

method when the response value is either 10-20% or 80-90%.

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4. We used the data which fall in the range of 10-90% from Table 1 in reference 3.

Semiempirical MO Study on Malonyl-CoA. 1. Malonic Acid and Malonyl Methyl Sulfide

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The conformational study on malonic acid, hydrogen malonate, malonate, malonyl methyl sulfide, and malonyl methyl sulfide anion, as the model compounds of malonyl-CoA, was carried out using the semiempirical MO methods (MNDO, AM1, and PM3) and hydration shell model. On the whole, the feasible conformations of malonic acid, hydrogen malonate, and malonate seem to be similar to each other. In malonic acid and malonate, two carboxyl groups are nearly perpendicular to the plane of the carbon skeleton, despite of different orientation of two carboxyl groups themselves. In particular, two carboxyl groups of hydrogen malonate are on the plane formed by carbon atoms with an intramolecular hydrogen bond. The calculated results on the geometry and conformation of three compounds are reasonably consistent with those of X-ray and spectroscopic experiments as well as the previous calculations. The orientation of two carbonyl groups of malonyl methyl sulfide is quite similar to that of malonic acid, but different from that of its anion. Especially, the computed probable conformations of the sulfide anion by the three methods are different from each other. The role of hydration seems not to be crucial in stabilizing the overall conformations of malonic acid, hydrogen malonate, malonate, and malonyl methyl sulfide. However, the probable conformations of the unhydrated sulfide anion obtained by the MNDO and AM1 methods become less stabilized by including hydration. The AM1 method seems to be appropriate for conformational study of malonyl-CoA and its model compounds because it does not result in the formation of too strong hydrogen bonds and significant change in conformational energy from one compound to another.

Introduction

Malonyl-CoA synthetase catalyses the formation of malonyl-CoA directly from malonate and CoA in the presence of ATP and Mg²⁺, which was first purified and characterized from *Bradyrhizobium japonicum*.¹ This enzyme has been proposed to play a role in regulation of glutamate in rat brain mitochondria² and in symbiotic nitrogen metabolism between soybean and *B. japonicum*.³ In spite of the recent kinetic studies on malonyl-CoA synthetase,⁴ the catalytic mechanism was not established yet. In addition, the substrate malonyl-CoA is known to participate in the biosynthesis of fatty acids.^{5a}

Malonate, an analog of succinate, is a strong competitive inhibitor of succinate dehydrogenase and therefore blocks the citric acid cycle.^{5b} The structure of malonate was studied

by X-ray experiments and theoretical methods.⁶ In particular, considerable experiments and calculations have been carried out on the conformations of malonic acid⁷ and hydrogen malonate⁸ in order to interpret the anomalous ratio of the first and second dissociation constants of malonic acid in terms of the formation of intramolecular hydrogen bonds.⁹

In the present study, the conformations of malonic acid, hydrogen malonate, malonate, and malonyl methyl sulfide in the unhydrated and hydrated states were studied using the semiempirical MO methods and hydration shell model to determine the detailed structure of the malonyl-CoA and the hydration effect as a first step in understanding the biochemical functions of malonyl-CoA synthetase.

Methods

The chemical structure and torsion angles of malonic acid and malonyl methyl sulfide are shown in Figure 1. The same

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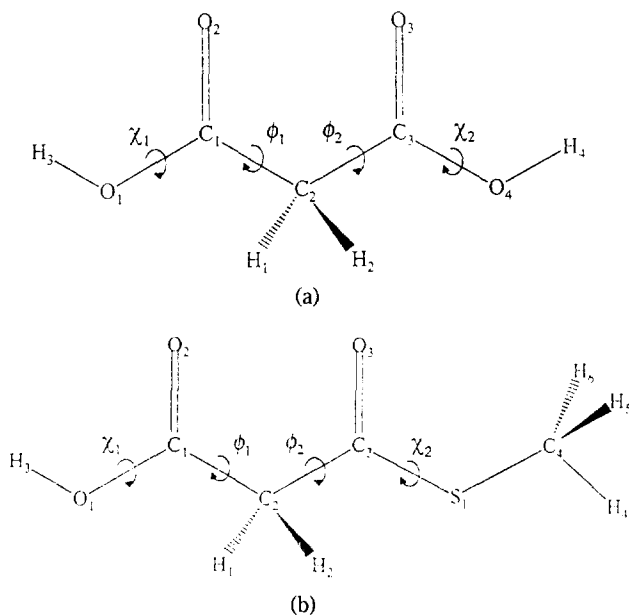


Figure 1. Definition of atomic numbering and torsion angles: (a) malonic acid and its derivatives and (b) malonyl methyl sulfide and its anion. Torsion angles are defined by hydroxyl groups and carbon skeleton.

definition of atomic numbering and torsion angles of malonic acid was used for hydrogen malonate and malonate. The initial bond lengths and bond angles adopted for malonyl and sulfide moieties of each compound were taken from those of X-ray crystal structures of malonate^{6a} and of microwave spectroscopic structure of ethyl methyl sulfide.¹⁰ In the conformational energy calculation, all internal variables were allowed to move during minimization.

All the conformational energy calculations were performed using the semiempirical MNDO, AM1, and PM3 methods of the MOPAC version 6.0 program.¹¹ The hydration shell model, improved recently, was used to calculate the hydration free energy (ΔG_{hyd}) of each conformation in the hydrated state, where the hydration free energy was obtained as the sum of two contributions from water-accessible volume and polarization.¹²

To the initial torsion angles ϕ_1 and ϕ_2 , six values of 0° , $\pm 60^\circ$, $\pm 120^\circ$, and 180° were assigned. The values of 0° and 180° were selected for the initial torsion angles χ_1 and χ_2 of malonic acid and χ_1 of malonyl methyl sulfide. However, to the torsion angles χ_1 of hydrogen malonate, and χ_2 of malonyl methyl sulfide and its anion, six values of 0° , $\pm 60^\circ$, $\pm 120^\circ$, and 180° were initially assigned. Therefore, the total number of initial conformations for malonic acid, hydrogen malonate, malonate, malonyl methyl sulfide, and malonyl methyl sulfide anion are 144, 216, 36, 432, and 216, respectively.

Conformational energy contour map of each compound was obtained as a function of torsion angles ϕ_1 and ϕ_2 , in which the energy was calculated at intervals of 10° in torsion angles. Contours were drawn at intervals of $0.5 \text{ kcal mol}^{-1}$ relative to the global energy minimum.

