>3</sup>), and C(sp<sup>2</sup>)-S-C(sp<sup>3</sup>)-C(sp<sup>3</sup>) torsions, and for the improper torsion regarding the C(sp<sup>3</sup>)-C(=O)-S four-atom substructure. All force fields modeling amino acids provide the C(sp<sup>3</sup>)-S-C(sp<sup>3</sup>)-C(sp<sup>3</sup>) torsion potential as a methionine parameter, which will be accepted here as applicable also for the C(sp<sup>2</sup>)-S-C(sp<sup>3</sup>)-C(sp<sup>3</sup>) torsion. The S-C(sp<sup>3</sup>) bond stretching and the S-C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond angle bending parameters of the given force field will also be accepted as relevant for the sulfur atom in a thioester group.

The minimum energy structure was optimized for the CH<sub>3</sub>-C(=O)-S-CH<sub>3</sub> molecule and for the CH<sub>3</sub>-C(=O)-S-CH<sub>2</sub>-

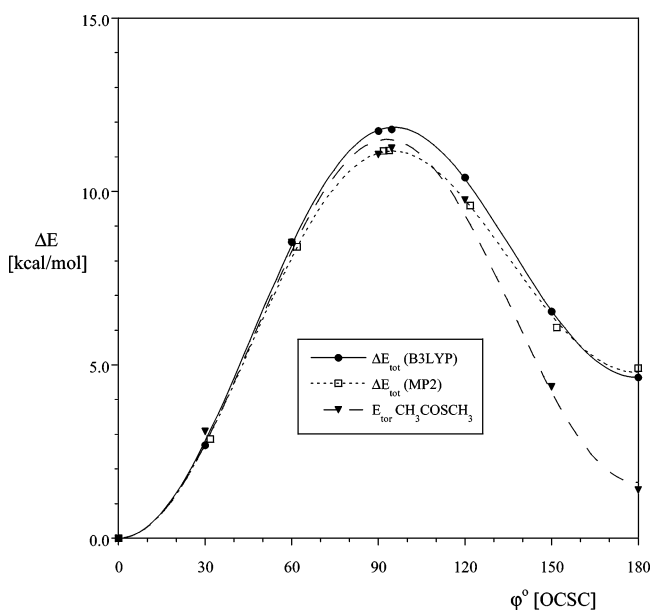
**TABLE 3: Energies and Free Energies (in kcal/mol) for Methyl Acetate and Methyl Thioacetate Relative to the O=C-X-C cis ( $\varphi = 0^\circ$ ) Conformer at  $T = 298$** 

	transition state				trans			
	$\Delta E$	$\Delta H$	$-T\Delta S^a$	$\Delta G$	$\Delta E$	$\Delta H$	$-T\Delta S$	$\Delta G$
CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub>								
MP2/6-311++G**	13.45 <sup>b</sup>				8.40			
B3LYP/6-311++G**	13.35 <sup>c</sup>	-1.02	0.77	13.10	7.97	-0.20	0.36	8.13
CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub>								
MP2/6-311++G**	11.18 <sup>d</sup>				4.91			
B3LYP/6-311++G**	11.80 <sup>e</sup>	-0.77	2.05	13.08	4.64	-0.08	1.57	6.13

<sup>a</sup> Including an entropy term of  $RT \ln 2$  for the mirror image transition state structures. <sup>b</sup>  $\varphi = 101.9^\circ$ . <sup>c</sup>  $\varphi = 100.3^\circ$ . <sup>d</sup>  $\varphi = 93.8^\circ$ . <sup>e</sup>  $\varphi = 94.6^\circ$ .



**Figure 1.** Rotational potential curves,  $\Delta E_{\text{tot}}$ , for CH<sub>3</sub>COOCH<sub>3</sub> at the B3LYP/6-311++G\*\* (filled circles) and the MP2/6-311++G\*\* (empty squares) levels.  $\varphi = 0^\circ$  corresponds to the O=C-O-C cis arrangement (Scheme 1, Table 2).



**Figure 2.** Rotational potential curves,  $\Delta E_{\text{tot}}$ , for CH<sub>3</sub>COSCH<sub>3</sub> at the B3LYP/6-311++G\*\* (filled circles) and the MP2/6-311++G\*\* (empty squares) levels.  $\varphi = 0^\circ$  corresponds to the O=C-S-C cis arrangement (Scheme 1, Table 2).  $E_{\text{tor}}$  is the derived torsional potential (Table 7).

CH<sub>3</sub> molecule with 196 basis functions. The equilibrium values for the cis methyl and ethyl thioacetate were similar (Tables 1 and S1 in the Supporting Information). (The optimum C-S-

C-C torsion angle in the ethyl ester is about  $85^\circ$ , corresponding to a gauche methyl conformation in the ethyl group.) The cis methyl thioacetate conformer is more stable than the trans conformer by 6 kcal/mol and is separated by a barrier of 13 kcal/mol (Table 3). Thus, the thioester moiety is expected to stay in its cis conformation most of the time. Taking all these together, the O=C-S-C cis conformers were considered for both molecules for calculating the C-S bond length and C-S-C angle parameters. The minimum energy conformation and four other structures were considered in parameter estimations. Studying the C-S bond parameters, we observed that the bond length was both stretched and shortened by up to  $\Delta R = \pm 0.06 \text{ \AA}$  relative to the equilibrium value (Figure 5). Energies were obtained from calculations with optimized internal coordinates while keeping the C-S distance at fixed values.

The quantum chemically calculated  $\Delta E_{\text{tot}}(\text{C-S})$  curve is, however, not equal to the C-S stretching potential, since many other contributions are also included in  $\Delta E_{\text{tot}}$ . Indeed, even the simplest force field can be characterized as

$$E_{\text{tot}} = E_{\text{str}} + E_{\text{bend}} + E_{\text{tor}} + E_{\text{imptor}} + E_{\text{elst}}(1-4) + E_{\text{elst}}(1-N) + E_{\text{vdW}}(1-4) + E_{\text{vdW}}(1-N)$$

where the individual terms account for all bond stretching, bond angle bending, proper and improper torsion energies, and for all nonbonded 1-4 and 1-N electrostatic and 1-4 and 1-N van der Waals interactions, respectively ( $N \geq 5$ ). Energy terms in the GROMACS,<sup>2</sup> AMBER,<sup>21a</sup> and Sybyl<sup>21b</sup> force fields can be grouped as provided above, irrespective of the actual form of the terms.

In a theoretical force field parametrization,  $E_{\text{tot}}$  (and  $\Delta E_{\text{tot}}$  relative to a reference structure) can be calculated quantum chemically, but a nonambiguous breakdown of the energy terms is difficult. Even in the simplest ester all energy contributions but the 1-N ( $N \geq 5$ ) nonbonded interactions are present. By the selection of a special conformation, some terms (proper and improper torsions) may be kept constant when the molecule is slightly distorted, but the nonbonded terms vary upon any geometric changes.

In the present study, the *cis*-ester conformation was selected with a basically planar heavy-atom moiety to obtain the C-S stretching and the new bond angle parameters. Although symmetry unrestricted geometry optimizations were performed in most cases, the nearly coplanar arrangement of the heavy atoms did not change either for the cis methyl acetate or thioacetate. Both  $E_{\text{str}}$  and  $E_{\text{bend}}$  were calculated in the harmonic oscillator approximation,  $E(X) = \frac{1}{2}k_X(X - X_0)^2$  where  $X$  refers to the corresponding distance and bond angle, and  $X_0$  is the reference value from Table 1. By a curve-fitting procedure, the  $k_X$  force constant can be determined.

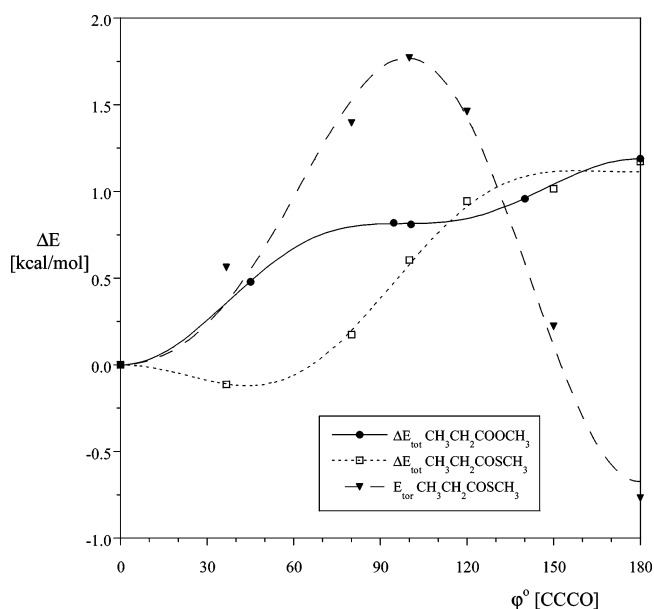
As mentioned before, the goal of the present parametrization process is providing parameters for the thioester moiety usable in the GROMACS package. These new parameters must be in