Results and Discussion

Table 1. Relative Energies and Torsion Angles of Low Energy Conformations of Malonic Acid^a

Conf. ^b	ΔE	$\Delta\Delta G_{hyd}$	ΔG^c	χ_1	ϕ_1	ϕ_2	χ_2
MNDO							
<i>tg⁻g⁺t</i>	0.000	0.000	0.000	179.6	53.4	53.3	179.6
<i>tn⁻g⁺t</i>	0.199	-0.041	0.158	-179.8	-134.7	57.7	-179.2
<i>tn⁻n⁻t</i>	0.395	-0.068	0.327	-179.1	120.5	126.9	-179.5
<i>teg⁻t</i>	0.559	-0.020	0.539	179.7	-4.7	89.9	-178.6
<i>telt</i>	3.816	-0.112	3.704	180.0	0.7	-179.9	180.0
<i>eg⁻n⁺t</i>	4.518	0.028	4.546	-5.5	83.0	107.7	-179.4
<i>en⁻g⁺t</i>	4.585	0.061	4.646	-6.6	95.0	-63.0	179.5
<i>eg⁻g⁻e</i>	8.335	0.113	8.448	4.1	-87.0	-86.9	4.1
AM1							
<i>tn⁺n⁺t</i>	0.000	0.000	0.000	179.4	121.0	134.5	180.0
<i>tg⁻n⁻t</i>	0.044	0.042	0.086	179.5	-47.7	131.3	179.5
<i>ttn⁻t</i>	0.088	-0.003	0.085	-178.7	166.5	96.5	179.5
<i>ten⁻t</i>	0.158	0.066	0.224	-178.8	-0.6	90.0	179.7
<i>en⁻g⁺t</i>	2.603	0.052	2.655	7.0	-143.9	-40.1	-179.2
<i>tete</i>	3.074	0.016	3.090	179.9	0.8	178.2	0.5
<i>eg⁺tt</i>	6.279	0.040	6.319	-0.3	88.3	176.8	-177.7
<i>eg⁻n⁻e</i>	8.562	0.102	8.664	2.8	-44.1	-138.5	7.7
PM3							
<i>ttee</i>	0.000	0.000	0.000	180.0	179.3	0.5	-0.2
<i>lttg⁻t</i>	0.064	-0.016	0.048	179.8	179.1	-85.0	177.4
<i>tn⁺n⁺t</i>	0.082	-0.011	0.071	-179.3	122.1	128.6	-179.7
<i>tg⁻n⁻t</i>	0.113	0.011	0.124	-178.4	61.8	-145.6	-179.2
<i>tg⁻g⁺t</i>	0.265	0.065	0.330	-179.8	60.6	51.9	179.8
<i>eg⁻n⁻t</i>	1.390	0.068	1.458	7.5	-56.1	-127.7	-179.7
<i>tg⁻g⁻e</i>	2.081	0.149	2.230	-179.4	72.3	-67.8	4.0
<i>teee</i>	2.188	0.072	2.260	179.9	-1.7	-2.5	1.9
<i>eete</i>	2.730	0.038	2.768	0.4	-0.6	-179.7	-0.1
<i>etg⁺t</i>	3.109	0.025	3.134	-0.1	-178.9	84.4	-176.7
<i>teg⁻e</i>	3.134	0.135	3.269	-177.9	1.8	-63.8	10.8
<i>eeg⁺t</i>	3.235	0.154	3.389	-3.5	1.2	72.2	177.2
<i>eg⁻n⁻e</i>	3.867	0.165	4.032	5.5	-60.2	-106.1	2.5

^aTorsion angles are defined in Figure 1. The values of heat of formation of global minima for the MNDO, AM1, and PM3 methods are -185.492 , -189.143 , and $-186.579 \text{ kcal mol}^{-1}$, respectively. ^bEach conformation is defined by conformational letter codes, i.e. $-30^\circ \leq e < 30^\circ$, $30^\circ \leq g^+ < 90^\circ$, $90^\circ \leq n^+ < 150^\circ$, $150^\circ \leq t \leq 180^\circ$ or $-180^\circ \leq t \leq -150^\circ$, $-150^\circ < n^- \leq -90^\circ$, and $-90^\circ < g^- \leq -30^\circ$. ^c $\Delta G = \Delta E + \Delta\Delta G_{hyd}$; ΔE is relative heat of formation and $\Delta\Delta G_{hyd}$ is relative hydration free energy.

Relative energies and torsion angles of low energy conformations of malonic acid, hydrogen malonate, and malonate are listed in Tables 1-3, respectively. For each conformation, the Tables contain (i) the conformational letter code, (ii) the relative conformational energy (ΔE), (iii) the relative hydration free energy ($\Delta\Delta G_{hyd}$), (iv) the relative free energy ($\Delta G = \Delta E + \Delta\Delta G_{hyd}$), and (v) torsion angles. Conformational letter codes are used for torsion angles defined in Figure 1. Table 4 lists the comparison of lowest energy geometries of the three compounds. In Tables 5 and 6, relative energies and torsion angles of low energy conformations of malonyl methyl sulfide and its anion with $\Delta E < 5 \text{ kcal mol}^{-1}$ are

Table 2. Relative Energies and Torsion Angles of Low Energy Conformations of Hydrogen Malonate^a

Conf.	ΔE	$\Delta\Delta G_{hyd}$	ΔG	χ_1	ϕ_1	ϕ_2
MNDO						
<i>eg'g</i>	0.000	0.000	0.000	10.4	72.0	-59.7
<i>en'g'</i>	0.002	-0.347	-0.345	-10.5	110.0	60.0
<i>etg'</i>	0.607	-0.778	-0.171	-18.9	-178.2	56.7
<i>teg</i>	1.547	0.251	1.798	169.4	-14.1	-78.7
<i>ete</i>	1.972	-0.958	1.014	-0.1	-179.9	0.3
<i>tn g'</i>	2.365	-0.336	2.029	-172.2	-92.8	83.8
AM1						
<i>en'g'</i>	0.000	0.000	0.000	-10.3	140.6	38.2
<i>eg'g</i>	0.001	0.624	0.625	10.4	40.3	-37.9
<i>eee</i>	0.522	0.552	1.074	-0.4	0.5	0.5
<i>ttn'</i>	6.194	-0.300	5.894	-172.6	161.0	95.7
PM3						
<i>ete</i>	0.000	0.000	0.000	-4.3	166.6	12.4
<i>eee</i>	0.004	0.045	0.049	-0.1	0.0	0.0
<i>eg'e</i>	7.779	0.916	8.695	-10.4	68.7	8.7
<i>eg t</i>	16.762	-0.108	16.654	0.0	-70.6	165.2
<i>tte</i>	18.151	-0.248	17.903	-180.0	178.4	-0.5

^aSee footnotes of Table 1. The values of heat of formation of global minima for the MNDO, AM1, and PM3 methods are -206.647, -220.975, and -228.655 kcal mol⁻¹, respectively.

Table 3. Relative Energies and Torsion Angles of Low Energy Conformations of Malonate^a

Conf.	ΔE	$\Delta\Delta G_{hyd}$	ΔG	ϕ_1	ϕ_2
MNDO					
<i>n+n'</i>	0.000	0.000	0.000	121.6	121.6
AM1					
<i>n+n'</i>	0.000	0.000	0.000	120.1	120.1
<i>tn'</i>	0.701	-0.119	0.582	176.2	91.7
PM3					
<i>n+n'</i>	0.000	0.000	0.000	122.3	121.8
<i>g'g'</i>	0.337	0.740	1.077	85.4	83.0
<i>eg'</i>	0.604	0.879	1.483	10.4	89.4
<i>tg'</i>	0.614	-0.066	0.548	172.8	89.0

^aSee footnotes of Table 1. The values of heat of formation of global minima for the MNDO, AM1, and PM3 methods are -135.138, -146.759, and -153.809 kcal mol⁻¹, respectively.

shown. Table 7 lists the comparison of their lowest energy geometries.

Malonic Acid. From the 144 starting conformations of malonic acid in the unhydrated state, we obtained 8, 8, and 13 different minimized conformations for the MNDO, AM1, and PM3 methods, respectively, which are shown in Table 1. The computed low energy conformations *tg'g't*, *tn'n't*, and *tte* seem to be the most probable conformations of malonic acid obtained by the MNDO, AM1, and PM3 methods, respectively. In particular, the conformation *tte* of the PM3 method has an intramolecular hydrogen bond between two carboxyl groups. The second conformations *tn g't*, *tg n't*,

Table 4. Comparison of Lowest Energy Geometries of Malonic Acid, Hydrogen Malonate, and Malonate

	Malonic acid		Hydrogen malonate		Malonate				
	MNDO	AM1	PM3	MNDO	AM1	PM3			
Bond length (Å)									
C ₁ -C ₂	1.530	1.497	1.503	1.578	1.541	1.553	1.556	1.526	1.544
C ₂ -C ₃	1.530	1.496	1.522	1.526	1.491	1.511	1.556	1.526	1.544
O ₁ -C ₁	1.356	1.362	1.346	1.261	1.258	1.245	1.271	1.276	1.266
O ₂ -C ₁	1.229	1.232	1.224	1.255	1.269	1.268	1.267	1.270	1.259
O ₁ -C ₃	1.356	1.362	1.343	1.363	1.359	1.337	1.271	1.276	1.266
O ₃ -C ₃	1.229	1.232	1.214	1.234	1.241	1.226	1.267	1.270	1.259
H ₁ -C ₂	1.115	1.125	1.110	1.114	1.119	1.106	1.118	1.122	1.108
H ₂ -C ₂	1.115	1.125	1.110	1.113	1.121	1.107	1.118	1.122	1.108
H ₄ -O ₄	0.950	0.972	0.962	0.947	0.980	0.976			
H ₃ -O ₁	0.950	0.972	0.953						
Bond angle (°)									
C ₁ -C ₂ -C ₃	114.8	111.7	114.2	114.7	115.2	115.8	119.4	119.3	118.7
O ₁ -C ₁ -C ₂	114.7	113.2	115.8	117.0	117.6	118.7	118.6	118.2	118.9
O ₂ -C ₁ -C ₂	125.9	129.2	127.5	117.8	118.0	119.2	120.2	121.0	121.7
O ₄ -C ₃ -C ₂	114.7	113.0	123.4	121.1	121.3	123.0	118.6	118.3	119.0
O ₃ -C ₃ -C ₂	125.9	129.6	124.4	125.3	125.8	125.5	120.2	121.0	121.7
H ₁ -C ₂ -C ₁	108.2	110.1	109.5	108.9	109.2	109.5	109.4	107.8	106.9
H ₂ -C ₂ -C ₁	109.4	108.3	109.4	109.7	107.1	108.4	106.7	106.7	109.0
H ₄ -O ₄ -C ₃	115.7	109.7	111.2	114.5	110.1	109.0			
H ₃ -O ₁ -C ₁	115.7	109.7	110.1						
Hydrogen bond distance (Å)									
H ₁ ...O ₂		1.823	2.551	1.903	1.712				

and *tgt t* of the MNDO, AM1, and PM3 calculations are energetically comparable with their own lowest energy conformations and agree reasonably with the structures of X-ray experiment^{7a} and *ab initio* calculations with STO-3G basis set,^{7b,c} in which the two carboxyl groups are orthogonal to each other and one of them are coplanar with the carbon skeleton. In addition, there are no intramolecular hydrogen bonds. The geometries of lowest free energy conformations are compared with each other in Table 4. The MNDO and PM3 calculations give almost the same geometry, which is similar to the X-ray structure except for the bond lengths O₁-C₁ and O₄-C₃ (longer about 0.05 Å) and the bond angles O₂-C₁-C₂ and O₃-C₃-C₂ (larger about 8°).

Figures 2(a)-(c) show adiabatic conformational energy contour maps of malonic acid using the three semiempirical methods in the unhydrated state as a function of torsion angles ϕ_1 and ϕ_2 with torsion angles χ_1 and χ_2 assigned initially to be *trans*. The three methods give the overall similar potential surfaces, and there are four energetically probable local minima in each map whose barriers for conformational changes are less than 1 kcal mol⁻¹.

In general, hydration free energies do not contribute significantly to affect the overall conformational changes, although there is to some extent the variation in hydration free energy from one conformation to another. As a result, the quite similar potential surfaces in the hydrated state to those in the unhydrated state were obtained and they were not drawn separately.