TABLE 4: Solvent Effects on the Methyl Acetate and Methyl Thioacetate Conformer Energies<sup>a</sup>

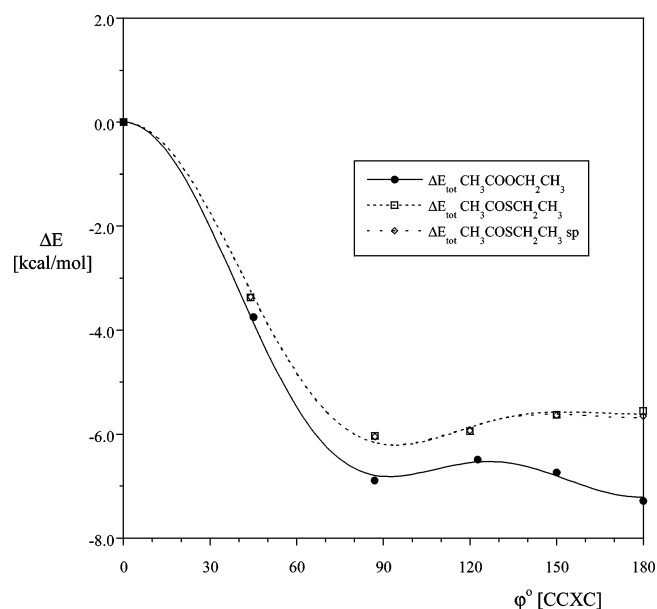
	$E_{\text{supol}}$	$1/2 E_{\text{elst}}^{\text{ss}}$	$G_{\text{dr}}$	$G_{\text{c}}$	$G_{\text{drc}}$	$G_{\text{solv}}$	DM
CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub>							
chloroform ( $\epsilon = 4.7$ )							
cis	0.10	-1.79	-8.26	8.89	0.63	-1.06	2.11
TS	0.23	-2.71	-8.17	8.99	0.82	-1.66	3.94
trans	0.39	-3.85	-8.20	8.79	0.59	-2.87	5.39
acetone ( $\epsilon = 20.5$ )							
cis	0.18	-2.42	-8.79	8.77	-0.02	-2.26	2.19
TS	0.42	-3.75	-8.69	8.86	0.17	-3.15	4.10
trans	0.69	-5.32	-8.73	8.67	-0.06	-4.69	5.60
acetonitrile ( $\epsilon = 35.7$ )							
cis	0.20	-2.51	-7.86	10.59	2.73	0.42	2.20
TS	0.46	-3.90	-7.77	10.71	2.94	-0.51	4.12
trans	0.74	-5.54	-7.81	10.47	2.66	-2.14	5.63
water ( $\epsilon = 78.4$ )							
cis	0.54	-5.01	-10.86	12.37	1.51	-2.95	2.30
TS	0.94	-6.68	-10.73	12.50	1.77	-3.97	4.32
trans	1.53	-8.98	-10.79	12.22	1.43	-6.02	5.96
CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub>							
chloroform ( $\epsilon = 4.7$ )							
cis	0.09	-1.48	-9.42	9.96	0.54	-0.85	1.52
TS	0.16	-2.02	-9.30	10.17	0.87	-0.99	3.41
trans	0.30	-2.78	-9.40	9.91	0.51	-1.97	5.02
acetone ( $\epsilon = 20.5$ )							
cis	0.15	-2.00	-10.00	9.83	-0.17	-2.02	1.58
TS	0.29	-2.78	-9.87	10.04	0.17	-2.33	3.55
trans	0.54	-3.85	-9.96	9.78	-0.18	-3.49	5.23
acetonitrile ( $\epsilon = 35.7$ )							
cis	0.16	-2.07	-8.95	11.90	2.95	1.04	1.59
TS	0.31	-2.89	-8.83	12.15	3.32	0.74	3.57
trans	0.58	-4.01	-8.92	11.83	2.91	-0.52	5.27
water ( $\epsilon = 78.4$ )							
cis	0.47	-4.13	-12.36	13.96	1.60	-2.07	1.70
TS	0.62	-4.93	-12.20	14.25	2.05	-2.26	3.70
trans	1.34	-7.02	-12.31	13.87	1.56	-4.11	5.66

<sup>a</sup> Energies in kcal/mol.  $G_{\text{solv}}$  calculated with eq 3.  $G_{\text{drc}} = G_{\text{dr}} + G_{\text{c}}$ .



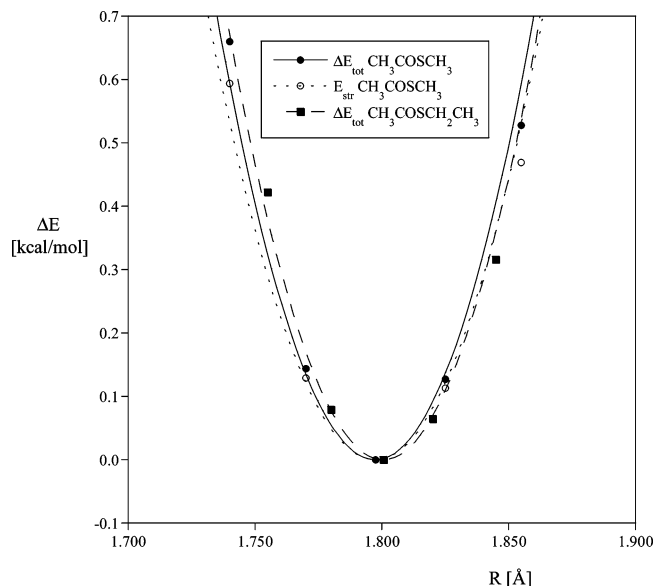
**Figure 3.** Rotational potential curves,  $\Delta E_{\text{tot}}$ , for CH<sub>3</sub>CH<sub>2</sub>COOCH<sub>3</sub> (filled circles) and CH<sub>3</sub>CH<sub>2</sub>COSCH<sub>3</sub> (empty squares) at the B3LYP/6-311++G\*\* levels.  $\varphi = 0^\circ$  corresponds to the C-C-C=O cis arrangement (Scheme 1, Table 2).  $E_{\text{tor}}$  is the derived torsional potential for CH<sub>3</sub>CH<sub>2</sub>COSCH<sub>3</sub> (Table 7).

accord with existing ones. The C=O, C(sp<sup>3</sup>)-C(sp<sup>2</sup>), and S-C(sp<sup>3</sup>) stretching force constants were taken from the GROMACS 3.1.4 ffgmxbon.itp file, but the equilibrium distances were set to their quantum chemically optimized values (Table 1). No C-H stretching parameters were considered, in

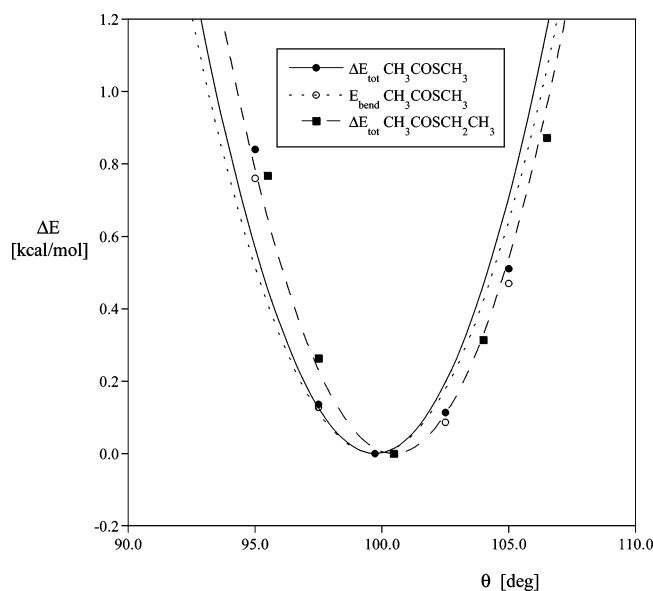


**Figure 4.** Rotational potential curves,  $\Delta E_{\text{tot}}$ , for CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub> (filled circles) at the B3LYP/6-311++G\*\* level, and for CH<sub>3</sub>COSCH<sub>2</sub>CH<sub>3</sub> (empty squares) at the B3LYP/6-311++G\*\* level. The  $\Delta E_{\text{tot}}$  curve with empty diamonds refers to the B3LYP/6-311++G\*\*//B3LYP/6-311++G\*\* single-point rotational potential for CH<sub>3</sub>COSCH<sub>2</sub>CH<sub>3</sub>.  $\varphi = 0^\circ$  corresponds to the C-X-C-C (X = O, S) cis arrangement (Scheme 1, Table 2).

conformity with the united CH<sub>2</sub> and CH<sub>3</sub> model of GROMACS. In calculations of  $\Delta E_{\text{tot}}$  as the function of the C(sp<sup>2</sup>)-S-C(sp<sup>3</sup>) angle in *cis*-methyl and *cis*-ethyl thioacetate, the angle values



**Figure 5.** Change of the total energy,  $\Delta E_{\text{tot}}$ , as a function of the C-S distance for  $\text{CH}_3\text{COSCH}_3$  (filled circles) and for  $\text{CH}_3\text{COSCH}_2\text{CH}_3$  (filled squares).  $E_{\text{str}} = 1/2 k_{\text{R}}(R-R_0)^2$  (empty circles) is the derived  $\text{C}(\text{sp}^2)\text{-S}$  harmonic bond stretching potential for  $\text{CH}_3\text{COSCH}_3$  (Table 7).



**Figure 6.** Change of the total energy,  $\Delta E_{\text{tot}}$ , as a function of the C-S-C angle for  $\text{CH}_3\text{COSCH}_3$  (filled circles) and for  $\text{CH}_3\text{COSCH}_2\text{CH}_3$  (filled squares).  $E_{\text{bend}} = 1/2 k_{\theta}(\theta-\theta_0)^2$  (empty circles) is the derived  $\text{C}(\text{sp}^2)\text{-S-C}(\text{sp}^3)$  harmonic bond bending potential for  $\text{CH}_3\text{COSCH}_3$  (Table 7).

varied in the range  $95\text{--}106.5^\circ$ , including the optimum value of  $105.5^\circ$  for the *trans*-methyl thioacetate (Figure 6).

To calculate the  $\text{O}=\text{CS}$  and  $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)\text{-S}$  bond angle parameters (and also the  $\text{CC}=\text{O}$  bending parameters for thioesters), the four atoms were forced to be exactly coplanar, resulting in the sum of the  $\text{OCS}$ ,  $\text{CCS}$ , and  $\text{CCO}$  bond angles to be equal to  $360^\circ$ . Nine different combinations of the bond angles were calculated for methyl thioacetate. The reference angles were set to the optimized values in the *cis* methyl thioacetate. The underscored angle value (Table S1) was kept fixed, and the rest of the molecule was optimized.

With a coplanar heavy atom moiety, the proper and improper torsion energies are equal to zero. Without 1-5 or larger

nonbonded interactions in methyl thioacetate, the quantum chemically calculated relative total energy was set to

$$\Delta E_{\text{tot}} = \Delta E_{\text{str}} + \Delta E_{\text{bend}} + \Delta E_{\text{elst}}(1-4) + \Delta E_{\text{vdW}}(1-4) \quad (5)$$

where all terms referred to the value calculated for the minimum energy structure. (In the reference state, both the  $E_{\text{str}}$  and  $E_{\text{bend}}$  terms are equal to zero, but the nonbonded terms have nonzero values even here.) The 1-4 interaction terms were, however, disregarded in calculating  $\Delta E_{\text{str}} + \Delta E_{\text{bend}}$ , as discussed later. Then the relative energy at some nonequilibrium geometry was assigned to the sum of  $\text{C}(\text{H}_3)\text{-C}$ ,  $\text{C}=\text{O}$ ,  $\text{C-S}$ , and  $\text{S-C}(\text{H}_3)$  stretching and the  $\text{C}(\text{H}_3)\text{-C}=\text{O}$ ,  $\text{O}=\text{C-S}$ ,  $\text{C}(\text{H}_3)\text{-C-S}$ , and  $\text{C-S-C}(\text{H}_3)$  bending energy terms, all of the form of  $1/2 k_{\text{X}}(X - X_0)^2$ . In the first step of a mutual refinement process, the quantum-chemically calculated  $\Delta E_{\text{tot}}(\text{CS})$  curve was set equal to  $1/2 k_{\text{CS}}(R(\text{CS}) - R(\text{CS})_0)^2$  (Figure 5). The starting values for the  $\text{CCO}$ ,  $\text{OCS}$ ,  $\text{CCS}$  bending force constant were obtained by a multivariable regression analysis using nine different combinations for the three angles (Table S1). The first approximation for the  $\text{CSC}$  bending force constant was obtained from the parabolic fit to the points of  $\Delta E_{\text{tot}}(\text{CSC})$  in Figure 6. In the next step, all stretching and bending energies were considered in  $\Delta E_{\text{tot}}(\text{CS})$ , with  $k$  values from the first approximations for the angles, and also using nonoptimized  $k$  values from the GROMACS file. The missing  $k_{\text{CS}}$  was obtained from a parabolic fit. This second approximation for  $k_{\text{CS}}$  was used in regression calculations for obtaining the second approximation values for the bending force constants. The iterative procedure was repeated for two more steps, reaching a change of less than 1% for the parameter values.

The  $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)\text{-C}(\text{sp}^2)\text{-S}$  torsion potential was calculated from energy data for methyl thiopropanoate. The  $\text{O}=\text{C-S-C}(\text{H}_3)$  moiety remained basically coplanar, thus the corresponding improper torsion energy was accepted as zero. Having the bond lengths and angles from quantum chemical calculations, and force constants from the above estimates,  $\Delta E_{\text{tot}} - (\Delta E_{\text{str}} + \Delta E_{\text{bend}}) - \Delta E(\text{nonbonded})$  was calculated and set equal to  $\Delta E_{\text{tor}}$ , the change in the torsion energy. Since the GROMACS force field assigns zero atomic charges to the united  $\text{CH}_2$  and  $\text{CH}_3$  atoms, the nonbonded interaction energies reduced to the  $\Delta E_{\text{vdW}}(1-4)$  and  $\Delta E_{\text{vdW}}(1-5)$  van der Waals terms. (In methyl thiopropanoate, the  $\text{CH}_3\cdots\text{CH}_3$  interaction is of the 1-5 type.)

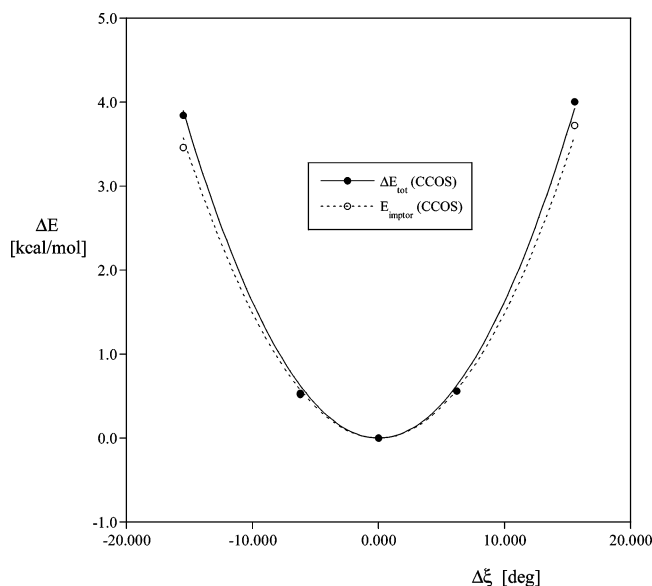
The rotation of the methyl group from the  $\text{C-C-C}=\text{O}$  *cis* arrangement to the *trans* position may also be considered, however, as a rotation from the  $\text{CCCS}$  *trans* to  $\text{CCCS}$  *cis* position. Thus, in this case the net torsion potential is a sum of two contributions: those of the  $\text{CCCO}$  and  $\text{CCCS}$  torsion potentials with  $\varphi$  and  $\psi$  torsion angles, respectively. In the studied conformations  $\varphi + \psi \approx 180^\circ$ , but at the out-of-plane motion of the  $\text{C}(\text{sp}^2)$  atom two independent torsion energy contributions have to be considered.

The  $\text{CCCS}$  torsion potential calculated here is a force-field dependent one, because the already existing  $\text{CCCO}$  potential,  $E_{\text{tor}}(\text{CCC}=\text{O}) = 0.1(1 + \cos 6\varphi)$  kcal/mol has been applied in its development. Values in Table 2 were derived for a more flexible torsion potential:

$$V = V_0 + 1/2[V_1(1 + \cos\psi) + V_2(1 - \cos 2\psi) + V_3(1 + \cos 3\psi)] \quad (6)$$

where  $\psi = 180^\circ - \varphi$ .