Table 5. Relative Energies and Torsion Angles of Low Energy Conformations of Malonyl Methyl Sulfide^a

Conf.	ΔE	$\Delta\Delta G_{hyd}$	ΔG	χ_1	ϕ_1	ϕ_2	χ_2
MNDO							
<i>tg⁺n⁻t</i>	0.000	0.000	0.000	-179.5	59.3	-138.9	179.9
<i>tn⁺n⁺t</i>	0.158	-0.038	0.120	-178.8	111.0	147.4	178.2
<i>ttn⁻t</i>	0.468	-0.012	0.456	-179.6	-171.0	-103.9	176.4
<i>tg⁺g⁺t</i>	0.646	0.115	0.761	178.8	59.0	68.5	179.9
<i>ten⁺t</i>	0.711	0.068	0.779	179.5	-7.4	101.8	-178.0
<i>tn⁻g⁻t</i>	0.753	0.089	0.842	179.9	123.9	-74.3	178.6
<i>tg⁻n⁻t</i>	0.968	0.045	1.013	-179.6	-67.3	-100.8	179.1
<i>tg⁻et</i>	2.017	0.128	2.145	179.6	-81.8	-19.4	-174.3
<i>tttt</i>	2.878	-0.141	2.737	179.9	175.1	178.5	-178.5
<i>tett</i>	3.546	-0.091	3.455	180.0	-0.7	179.5	179.7
<i>eg⁻n⁻t</i>	4.417	0.098	4.515	1.4	-78.3	-108.1	178.0
AM1							
<i>tn⁺n⁺t</i>	0.000	0.000	0.000	-179.8	122.4	122.0	179.6
<i>tg⁻n⁺t</i>	0.263	0.031	0.294	179.2	-60.5	133.3	178.5
<i>ttn⁺t</i>	0.354	-0.015	0.339	180.0	175.6	110.5	-179.6
<i>ten⁻t</i>	0.608	0.047	0.655	-179.0	8.7	-118.2	-178.7
<i>tn⁺n⁻t</i>	0.859	0.034	0.893	179.4	121.3	-104.8	180.1
<i>tn⁻g⁻t</i>	0.935	0.107	1.042	-178.8	-127.8	66.0	-178.6
<i>tg⁻n⁻t</i>	0.943	0.038	0.981	-179.9	-63.8	-111.2	-179.2
<i>eg⁻n⁺t</i>	2.353	0.064	2.417	-9.9	54.5	128.6	179.3
<i>tn⁺g⁺e</i>	3.862	0.092	3.954	-179.8	107.9	86.7	-3.0
<i>tg⁻ne</i>	4.541	0.145	4.686	-179.8	78.2	-96.3	3.9
PM3							
<i>tn⁻nt</i>	0.000	0.000	0.000	179.1	-117.3	-136.2	-178.6
<i>tg⁻tt</i>	0.069	0.001	0.070	178.1	-71.0	156.0	177.5
<i>ee⁺tt</i>	0.830	-0.021	0.809	-0.1	-2.7	-175.2	-179.5
<i>ten⁺t</i>	0.950	0.086	1.036	179.7	-9.2	110.9	-179.1
<i>tg⁻nt</i>	0.953	0.006	0.959	179.0	-68.5	-137.3	-178.1
<i>tn⁺n⁻t</i>	1.030	0.082	1.112	179.6	127.2	-96.2	178.3
<i>tg⁻g⁻t</i>	1.202	0.131	1.333	-179.3	-35.0	-89.9	177.2
<i>eg⁻n⁻t</i>	1.538	0.100	1.638	6.8	-62.0	-122.3	-177.9
<i>eg⁻n⁺t</i>	2.415	0.255	2.670	2.6	-56.7	96.2	-177.2
<i>een⁻t</i>	2.937	0.085	3.022	-7.1	-3.4	-130.1	-177.3
<i>etn⁺t</i>	3.275	0.050	3.325	-2.3	170.8	111.9	-178.1
<i>ttn⁺e</i>	3.861	0.037	3.898	-179.6	162.7	105.4	-13.3
<i>ee⁺te</i>	4.006	-0.108	3.898	0.0	10.5	163.6	-2.4
<i>tg⁺g⁻e</i>	4.061	0.145	4.206	-179.7	70.2	86.3	8.2
<i>tn⁻n⁺e</i>	4.384	0.126	4.510	-179.3	-110.9	103.0	-10.1
<i>en⁺g⁻t</i>	4.670	0.249	4.919	-12.3	99.3	-58.6	178.4

^aSee footnotes of Table 1. The values of heat of formation of global minima for the MNDO, AM1, and PM3 methods are -135.846, -130.931, and -128.237 kcal mol⁻¹, respectively. Only the conformations with $\Delta E < 5$ kcal mol⁻¹ are listed.

Table 6. Relative Energies and Torsion Angles of Low Energy Conformations of Malonyl Methyl Sulfide Anion^a

Conf.	ΔE	$\Delta\Delta G_{hyd}$	ΔG	ϕ_1	ϕ_2	χ_2
MNDO						
<i>en⁻t</i>	0.000	0.000	0.000	-10.7	100.0	-164.6
<i>n⁻n⁻t</i>	0.129	-2.127	-1.998	-128.8	-107.7	164.8
<i>g⁻g⁻t</i>	0.394	-0.079	0.315	41.3	72.3	-166.5
<i>en⁻g</i>	1.317	1.118	2.435	-0.3	90.3	-34.7
<i>g⁻g⁻g⁻</i>	1.325	0.439	1.764	-43.7	-84.0	34.4
<i>g⁺n⁻g⁻</i>	1.483	1.046	2.529	54.2	-104.3	30.9
<i>g⁻tt</i>	1.492	-1.540	-0.048	-67.6	157.0	-176.8
<i>n⁻g⁻e</i>	1.625	0.280	1.905	-121.3	76.7	-6.8
<i>n⁻g⁻g⁻</i>	2.194	0.193	2.387	118.6	-87.7	78.7
<i>ttt</i>	4.627	-2.668	1.959	175.9	172.3	-175.2
<i>g⁻n⁺g⁻</i>	4.719	-1.197	3.522	-64.8	142.0	32.7
<i>n⁺te</i>	4.887	-2.182	2.705	114.7	167.1	-8.3
<i>n⁻n⁻g</i>	4.952	-2.159	2.793	-126.4	-111.4	-69.1
AM1						
<i>g⁻ne</i>	0.000	0.000	0.000	81.1	-91.3	10.0
<i>n⁻ne</i>	0.002	-2.108	-2.106	-99.4	-90.6	9.2
<i>eg⁻e</i>	0.647	0.360	1.007	28.7	-86.9	16.4
<i>n⁻g⁻e</i>	0.819	-0.334	0.485	-111.8	9.6	-5.5
<i>g⁻g⁻e</i>	0.922	-0.567	0.355	-63.4	-64.3	12.0
<i>n⁻nt</i>	1.341	-3.203	-1.862	-129.0	-111.8	179.2
<i>g⁻n⁻t</i>	1.861	-2.124	-0.263	-60.8	-96.5	177.5
<i>tet</i>	1.935	-3.057	-1.122	178.4	0.3	-179.8
<i>eg⁻e</i>	2.147	0.151	2.298	-20.5	-77.3	21.4
<i>g⁺ee</i>	2.368	-0.268	2.100	87.4	10.4	-5.3
<i>n⁻g⁺t</i>	2.937	-2.046	0.891	-111.0	52.4	177.7
<i>n⁺et</i>	4.095	-2.145	1.950	110.5	-16.0	-176.4
<i>g⁺et</i>	4.351	-1.440	2.911	68.6	8.1	174.8
<i>eg⁺n⁻</i>	4.567	0.573	5.140	2.7	86.4	-103.8
PM3						
<i>n⁺g⁺e</i>	0.000	0.000	0.000	102.5	90.0	-23.7
<i>tn⁻g⁺</i>	1.671	-0.320	1.351	-150.8	-95.3	58.9
<i>tg⁻e</i>	4.367	0.131	4.498	178.0	-89.4	25.3
<i>g⁻n⁺t</i>	4.774	0.171	4.945	-58.7	125.0	-178.4
<i>tn⁺t</i>	4.862	-1.397	3.465	161.9	113.7	-173.8