The  $\text{O}=\text{C-S-C}$  torsion potential and the out of plane (improper torsion) parameters were estimated in a coupled iterative process by using data for the methyl- and ethyl



**Figure 7.** Change of the total energy,  $\Delta E_{\text{tot}}$ , as a function of the  $\text{C}(\text{sp}^2)\text{C}(\text{sp}^3)\text{OS}$  improper torsion angle for  $\text{CH}_3\text{COSCH}_3$  (filled circles) and the derived  $E_{\text{imptor}} = \frac{1}{2} k_{\xi}(\xi - \xi_0)^2$  (empty circles) harmonic  $\text{C}(\text{sp}^2)\text{C}(\text{sp}^3)\text{OS}$  improper torsion potential (Table 7).

thioacetate, respectively. In the first step,  $\Delta E_{\text{tor}}(\text{OCSC})$  was set equal to  $\Delta E_{\text{tot}}(\text{OCSC}) - (\Delta E_{\text{str}} + \Delta E_{\text{bend}} + \Delta E_{\text{vdW}}(1-4))$  and a curve fit, according to eq 6 with conditions  $V_0 = -V_1 - V_3$ , was performed. Quantum chemical values for  $\Delta E_{\text{tot}}(\text{OCSC})$  were taken as they appear in Figure 2. In calculation of  $\Delta E_{\text{imptor}}(\text{CCOS})$  it was studied whether the emergence of the carbonyl carbon toward or away from the gauche methyl group in the  $\text{C}-\text{S}-\text{CH}_2-\text{CH}_3$  moiety has a remarkable effect on the distortion energy. The improper torsion angle was defined as the angle of the planes  $\text{C}(\text{H}_3)\text{CO}$  and  $\text{C}(\text{H}_3)\text{OS}$ . Figure 7 shows the results from energy optimization calculations keeping the angle of planes at about  $\xi = \pm 6^\circ, \pm 15^\circ$ . Taking these values,  $\Delta E_{\text{imptor}}(\text{CCOS}) = \Delta E_{\text{tot}}(\text{CCOS}) - (\Delta E_{\text{str}} + \Delta E_{\text{bend}} + \Delta E_{\text{vdW}}(1-4))$  was accepted as a first approximation, and a parabolic fit of the form  $\Delta E_{\text{imptor}}(\xi) = k_{\xi}(\xi - \xi_0)^2$  ( $\xi_0 = 0$ ) was performed for determining  $k_{\xi}$ . In further steps,  $\Delta E_{\text{tor}}(\text{OCSC})$  was considered in calculating  $\Delta E_{\text{imptor}}(\text{CCOS})$  and vice versa until self-consistency was obtained.

When the GROMACS force field is used, united-atom  $\text{CH}_2$  and  $\text{CH}_3$  groups with zero charges are considered. This is a serious simplification, because even small geometric changes for polar molecules can result in remarkable redistribution of the electron density. To study this effect, net atomic charges (Tables 5 and S3–S5) were calculated by a fit to the gas-phase molecular electrostatic potential, using the CHELPG procedure.<sup>22</sup> These values were used in calculating the effect of the 1–4 and 1–5 electrostatic interactions on bond stretching and bond angle bending potentials. The van der Waals interactions were calculated as  $(C_{12}/R_{ij}^{12} - C_6/R_{ij}^6)$ . The C12 and C6 constants were taken from the ffgmxnb.itp GROMACS file, and the combination rule of  $C_{ij} = (C_{ii}C_{jj})^{1/2}$  was applied where needed (Tables S3 and S4).

## Results and Discussion

**Methyl Acetate and Methyl Thioacetate.** Table 1 contains the calculated geometric parameters for  $\text{CH}_3\text{COOCH}_3$  and  $\text{HCOSCH}_3$ , calculated both at the MP2/6-311++G\*\* and B3LYP/6-311++G\*\* levels. The B3LYP method predicts all bond angles in good agreement with the experiment, whereas the MP2 method underestimates the  $\text{C}-\text{X}-\text{C}$  angles ( $\text{X} = \text{O}$ ,

S) by  $1.6\text{--}2.1^\circ$ . In the MP2 method, the  $\text{C}=\text{O}$  and the  $\text{C}-\text{S}$  distances are too long and too short, respectively. On the other hand, B3LYP overestimates the  $\text{S}-\text{CH}_3$  distance by  $0.025 \text{ \AA}$ .

No experimental data are available for the trans methyl acetate and even for the cis-methyl thioacetate structures. The two theoretical methods are consistent, and the corresponding parameters for the cis and trans conformers differ generally by nearly the same amount at the two levels. The largest geometric change was calculated for the  $\text{C}-\text{X}-\text{C}$  angle, which increases by  $5\text{--}6^\circ$  throughout the methyl rotation from the OCXC cis to the trans position. The  $\text{C}-\text{X}$  bond lengths also increase in this transformation by up to  $0.01 \text{ \AA}$ . The modification of the  $\text{X}-\text{CH}_3$  bond length is, however, different for oxo and thioesters wherein the  $\text{O}-\text{CH}_3$  distance decreases but the  $\text{S}-\text{CH}_3$  bond length increases throughout the cis to trans transformation.

The basis set effect on the calculated geometric parameters was studied by utilizing the aug-cc-pVTZ basis set at the MP2 and B3LYP level in geometry optimizations. Obtained values are in parentheses in Table 1 for the cis  $\text{CH}_3-\text{C}(=\text{O})-\text{O}-\text{CH}_3$  and  $\text{H}-\text{C}(=\text{O})-\text{S}-\text{CH}_3$ . Lengths of the single bonds generally shorten, lengths of the  $\text{C}=\text{O}$  double bond remain practically unchanged in the two molecules. Since in general single bonds were calculated too long with the 6-311++G\*\* basis set, the basis set increase is favorable in this respect. The  $\text{C}-\text{O}$  bond length in methyl acetate, however, further shortens instead of elongating, as would be needed for approaching the experimental value. Changes in the bond angles are small, up to  $0.3^\circ$ , thus the  $\text{C}-\text{O}-\text{CH}_3$  and  $\text{C}-\text{S}-\text{CH}_3$  bond angles remain underestimated by about  $2^\circ$  at the MP2 level even when the aug-cc-pVTZ basis set is used in the geometry optimization. At the B3LYP level, the  $\text{S}-\text{C}$  bond length is still too long by about  $0.02 \text{ \AA}$ .

The MP2/6-311++G\*\* and B3LYP/6-311++G\*\* rotational potentials for the  $\text{CH}_3-\text{C}(=\text{O})-\text{X}-\text{CH}_3$  molecules ( $\text{X} = \text{O}, \text{S}$ ) are compared in Figures 1 and 2. By utilizing a four-term expression for the rotational potential of the form in eq 6 (differing from the OPLS potential<sup>23</sup> by adding the  $V_0 = -(V_1 + V_3)$  term and setting all phase-angles to zero), it was possible to obtain good fits to the calculated relative energies. For the reference structure, the  $\varphi$  ( $\text{O}=\text{C}-\text{X}-\text{C}$ ) =  $0^\circ$ , cis conformation has been chosen in every case. The potential parameters are provided in Table 2.

The calculated barriers for the  $\text{CH}_3-\text{C}(=\text{O})-\text{O}-\text{CH}_3$  transition state (TS) are  $13.45$  ( $\varphi = 101.9^\circ$ ) and  $13.35$  kcal/mol ( $\varphi = 100.3^\circ$ ) at the MP2 and B3LYP levels, respectively. For  $\text{CH}_3-\text{C}(=\text{O})-\text{S}-\text{CH}_3$ , the TS energies are  $11.18$  ( $\varphi = 93.8^\circ$ ) and  $11.80$  kcal/mol ( $\varphi = 94.6^\circ$ ) at the two levels (Table 3). Thus, the torsion angles for the TS structures are very close to each other at the two levels, and the barrier heights differ also moderately. The relative energies for the trans conformers ( $\varphi = 180.0^\circ$ ) are  $8.40$  and  $7.97$  kcal/mol with MP2 and B3LYP methods, respectively, providing deviation of only  $0.43$  kcal/mol for  $\text{CH}_3-\text{C}(=\text{O})-\text{O}-\text{CH}_3$  (Table 3). The relative trans conformational energies for  $\text{CH}_3-\text{C}(=\text{O})-\text{S}-\text{CH}_3$  are  $4.91$  and  $4.64$  kcal/mol, respectively. Overall, the parallel calculations provide fairly close results with the 6-311++G\*\* basis set both for the oxo- and thioesters.

Table 3 also contains the thermal corrections and the gas-phase free energy for the two molecules calculated at the B3LYP/6-311++G\*\* level. The  $\Delta H(T)$  and  $-\Delta S(T)$  terms are of opposite signs; thus there is a partial cancellation in their sum in eq 1. As a result, the relative free energies for the TS and trans-methyl acetate are close to the relative gas-phase energies. For methyl thioacetate, the relative entropy is strongly

reduced ( $-T\Delta S(T)$  is a fairly large positive number). Since the vibrational entropy contribution is the largest for the small frequencies, the entropy decrease is not surprising for the transition state where the otherwise relatively small frequency of the torsional reaction coordinate is imaginary and has not been counted. The considerable entropy decrease for the *trans*-methyl thioacetate, mainly in comparison with the corresponding value for methyl acetate, is much more surprising. The two lowest frequencies correspond to methyl torsions in both molecules and in both conformers. The C(methyl)⋯C(methyl) distances are 3.69 and 2.82 Å for the *cis* and *trans* methyl acetate conformers, respectively. The corresponding values for methyl thioacetate are 4.18 and 3.07 Å. Methyl torsions are the least coupled with the largest C⋯C distance, resulting in a low, 15.7  $\text{cm}^{-1}$  frequency for the *cis* methyl thioacetate and a frequency of 86.4  $\text{cm}^{-1}$  for the *trans* form. For methyl acetate two closer frequencies, 47.1 and 73.3  $\text{cm}^{-1}$ , were calculated for the *cis* and *trans* forms, respectively. The lower frequency corresponds also here to the less coupled methyl torsions with more separated C⋯C atoms in the *cis* conformation. The large difference in the lowest thioester frequencies causes a change of 1.00 kcal/mol in the  $T\Delta S(T)$  term in the harmonic oscillator approximation. Overall, the gas-phase energy and the free energy are similar for methyl acetate regarding both the rotation to the barrier and the *cis*–*trans* separation. However, the free energy is higher by 1.3–1.5 kcal/mol than the corresponding energy value both for the barrier and the *cis*–*trans* separation for methyl thioacetate.

The calculation results in solution phase, including values for the *cis* conformer, are summarized in Table 4.  $E_{\text{suppl}} = E_{\text{int}}^{\text{s}} - E(\text{gas})$  accounts for the change of the internal energy upon solvation. This term gradually increases in parallel with the increasing dielectric constant, but even the largest value is only 1.5 kcal/mol (*trans*-methyl acetate in water). Generally, the value increases throughout the *cis* to TS to *trans* transformations for both esters in all solvents studied. The corresponding values, however, are larger for the oxo- than the thioesters.

The same trend is valid for the  $\frac{1}{2}E_{\text{elst}}^{\text{ss}}$  term with a negative sign. The (half of) the solute–solvent interaction energy becomes gradually more negative with increasing dielectric constant; the value is always most negative for the *trans* conformer, and the corresponding values for the thioester are less negative. Thus, the *trans* form seems to be the most polarizable conformation for both type of esters.

Dispersion–repulsion and cavity formation terms for the present structures are larger, in absolute value, than the electrostatic terms (Table 4). This finding is noticeable if considering that the dipole moments are as large as about 6 D for some conformers of these neutral molecules. (For ionic<sup>24a</sup> and zwitterionic<sup>24b</sup> species,  $\frac{1}{2}E_{\text{elst}}^{\text{ss}}$  is the leading term.) The  $G_{\text{dr}}$  and  $G_{\text{c}}$  terms are, however, always of opposite sign, and their sum,  $G_{\text{drc}}$  is already smaller (in absolute value) than  $\frac{1}{2}E_{\text{elst}}^{\text{ss}}$  for the studied system. Overall,  $G_{\text{solv}}$  becomes gradually more negative in the *cis*, TS, and *trans* series, in line with the in-solution dipole moment, DM.

The trend in  $G_{\text{solv}}$  means that the *trans* form is always preferably solvated relative to the *cis*. By addition of the  $\Delta G_{\text{solv}} = G_{\text{solv}}(\text{TS or trans}) - G(\text{cis})$  values to the relative gas-phase free energies, the in-solution conformational free energies can be obtained (eq 4).  $\Delta G_{\text{solv}}$  for the *trans*-methyl acetate in water has been calculated as  $-6.02 - (-2.95) = -3.07$  kcal/mol. The differential solvent effect is less than 3 kcal/mol for the *trans* conformer in other solvents. Using the  $\Delta G$  value from Table 3, thus accepting the relevance of the gas-phase relative thermal

correction, eq 4 gives  $\Delta G(\text{sol}) = 8.13 - 3.07 = 5.06$  kcal/mol. The gas-phase barrier (TS) decreases from 13.10 to 12.08 kcal/mol in aqueous solutions. The relative free energy for the *trans*-methyl thioacetate in aqueous solution is  $\Delta G(\text{sol}) = 6.13 - 2.04 = 4.09$  kcal/mol, whereas the barrier decreases only by 0.19 kcal/mol to 12.89 kcal/mol.

If the free energy difference is at least 2.7 kcal/mol at  $T = 298$ , then the fraction of the less stable conformer is less than 1% in the equilibrium mixture. Thus, this study predicts that only the *cis*-methyl acetate and the *cis*-methyl thioacetate are expected to be present in any common solvents if a conformational equilibrium has been reached.

By performing explicit solvent Monte Carlo simulations, Evanseck et al.<sup>25</sup> found  $\Delta G_{\text{solv}} = -3.0 \pm 0.2$  kcal/mol relative solvation free energy for the *trans* methylacetate, in agreement with the present value of  $-3.07$  kcal/mol. Byun et al.<sup>7c</sup> carried out a combined QM/MM simulation study where the polarization of the solute was also considered. Their calculated  $\Delta G_{\text{solv}}$  value of  $-4.4 \pm 0.5$  kcal/mol still maintains the *cis* conformation as almost the exclusive form in aqueous solution.

In the acetonitrile solvent, Monte Carlo studies<sup>25</sup> provided  $\Delta G_{\text{solv}}$  of  $-2.7 \pm 0.1$  kcal/mol for the *trans*-methyl acetate compared to the present value of  $-2.56$  kcal/mol. Thus, the Monte Carlo and the present PCM results agree very well both in water and in acetonitrile. Using Onsager's reaction field model,<sup>26</sup> Wiberg and Wong<sup>27</sup> calculated  $\Delta G_{\text{solv}} = -3.3$  kcal/mol in the acetonitrile solution modeled with a dielectric constant of 35.9.

Regarding our  $G_{\text{solv}}$  values in acetonitrile, the solvent effect itself is positive for the *cis* conformer of both the oxo and thioester. The results suggest that solvation is unfavorable for the *cis* conformer in acetonitrile. The *trans* form dissolves, but a conformational change to the internally more stable *cis* form in solution would result in the return to the gas phase. These authors believe that the calculated values indicate a parametrization problem for acetonitrile in the PCM approach. The positive  $G_{\text{solv}}$  has been attributed to the large  $G_{\text{drc}}$  value (Table 4), which may indicate exaggerated cavity formation energy,  $G_{\text{c}}$  or the underestimation of the dispersion–repulsion  $G_{\text{dr}}$  term. This possible weakness disappears in  $\Delta G_{\text{solv}}$  (see the close value to that from the Monte Carlo study above), but would affect the calculated free energy of solvation for gas-phase molecules in acetonitrile solvent.

**Methyl Propanoate and Methyl Thiopropanoate.** B3LYP/6-311++G\*\* rotational potential curves for these two molecules, where the methyl group, as a unit, is rotated about the  $\text{CH}_2\text{--C}$  bond, are compared in Figure 3. On the basis of the results with methyl acetate/thioacetate, the  $\text{O}=\text{C}\text{--X}\text{--C}$  torsion angle was set to  $0^\circ$  (*cis* ester conformation) at the beginning of any calculations with different  $\varphi(\text{CCCCO})$  values. Although the  $\text{OCXC}$  torsion angle was allowed to change throughout the optimization while  $\varphi$  was kept at some specific value, the nearly perfect *cis* arrangement of the  $\text{OCXC}$  moiety was reserved in all cases.

In contrast to the close similarity of the curves in Figures 1 and 2, the methyl rotation about the  $\text{CH}_2\text{--C}$  bond is sensitive to the chemical character of the X atom in the ester/thioester group. For methyl propanoate, the  $\varphi(\text{C}\text{--C}\text{--C}=\text{O}) = 0^\circ$ , *cis* arrangement is the global energy minimum. A transition state structure with  $\Delta E$  barrier energy of 0.821 kcal/mol was assigned at  $94.55^\circ$ . A very mild local minimum was found at  $\varphi = 100.59^\circ$  with  $\Delta E = 0.809$  kcal/mol, and then further torsion leads to another TS at  $\varphi = 180^\circ$  with  $\Delta E = 1.19$  kcal/mol. This profile is qualitatively similar to the rotation potential calculated at the



4-21G level by Klimkowski et al.,<sup>8</sup> where, however, a barrier of 1.95 kcal/mol ( $\varphi = 75^\circ$ ) and a local minimum of 1.07 kcal/mol ( $\varphi = 121.9^\circ$ ) were identified.

In the global energy-minimum cis conformation, the methyl hydrogens of the propanoic acid moiety are in staggered positions relative to the hydrogen atoms in the  $-\text{CH}_2-$  group. A rotation of this methyl group by about  $60^\circ$  (eclipsed methyl) represents a transition state with an energy increase of 2.18 kcal/mol. If the ester-methyl group is rotated into the  $\text{O}=\text{C}-\text{O}-\text{C}$  trans position, the calculated relative energy (7.99 kcal/mol) is practically equal to that for methyl acetate (Table 3).

The rotational potential for methyl thiopropanoate has a shallow minimum,  $\Delta E = -0.11$  kcal/mol at  $\varphi(\text{C}-\text{C}-\text{C}=\text{O}) = 36.7^\circ$ , corresponding to  $\psi(\text{C}-\text{C}-\text{C}-\text{S})$  about  $143.3^\circ$ . (The  $\text{C}-\text{C}(\text{O})-\text{S}$  atoms are very close to being coplanar in all stable conformations, thus  $\varphi + \psi \approx 180^\circ$ .) There were no transition state and local minimum sought in the  $\varphi = 120-150^\circ$  region, where a plateau was calculated with set torsion angles. The conformation at  $\varphi = 180^\circ$  corresponds to a transition state with relative energy of  $\Delta E = 1.17$  kcal/mol. When the ester-methyl group was rotated to the  $\text{O}=\text{C}-\text{S}-\text{C}$  trans position, the energy increased by 4.42 kcal/mol relative to the cis form, which is also not a local energy minimum as shown in Figure 3. The cis-trans energy separation is, however, close to the corresponding value of 4.64 kcal/mol for methyl thioacetate (Table 3).