^aSee footnotes of Table 1. The values of heat of formation of global minima for the MNDO, AM1, and PM3 methods are -154.450, -155.398, and -155.632 kcal mol⁻¹, respectively. Only the conformations with $\Delta E < 5$ kcal mol⁻¹ are listed.

hydrogen bond between two carboxyl groups and the planar structure. The hydrogen bond ($H_1 \cdots O_2$) distances decrease in the order of the MNDO (2.55 Å), AM1 (1.90 Å), and PM3 (1.71 Å) methods. In the case of the MNDO calculations, the energy difference between the conformations with and without hydrogen bonds is not of significance, but the results of the AM1 and PM3 methods yield somewhat larger energy differences. It is believed that the smaller number of low energy conformations of hydrogen malonate than that of malonic acid arises from these larger energy differences. The adiabatic conformational energy contour maps in the unhydrated state shown in Figures 3(a)-(c) as a function of torsion angles ϕ_1 and ϕ_2 support the important role of hydrogen

Hydrogen Malonate. Only six, four, and five low energy conformations of hydrogen malonate were obtained starting from 216 initial conformations for the MNDO, AM1, and PM3 methods, respectively, which are summarized in Table 2. The most probable conformations in the unhydrated state are *e⁻g⁻g⁻*, *en⁻g⁻*, and *ete* for the three methods, respectively, and each of them has in common an intramolecular

Table 7. Comparison of Lowest Energy Geometries of Malonyl Methyl Sulfide and Its Anion

	Malonyl methyl sulfide			Malonyl methyl sulfide anion		
	MNDO	AM1	PM3	MNDO	AM1	PM3
Bond length (Å)						
C ₁ -C ₂	1.530	1.496	1.509	1.585	1.559	1.572
C ₂ -C ₃	1.534	1.507	1.521	1.516	1.483	1.491
O ₁ -C ₁	1.357	1.362	1.353	1.256	1.263	1.248
O ₂ -C ₁	1.229	1.232	1.216	1.257	1.256	1.247
O ₃ -C ₃	1.223	1.233	1.212	1.225	1.235	1.206
S ₁ -C ₃	1.709	1.714	1.806	1.732	1.767	1.874
S ₁ -C ₄	1.727	1.754	1.802	1.721	1.758	1.801
H ₁ -C ₂	1.114	1.125	1.111	1.113	1.118	1.110
H ₂ -C ₂	1.115	1.125	1.111	1.112	1.121	1.112
H ₄ -C ₄	1.107	1.114	1.097	1.108	1.112	1.099
H ₅ -C ₄	1.106	1.113	1.096	1.106	1.122	1.093
H ₆ -C ₄	1.106	1.113	1.096	1.107	1.111	1.091
H ₃ -O ₁	0.950	0.972	0.952			
Bond angle (°)						
C ₁ -C ₂ -C ₃	114.5	111.7	112.2	115.2	113.6	113.5
O ₁ -C ₁ -C ₂	114.6	113.3	114.7	118.6	117.5	116.8
O ₂ -C ₁ -C ₂	126.0	129.7	128.7	115.9	117.3	117.8
S ₁ -C ₃ -C ₂	113.0	109.8	110.5	113.9	119.2	109.2
C ₄ -S ₁ -C ₃	111.5	105.1	105.6	111.7	107.4	106.2
O ₃ -C ₃ -C ₂	122.9	122.8	122.4	125.0	123.9	128.4
H ₁ -C ₂ -C ₁	108.1	109.6	108.4	108.7	107.6	109.3
H ₂ -C ₂ -C ₁	109.4	107.7	111.2	107.7	107.1	109.3
H ₄ -C ₄ -S ₁	106.3	106.3	107.4	107.1	106.0	108.6
H ₅ -C ₄ -S ₁	112.2	111.2	112.8	112.4	111.6	112.7
H ₆ -C ₄ -S ₁	112.2	111.8	112.8	112.6	111.1	113.0
H ₃ -O ₁ -C ₁	115.6	109.7	110.2			

bond in stabilizing hydrogen malonate.

The hydrogen malonate has been found to adopt various conformations with different types of hydrogen bonds in its crystalized acid salts. In potassium^{8a} and magnesium^{8d} salts, the planar conformation of the carboxyl groups are observed whereas in sodium^{8b} and ammonium^{8c} salts, the carboxyl groups are nearly perpendicular to each other. The intermolecular hydrogen bonds are of consequence in stabilizing the overall conformations of these salts in crystal. In addition, the Raman^{8h} and infrared^{8g} experiments confirm the lack of intramolecular hydrogen bonds in hydrogen malonate. On the other hand, the results of infrared, X-ray, and NMR experiments^{8e,i,f,j} support that the bent intramolecular hydrogen bond of carboxyl groups is responsible for stabilizing the planar hydrogen malonate, which are also consistent with those of *ab initio* studies on isolated hydrogen malonate.^{7c,8j,8k} These results indicate that packing forces in crystal may suppress the formation of intramolecular hydrogen bonds and force to form intermolecular hydrogen bonds, and that these two conformations are energetically comparable with each other. Our calculated results by the MNDO and AM1