In Table 2, the coefficients of a four member Fourier series approximation (with three cosine terms) of the potential curves are summarized. If an atom, like the  $\text{C}(\text{sp}^2)$  atom for esters, allows a branch along the torsion path, the assignment of the torsion potential to a specific  $\text{A}-\text{B}-\text{C}-\text{D}$  moiety is difficult. In methyl acetate/thioacetate, the quantum chemically calculated rotational potential must have contributions both from the  $\text{O}=\text{C}-\text{X}-\text{C}$  and  $\text{C}-\text{C}-\text{X}-\text{C}$  torsions. In the case of methyl propanoate/thiopropanoate, the considered potential curves have contributions both from the  $\text{C}-\text{C}-\text{C}=\text{O}$  and  $\text{C}-\text{C}-\text{C}-\text{X}$  ( $\text{X}$  is oxygen or sulfur) torsions and from changes in the total energy due to geometric changes in bond lengths and bond angles. A breakdown of the net torsion potential energy to different types of energy contributions is not a straightforward procedure. Hence, a strategy will be proposed in the section dealing with the development of molecular mechanics parameters based on quantum chemical calculations.

**Ethyl Acetate and Ethyl Thioacetate.** In Figure 4, the reference conformation is the  $\varphi(\text{CH}_3-\text{CH}_2-\text{X}-\text{C}) = 0^\circ$  structure (Scheme 1). Similar to the previous procedure, an unforced cis  $\text{O}=\text{C}-\text{X}-\text{C}$  arrangement was chosen at the beginning of any optimizations with different  $\varphi$ 's, and the basically cis ester conformation was reserved in all cases.

The  $\varphi = 0^\circ$  conformers are of high relative energy structures for both esters. In this conformation, the methyl group is close to the carbonyl oxygen and strong repulsion exists in this structural arrangement. Since the  $\varphi = 0^\circ$  torsion angle was fixed throughout the optimization, geometry relaxation was possible only at the expense of increases in bond lengths and bond angles. The oxoester has a local energy minimum of  $-6.89$  kcal/mol with a gauche methyl group at  $\varphi = 87.0^\circ$ , whereas the global minimum was found with the trans methyl position at  $\varphi = 180^\circ$ , with a relative energy of  $-7.28$  kcal/mol. The transition state structure at  $\varphi = 122.7^\circ$  has an energy of  $-6.49$  kcal/mol, providing a barrier of 0.79 kcal/mol for the CCOC rotation of the trans methyl group to its gauche position. In a calculation with the  $\text{O}=\text{C}-\text{O}-\text{CH}_2$  arrangement of about  $180^\circ$ , and maintaining the CCOC torsion angle of about  $180^\circ$ , the

calculated relative energy is 7.60 kcal/mol, which also is close to the relative value for the trans ester conformation calculated for methyl acetate (Table 3).

The present CCOC torsional results are in contrast to those at the 4-21G level by Manning et al.<sup>9</sup> These authors found the gauche methyl position as the lowest energy conformation at  $\varphi = 81.0^\circ$ , and the trans methyl arrangement is higher in energy by 0.2 kcal/mol at  $\varphi = 180^\circ$ . The barrier from the gauche to the trans form was estimated at 0.7 kcal/mol.

For ethyl thioacetate, two almost coinciding curves are indicated in Figure 4. As mentioned in the methodology section, geometry optimizations at the B3LYP/6-311++G\*\* level failed for this molecule at some  $\varphi$  values because of basis set orthogonality errors found by the Gaussian. Thus, the curves were constructed based on B3LYP/6-311+G\*\* optimized geometry and energy data, and energy values from B3LYP/6-311++G\*\*//B3LYP/6-311+G\*\* single-point calculations.

The rotational potential has a single-minimum character, in contrast to the corresponding curve for the oxoester. The minimum appears at  $\varphi = 87.1^\circ$  from B3LYP/6-311+G\*\* optimizations. A potential curve calculated at the B3LYP/6-31G\* level provided a shape very similar to that in Figure 4, with a minimum at  $\varphi = 83.3^\circ$ . Optimization of the minimum energy conformer was successful at the B3LYP/6-311++G\*\* level, too, providing  $\varphi = 85.5^\circ$  for the optimal CCSC torsion angle. Thus, the B3LYP calculations provided only slightly different optimal CCSC torsion angles in the  $83-87^\circ$  range even with basis sets as different as 6-31G\* and 6-311++G\*\*. The relative minimum energies are almost equal:  $-6.07$ ,  $-6.03$ , and  $-6.05$  kcal/mol with the 6-31G\* and 6-311+G\*\* basis sets, and from 6-311++G\*\*//6-311+G\*\* calculations, respectively.

The conformer with  $\varphi = 180.0^\circ$  seems to be a transition structure. The energy increases by some hundredths of a kilocalorie per mole in the  $\varphi = 150.0-180^\circ$  range from B3LYP/6-311+G\*\* calculations, and decreases by 0.01 kcal/mol at  $\varphi = 180.0^\circ$  at the B3LYP/6-311++G\*\*//B3LYP/6-311+G\*\* level. A very similar plateau was found at the B3LYP/6-311+G\*\* level by Bohn and Wiberg<sup>13</sup> for ethyl thioformate. Thus, it seems that higher-level calculations are necessary for determining whether the trans methyl arrangement corresponds to a real local minimum structure for ethyl thioacetate. At the present level of theory, only a very shallow minimum has been obtained on the rotational potential at  $\varphi = 180.0^\circ$  which, however, may disappear if the zero-point energy correction is also considered. For several substituted thioformates and trifluorothioacetate this trans methyl conformer was not found experimentally.<sup>28</sup>

**Parameter Estimation.** As can be seen from eq 5,  $\Delta E_{\text{tot}}$  has contributions from the nonbonded energy terms in the case of any geometric changes. Thus, when stretching or bending potentials are being studied, the relative nonbonded energy terms have to be subtracted from the calculated relative total energy.

The van der Waals term, in the simplest case, is an atom-atom distance dependent pair-interaction energy function, although the actual mathematical form and parametrization vary in different force fields. Then the "recipe" for calculating the van der Waals interaction is provided for any conformations and in any distorted geometries.

Relevant calculation of the electrostatic term, however, raises many problems. The electrostatic term is generally calculated as the Coulomb energy of two separated point charges. The usefulness of a force field largely rests on the selected atomic charges. In molecular dynamics modeling of large systems, the software programs presently use molecular-geometry indepen-

**TABLE 5: Net Atomic Charges from CHELPG Fit to the B3LYP/6-311++G\*\* Molecular Electrostatic Potential**

	CH <sub>3</sub> -C(=O)-O-CH <sub>3</sub>					
	C		=O	-O-		
cis	0.902		-0.598			-0.462
TS	0.898		-0.550			-0.507
trans	0.906		-0.601			-0.475

	CH <sub>3</sub> -C(=O)-S-CH <sub>3</sub>			CH <sub>3</sub> -C(=O)-S-CH <sub>2</sub> -CH <sub>3</sub>		
	C	=O	S	C	=O	S
cis	0.650	-0.496	-0.279	0.592	-0.474	-0.344
TS	0.845	-0.534	-0.341			
trans	0.609	-0.490	-0.226			

	C-S			C-S				
	cis	1.740	0.654	-0.515	-0.264	1.755	0.606	-0.491
	1.798	0.650	-0.496	-0.279	1.801	0.592	-0.474	-0.344
	1.855	0.637	-0.478	-0.295	1.845	0.579	-0.457	-0.357

	CSC			CSC			
	95.00	0.546	-0.469	-0.254	95.50	0.575	-0.459
99.73	0.650	-0.496	-0.279	100.47	0.592	-0.474	-0.344
105.00	0.580	-0.474	-0.314	106.50	0.627	-0.491	-0.379

dent charges. Table 5 shows that the atomic charges for esters are not geometry independent. (The sum of the charges is not zero and the full set of charges calculated in the united methyl- and methylene-atom model is provided in Tables S3–S5.) Even Table 5 shows, however, that the atomic charges change considerably, and they must have large contributions to the relative molecular energies, if the total energy changes are up to only 1–2 kcal/mol (Figures 3, 5, and 6).

Comparison of methyl acetate and thioacetate indicates that the C(sp<sup>2</sup>) atom is much more positive in the oxoester than the thioester. This is not surprising given a more electronegative oxygen atom instead of a sulfur atom in methyl acetate. The two esters show, however, different trends in the electron redistribution throughout the methyl rotation. The atomic charge remains practically constant on the central C atom in the oxoester. In contrast, this C atom bears a 0.845 positive charge in the transition state for the thioester; a value more positive by 0.20–0.25 units than those in the planar forms, and the negative charge spreads out to the neighboring atoms. The S charge changes going from the cis to the trans conformation, while the corresponding oxygen charges are nearly constant in the planar methyl acetate conformers.

Calculated C and S charges show dependence on the length of the alkyl group, as revealed from a comparison of the *cis*-methyl and *cis*-ethyl thioacetates. The longer alkyl group increases the negative charge on the sulfur atom and the positive charge is decreased on the C atom, as compared to the methyl derivative. The electron redistribution slightly reduces the negative charge of the carbonyl oxygen.

Increase of the C–S bond length leads to similar trends in the changes of charges for the two thioesters. The negative charges decrease and increase on the O and S atoms, respectively, and the C atom becomes less positive at larger C–S separations. The similarity of the trends disappears, however, upon increasing the CSC angle. Although the negative charge increases on the S atom in both esters, the C and O charges change monotonically with ethyl thioacetate, but a maximum (in absolute values) was found for both atoms at the optimized geometry (CSC = 99.73°) of methyl thioacetate.

The calculated relative 1–4 electrostatic and van der Waals energies are compared in Table 6 for methyl thioacetate with different C–S bond lengths and O=C–S and C–S–C bond

**TABLE 6: 1–4 Electrostatic and van der Waals Energies for the *cis*-Methyl Thioacetate with Different Molecular Geometries<sup>a</sup>**

C–S	$\Delta E_{\text{elst}}$	$\Delta E_{\text{elst}}(\text{opt charges})$	$\Delta E_{\text{vdw}}$
1.740	-0.63	-0.08	0.11
1.770	-0.26	-0.05	0.05
1.798	0.0	0.0	0.0
1.825	0.32	0.03	-0.07
1.855	0.66	0.07	-0.13

OSC	$\Delta E_{\text{elst}}$	$\Delta E_{\text{elst}}(\text{opt charges})$	$\Delta E_{\text{vdw}}$
117.50	-0.71	-0.37	0.74
120.00	-0.21	-0.20	0.27
122.53	0.0	0.0	0.0
125.00	0.31	0.18	-0.30
127.50	0.37	0.44	-0.59

CSC	$\Delta E_{\text{elst}}$	$\Delta E_{\text{elst}}(\text{opt charges})$	$\Delta E_{\text{vdw}}$
95.00	1.87	-0.50	1.17
97.50	0.53	-0.24	0.46
99.73	0.0	0.0	0.0
102.50	-0.40	0.33	-0.47
105.00	-0.81	0.56	-0.67

<sup>a</sup> Energies are in kcal/mol, distances in Å, and angles in deg. “opt charges” in parentheses means that the atomic charges derived for the minimum energy structure were used in all calculations.

angles. The electrostatic terms strongly depend on whether the corresponding individual, electrostatic-potential fitted charges were utilized ( $\Delta E_{\text{elst}}$ ), or the charge set derived for the minimum energy structure was applied in all cases ( $\Delta E_{\text{elst}}(\text{opt charges})$ ).

When the C–S bond length is modified, the  $\Delta E_{\text{elst}}$  and  $\Delta E_{\text{elst}}(\text{oc})$  (meaning  $\Delta E_{\text{elst}}(\text{opt charges})$ ) terms differ considerably, although the trend (from negative to positive) is maintained. The sum  $\Delta E_{\text{elst}}(\text{oc}) + \Delta E_{\text{vdw}}$  is nearly zero in the considered range of the C–S separation. Throughout the OSC bending the trend for the two electrostatic series is still maintained; not even the values differ greatly. The  $\Delta E_{\text{vdw}}$  term cancels mostly, however, the  $\Delta E_{\text{elst}}$  term. Throughout the variation of the CSC angle, the trends are different for the two sets of the electrostatic energy, and there is no cancellation between the  $\Delta E_{\text{vdw}}$  and any electrostatic terms. The sum  $\Delta E_{\text{elst}}(\text{oc}) + \Delta E_{\text{vdw}}$  is 0.67 and -0.11 kcal/mol for CSC = 95.0 and 105.0°, respectively.  $\Delta E_{\text{tot}}$  as a function of the CSC angle

(Figure 6) is 0.84 and 0.51 kcal/mol at CSC = 95.0 and 105.0°, respectively. Thus, this course corresponds to an anharmonic potential with faster increase of the bending energy toward angle-closing as compared to angle-opening. Contributions to  $\Delta E_{\text{tot}}$  from the C–S stretching and other bond angle bending terms were estimated as a few hundredths of a kcal/mol (see below). If the  $\Delta E_{\text{elst}}(\text{oc}) + \Delta E_{\text{vdW}}$  term is considered,  $\Delta E_{\text{tot}} - (\Delta E_{\text{elst}}(\text{oc}) + \Delta E_{\text{vdW}}) \approx \Delta E_{\text{bend}}$  becomes 0.17 and 0.62 kcal/mol at CSC = 95.0° and 105.0°, respectively. Thus, consideration of the 1–4 nonbonded interactions would modify the CSC bending potential curve just opposite to that expected. The  $(\Delta E_{\text{elst}}(\text{oc}) + \Delta E_{\text{vdW}})$  sum changes by only 0.09 kcal/mol in the C–S = 1.740 to 1.855 Å range and hardly affects the  $\Delta E_{\text{str}}(\text{C–S})$  term. In contrast, consideration of the 1–4 interaction by the  $\Delta E_{\text{elst}} + \Delta E_{\text{vdW}}$  energy sum leads to a C–S stretching potential more anharmonic than calculated quantum chemically.

If one wants to be consistent with the GROMACS parametrization, then all 1–4 and 1–5 electrostatic interactions are zero for these small esters. A CH<sub>3</sub> or a CH<sub>2</sub> group is always involved in these interactions, and their united atom charges are zero in this force field. Then only the  $\Delta E_{\text{vdW}}$  energy is to be counted, and the  $\Delta E_{\text{tot}} - \Delta E_{\text{vdW}}$  term will reduce  $\Delta E_{\text{str}}$  and  $\Delta E_{\text{bend}}$  at shorter C–S distances and smaller CSC angles, respectively, and will increase these functions at larger C–S and CSC values (Table 6). This effect is, however, just opposite to that expected on the basis of the quantum chemical potential curves. Thus, it is not clear from this study whether the 1–4 and higher nonbonded interactions should (and if yes, how) or should not be considered in estimating the stretching and bending force constants. In the subsequent procedures nonbonded interaction energies were not considered when these force constants were determined.

From the B3LYP/6-311++G\*\* calculations, the C(sp<sup>2</sup>)–S distance is 1.798 and 1.801 Å in the cis methyl thioacetate and in the minimum-energy conformer (gauche methyl) of ethyl thioacetate, respectively (Tables S1 and S2). The two values are close, just like the equilibrium CSC bond angles (Figure 6): 99.73 and 100.47° for the methyl and ethyl esters, respectively (Tables S1 and S2). Using the mutual refinement procedure described in the Methods section, the new estimated force constants are provided in Table 7.

Torsion potentials can considerably differ from the  $\Delta E_{\text{tor}}$  (B3LYP) curve as seen in Figure 2. Although the basic characters of the  $E_{\text{tor}}(\text{CH}_3\text{COSCH}_3)$  and  $\Delta E_{\text{tot}}$  curves are similar, the relative torsion energy at  $\varphi = 180^\circ$  is 1.4 kcal/mol as compared to the  $\Delta E_{\text{tot}}$  value of 4.6 kcal/mol here. The difference, again, is due to 1.66 and 1.59 kcal/mol relative stretching-bending and van der Waals energies, respectively.

$E_{\text{tor}}(\text{CH}_3\text{COSCH}_3)$  is, in fact, the sum of the O=C–S–C and C–C–S–C torsion potentials. Following Cornell et al.,<sup>21a</sup> equal contributions of the OCSC and CCSC torsion potentials to the net  $E_{\text{tor}}(\text{CH}_3\text{COSCH}_3)$  were accepted. The OCSC cis, corresponding to the CCSC trans, arrangement is more stable than the OCSC trans, CCSC cis arrangement by about 1.4 kcal/mol. Since GROMACS requires determination of any torsion potentials with reference to the cis structure, the derived four-term fitting of the two torsion potentials (Table 7) differs slightly in the absolute values of the parameters. (The different signs are the consequence of the restriction  $E_{\text{tor}} = 0$  at  $\varphi = 0$ .)