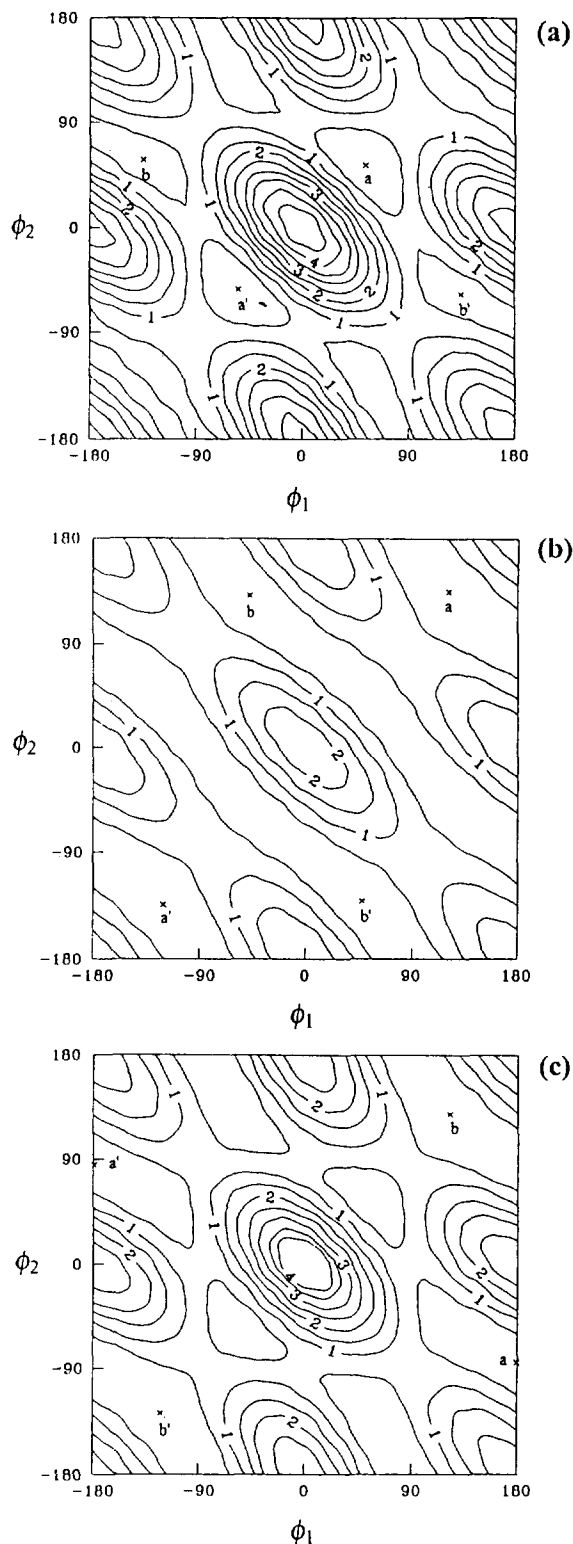


Figure 2. Conformational energy contour maps of the unhydrated malonic acid obtained by the (a) MNDO, (b) AM1, and (c) PM3 methods as a function of torsion angles ϕ_1 and ϕ_2 . Contours are drawn at intervals of 0.5 kcal mol⁻¹ relative to the global energy minimum. The first two energy minima are represented by **a** and **b**, which are geometrically equivalent to **a'** and **b'**, respectively.

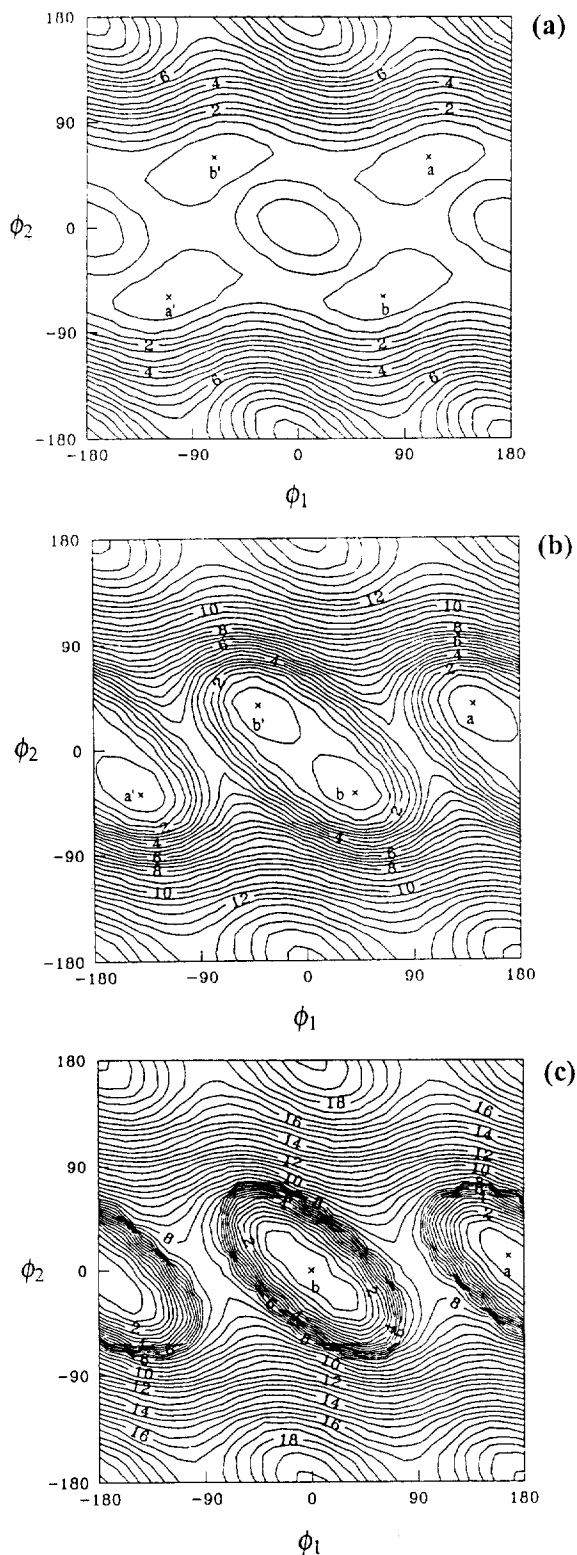


Figure 3. Conformational energy contour maps of the unhydrated hydrogen malonate obtained by the (a) MNDO, (b) AM1, and (c) PM3 methods as a function of torsion angles ϕ_1 and ϕ_2 . See legend of Figure 2. The first two energy minima are represented by **a** and **b**, which are geometrically equivalent to **a'** and **b'**, respectively.

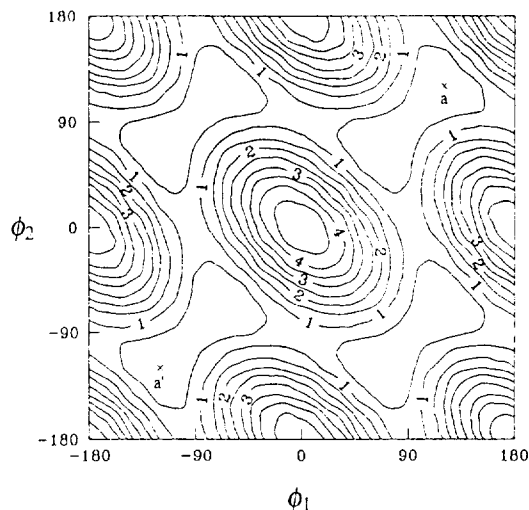


Figure 4. Conformational energy contour map of the unhydrated malonate obtained by the AM1 method as a function of torsion angles ϕ_1 and ϕ_2 . See legend of Figure 2. The two equivalent global energy minima are represented by **a** and **a'**.

methods shown in Table 2 and Figure 3 are reasonably consistent with them.

In particular, the relative stability of the planar conformation of two carboxyl groups to the perpendicular conformation increases in the order of the MNDO, AM1, and PM3 methods. As the same as for malonic acid, hydration free energy does not alter significantly the overall conformations obtained in the unhydrated state. However, the strength of intramolecular hydrogen bonds of the MNDO calculations is not enough to sustain the planar conformation (eg^+g^-) and the perpendicular conformation (en^+g^+) is more favored in the hydrated state. The geometries of lowest energy conformations are compared with each other in Table 4.

Malonate. The 36 starting conformations of malonate in the unhydrated state yield one, two, and four different low energy conformations for the MNDO, AM1, and PM3 methods, respectively. Their relative energies and torsion angles are shown in Table 3. The lowest energy conformations of the three methods are n^+n^+ altogether, in which two carboxylate groups are nearly perpendicular to the plane through the carbon atoms and parallel each other. This conformation is somewhat similar to the conformations of malonate found in the crystals of calcium malonate dihydrate and strontium malonate^{6a} and obtained by *ab initio* study with STO-3G basis set.^{6b} Also, the similar conformation is found in malonic acid.^{7a} The geometries of these lowest energy conformations are compared with each other in Table 4. Although the three methods give quite similar geometries, the geometry of the AM1 method is well consistent with the X-ray structures.^{6a}

The adiabatic conformational energy contour map of the unhydrated malonate using the AM1 method as a function of torsion angles ϕ_1 and ϕ_2 are shown in Figure 4. Because the MNDO and PM3 calculations give the quite similar energy contour maps to that obtained from the AM1 calculation,

they do not shown separately. The shape of potential surfaces is similar to that of malonic acid, but the potential wells become deeper than those of malonic acid (see Figure 2). In addition, the contribution of hydration free energy to the total free energy seems to be negligible, as the same as for malonic acid.

Malonyl Methyl Sulfide. From the 432 starting conformations of malonyl methyl sulfide (Figure 1(b)), we obtained 11, 10, and 16 different low energy conformations with $\Delta E < 5$ kcal mol⁻¹ for the MNDO, AM1, and PM3 methods, respectively, which are shown in Table 5. The computed lowest energy (or free energy) conformations for the MNDO, AM1, and PM3 methods are tg^+n^-t , tn^+n^+t , and tn^-n^-t , respectively, in which two carbonyl groups are nearly perpendicular to each other. In the case of the AM1 study, the first three lowest energy conformations of malonic acid are conserved for malonyl methyl sulfide, whereas the second and fourth lowest energy conformations of malonic acid disappeared in the MNDO results. In particular, all the first four lowest energy conformations of malonic acid obtained by the PM3 method are no longer stable for malonyl methyl sulfide. The calculated results of the three methods indicate that the probable conformations of torsion angle χ_1 is *trans* except the third lowest energy conformation *ett* of the PM3 method. This implies that the overall conformation of malonyl methyl sulfide is quite similar to that of malonic acid, and may be ascribed to the lack of the hydrogen bond acceptor for the hydrogen atom of terminal carboxyl group.

Table 7 summarizes the geometries of malonyl methyl sulfide obtained by the three methods. The calculated bond lengths of malonyl moiety are almost the same as for malonic acid, but the PM3 method allows the bond angles to be about 1° larger. In particular, the bond angle O₃-C₃-C₂ of malonyl methyl sulfide becomes about 2° to 7° larger than that of malonic acid. The calculated bond length S₁-C₄ of sulfide moiety by the PM3 method is exactly the same as the initial value, but the values of the MNDO and AM1 methods are shortened by about 0.07 Å and 0.05 Å, respectively. The calculated value of bond angle C₄-S₁-C₃ by the AM1 and PM3 methods is about 105°, which is close to the value of ethyl methyl sulfide.¹⁰ Whereas the *gauche* conformation of torsion angle χ_2 is found to be predominant for ethyl methyl sulfide, the *trans* conformation is preferred for malonyl methyl sulfide, because the *gauche* conformation causes the close contact between sulfur atom and carboxyl oxygen atoms.

The comparison of calculated geometries and torsion angles of the three methods may allow us to choose the AM1 method to be appropriate for the conformational analysis of malonyl methyl sulfide. Figure 5(a) shows the adiabatic conformational energy contour map for the unhydrated malonyl methyl sulfide obtained by the AM1 method as a function of torsion angles ϕ_1 and ϕ_2 with torsion angles χ_1 and χ_2 assigned initially to be *trans*. The overall shape of potential surface is similar to that of malonic acid shown in Figure 2(b). However, the local minima with *trans* torsion angles become deeper, whereas the *gauche* conformations are no longer local minima due to the reason explained in the previous paragraph. The lowest energy conformation tn^+n^+t obtained by the AM1 method is drawn in Figure 6(a). The effect of hydration on the conformations of malonyl methyl sulfide is negligible, as the same as for malonic acid, hydro-