The four-term OPLS potential is not, however, the standard one in GROMACS. Although these parameters can be utilized in developing the Ryckaert–Bellemans function, also available in this modeling package, the standard form for the proper torsion is a single-term expression,  $E_{\text{tor}} = k_\varphi(1 + \cos(n\varphi -$

**TABLE 7: Molecular Mechanics Parameters for the Thioester Moiety**

$E_{\text{str}} = 1/2k_R(R - R_0)^2$	$k_R^a$	$R_0^b$		
C(sp <sup>2</sup> )–S	322	1.800		
$E_{\text{bend}} = 1/2k_\theta(\theta - \theta_0)^2$	$k_\theta^c$	$\theta_0^d$		
O=C–S	122	122.5		
C–C=O	122	123.7		
C–C–S	86	113.8		
C–S–C	152	100.0		
$E_{\text{tor}}^e = V_0 + 1/2[V_1(1 + \cos\varphi) + V_2(1 - \cos 2\varphi) + V_3(1 + \cos 3\varphi)]$				
	$V_0$	$V_1$	$V_2$	$V_3$
OCSC	0.799	−0.879	5.336	0.080
CCSC	−0.562	0.760	5.315	−0.198
CCCS	0.880	−0.241	2.030	−0.639
$E_{\text{tor}}^e = k_\varphi(1 + \cos(2\varphi - \varphi^\circ))$				
	$k_\varphi^e$	$\varphi^\circ$		
OCSC	5.325	180.0		
CCSC	5.325	180.0		
CCCO	1.115	180.0		
CCCS	1.115	180.0		
$E_{\text{imptor}} = k_\xi(\xi - \xi_0)^2$	$k_\xi^f$	$\xi_0^f$		
CCOS	0.0149	0.0		

<sup>a</sup>  $k_R$  in kcal/mol/Å<sup>2</sup>. The value is to be multiplied by 418.4 to convert into kJ/mol/nm<sup>2</sup>, as used in GROMACS. <sup>b</sup>  $R$  in Å. <sup>c</sup>  $k_\theta$  in kcal/(mol/rad<sup>2</sup>). <sup>d</sup>  $\theta$  in deg. <sup>e</sup>  $E_{\text{tor}}$  and  $k_\varphi$  in kcal/mol;  $\varphi$  in deg. <sup>f</sup>  $k_\xi$  in kcal/deg<sup>2</sup>;  $\xi$  in deg.

$\varphi^\circ$ ). Out of the  $V_1$ ,  $V_2$ , and  $V_3$  coefficients,  $V_2$  is the largest, indicating the basic contribution from the  $\cos 2\varphi$  term. Considering only this type of contribution, a single-term GROMACS torsion potential has also been provided in Table 7. Using such a symmetrical potential, however, the small torsion energy difference between the cis and trans forms disappears.

The coupling between the out-of-plane motion (improper torsion) of the central carbon atom and the OCSC torsion is weak. It can be concluded from the result that the mutual refinement of the proper and the improper torsion contributions to the total energy leads only to a small difference between the quantum mechanical  $\Delta E_{\text{tot}}(\xi)$  and the molecular mechanics  $\Delta E_{\text{imptor}}(\xi)$  curves (Figure 7). The derived  $k_\xi$  is given in Table 7.

The net torsion potential for the methyl-group rotation in methyl thiopropanoate is shown in Figure 3. The course of the  $E_{\text{tor}}(\text{CH}_3\text{CH}_2\text{COSCH}_3)$  curve differs basically from that of the corresponding total energy,  $\Delta E_{\text{tot}}$  curve. The turn of  $E_{\text{tor}}$  into the negative energy region indicates that the CH<sub>3</sub>–CH<sub>2</sub>–C–S cis arrangement,  $\varphi = 180^\circ$  ( $\psi = 0^\circ$ ), is the favorable conformation from the torsion point of view. The total energy is, however, +1.17 kcal/mol, largely due to the increase of the CCC and CCS angles from their equilibrium values of 112.7 and 113.5° to 118.3 and 116.2°, respectively. Even at larger bond angles, the relative van der Waals energy is still positive and the total relative  $\Delta E_{\text{str}} + \Delta E_{\text{bend}} + \Delta E_{\text{imptor}} + \Delta E_{\text{vdW}}$  energy amounts to 2 kcal/mol accounting for the energy increase from  $E_{\text{tor}}(\varphi = 180^\circ) = -0.74$  kcal/mol to  $\Delta E_{\text{tot}}(\varphi = 180^\circ) = 1.17$  kcal/mol.

The derived  $E_{\text{tor}}$  function is an effective CCCS torsion function in our approach. It is called effective, because at its derivation the zero-charge, united-atom model for the CH<sub>3</sub> and CH<sub>2</sub> groups was accepted. Thus, the changes in the electrostatic interactions, which are included in the quantum mechanical  $\Delta E_{\text{tot}}$  values, have been implicitly taken into account in the present derivation.



By accepting the GROMACS CCC=O torsion potential, the net torsion energy has maximum contributions of 0.2 and 2.0 kcal/mol from the CCCO and CCCS components, respectively. This large asymmetry may not be justified. A better approximation may be to develop the force field for the thioester (and ester) carbonyl group. The present calculation shows that the equilibrium C=O distances in esters and thioesters are about 1.207 Å (Table 1) in agreement with the experiment. The reference C=O distance is 1.23 Å in GROMACS and 1.229 in AMBER.<sup>21a</sup> Thus, we propose an ester-carbonyl equilibrium value of 1.207 Å, which may have a force constant different of the GROMACS value 600 kcal/mol/Å<sup>2</sup> (accepted in the present study) and the similar AMBER value of 570 kcal/mol/Å<sup>2</sup>. With this new ester-carbonyl in mind, the  $E_{\text{tor}}$  (CH<sub>3</sub>CH<sub>2</sub>COSCH<sub>3</sub>) curve was equally shared between its contributors, and a GROMACS-type, single-term potential has been calculated (Table 7).

Finally, the sensitive problem of the estimation of the atomic charges remains. From Table 5, the sum of the C + O + S charges is not zero. As has been emphasized above, in all parameter derivations the 1-4 and 1-5 electrostatic interaction energies have been disregarded. As a consequence, they are implicitly included in the derived parameters. To remain consistent, one needs to maintain the zero-charge united-atom model, but for charge neutrality, the C + O + S charges have to be modified to give a zero sum.

GROMACS allows large freedom for the user to find a charge assignment procedure, in contrast to AMBER<sup>21a</sup> using the RESP charges. Tentatively, it is proposed here that methyl charges should be added to the nearest neighbor, thus to the C(sp<sup>2</sup>) and S atoms in the cis methyl thioacetate, resulting in C, O, and S charges of +0.599, -0.496, and -0.103. Future studies utilizing available experimental data are, however, necessary for thioesters, and development of a scaling factor may be appropriate.

## Conclusions

The ab initio MP2 and DFT/B3LYP quantum chemical methods applying the 6-311++G\*\* basis set are equally useful for the conformational analysis of simple esters and thioesters. Both methods provide equilibrium geometric parameters close to the experimental ones for the cis methyl acetate and methyl thioformate. By applying the aug-cc-pVTZ basis in geometry optimization, the agreement with the experimental values improves for a number of calculated parameters, but some deficiencies of the calculations still remain. Calculated rotational barriers are similar for the two methods. The DFT computational time is, however, nearly half of that needed at the ab initio MP2 level.

For the CH<sub>3</sub>-C(=O)-X-CH<sub>3</sub> esters (X = O, S), the O=C-X-C cis, planar form is favored. The planar trans conformation also corresponds to a local energy minimum, but is higher in free energy by about 8 and 6 kcal/mol for methyl acetate and methyl thioacetate, respectively, in the gas phase. Differential solvent effects are negative for the trans conformers, and become more negative with increasing dielectric constants. Despite the favorable relative solvent effects for the trans form, the cis conformer is expected to prevail even in the most polar solvents.

Although the energy of the barrier to rotation was calculated as 13.4 and 11.8 kcal/mol for methyl acetate and methyl thioacetate, respectively, at the B3LYP/6-311++G\*\* level, both free energies for the barriers are equal, 13.1 kcal/mol. The cis barrier energies decrease in solution by up to 1 kcal/mol.

The trans CH<sub>3</sub>-CH<sub>2</sub>-C=O structure (with cis O=C-X-C ester moiety) is a transition state both in methyl propanoate and

methyl thioacetate, and a basically cis arrangement is preferred for both esters, with energies lower than the trans form by 1.2-1.3 kcal/mol. The potential curve for the rotation of the methyl-group of ethyl acetate has double minima at  $\varphi = 87^\circ$  and  $\varphi = 180^\circ$ . The trans structure is preferred by 0.4 kcal/mol over the gauche, and the trans to gauche barrier is 0.8 kcal/mol. Only the gauche methyl position ( $\varphi = 85^\circ$ ) corresponds to an energy minimum structure in ethyl thioacetate with the cis-O=C-S-C ester moiety.

Using the results of the conformational analyses, stretching, bending, torsion, and improper torsion (out-of-plane) parameters have been derived for the -CH<sub>2</sub>-CH<sub>2</sub>-C(=O)-S-CH<sub>2</sub>-CH<sub>2</sub>- thioester moiety in compliance with parameters in the GROMACS force field, and by accepting the united CH<sub>3</sub> and CH<sub>2</sub> atom models with zero net-charge for these groups.

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**Supporting Information Available:** Tables S1 and S2, showing geometric and relative energy data utilized in developing the C-S stretching and the CSC bending force constants, and Tables S3-S5, giving atomic charges, nonbonded distances, and the van der Waals parameters used. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References and Notes

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