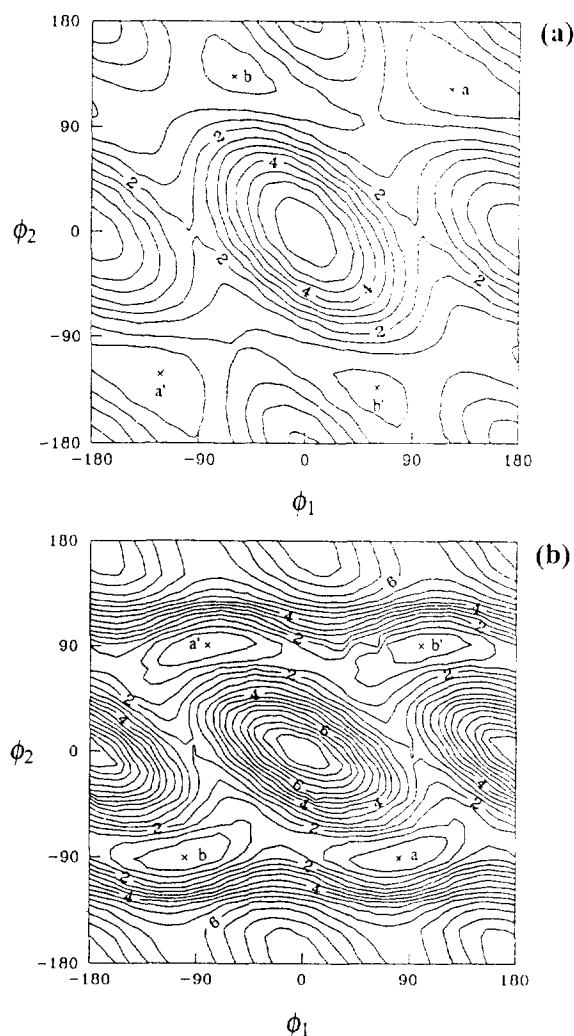


Figure 5. Conformational energy contour maps of the unhydrated (a) malonyl methyl sulfide and (b) its anion obtained by the AM1 method as a function of torsion angles ϕ_1 and ϕ_2 . Contours are drawn at intervals of 0.5 kcal mol⁻¹ relative to the global energy minimum. The first two energy minima are represented by **a** and **b**, which are geometrically equivalent to **a'** and **b'**, respectively. Initially, torsion angles χ_1 and χ_2 are assumed to be *trans* for the neutral sulfide, whereas torsion angle χ_2 to be 10° for the sulfide anion. For each grid point of (ϕ_1 , ϕ_2) space, all variables are relaxed.

gen malonate, and malonate.

Malonyl Methyl Sulfide Anion. Table 6 includes 13, 14, and 5 low energy conformations of malonyl methyl sulfide anion with $\Delta E < 5$ kcal mol⁻¹ obtained from 216 initial conformations by the MNDO, AM1, and PM3 methods, respectively. The most stable conformations in the unhydrated state are en^-t , g^+n^-e , and n^+g^+e for the three methods, respectively. However, there are no any common structural features among these three conformations. In the conformation en^-t , two carbonyl groups are on the plane of carbon skeleton of malonyl moiety and perpendicular to each other. On the other hand, two carbonyl groups of the conformation g^+n^-e are perpendicular to the plane formed by carbon atoms but parallel each other. The anion oxygen atom and

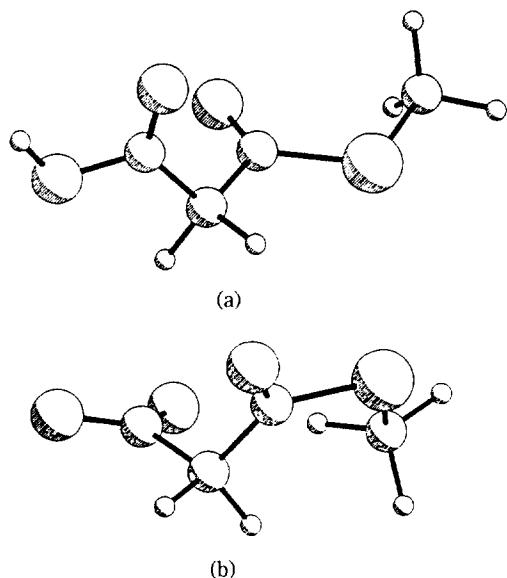


Figure 6. Lowest energy conformations tn^+n^+t and g^+n^-e of (a) malonyl methyl sulfide and (b) its anion obtained by the AM1 method, respectively.

the methyl hydrogen atom of sulfide moiety are located close to each other. The orientation of two carbonyl groups of the conformation n^+g^+e , in which they are perpendicular to the plane formed by carbon atoms but antiparallel each other, results in a close contact between carbonyl oxygen atom and methyl hydrogen atom. The lowest energy conformation g^+n^-e obtained by the AM1 method is drawn in Figure 6(b).

Only the eighth lowest energy conformation n^-g^+e of the MNDO method is conserved, which is the fifth lowest energy conformation of hydrogen malonate, and other low energy conformations of hydrogen malonate and malonate obtained by the three methods are not sustained. In the case of the MNDO calculation, the fifth lowest free energy conformation en^+t of malonyl methyl sulfide with $\Delta E=0.71$ kcal mol⁻¹ becomes the most probable conformation for its anion. The tenth lowest free energy conformation tg^+n^-e of the neutral sulfide with $\Delta E=4.54$ kcal mol⁻¹ calculated by the AM1 method is stabilized as the fifth lowest free energy for the first lowest energy conformation of the sulfide anion. However, only the conformation tg^+g^+e of neutral sulfide with $\Delta E=4.06$ kcal mol⁻¹ obtained by the PM3 method is nearly similar to the lowest free energy conformation n^+g^+e . In particular, the probable conformations of torsion angle χ_2 for sulfide anion are t/g^- (or g^-), e/t , and e/g^+ for the MNDO, AM1, and PM3 methods, and the increased stability of *gauche* conformations are different from the neutral sulfide.

The adiabatic conformational energy contour map of the unhydrated sulfide anion obtained by the AM1 method is shown as a function of torsion angles ϕ_1 and ϕ_2 in Figure 5(b) with torsion angle χ_2 assigned initially to be 10°. The overall shape of potential surface become stiffer than but is similar to that of the neutral sulfide, except the higher hill areas with *trans* ϕ_2 and the shift of valley from $\phi_2 \approx 120^\circ$ to 90° .

Different from the results for other malonyl derivatives,

hydration significantly plays a role in stabilizing the conformation of malonyl methyl sulfide anion. Especially, the conformations with *trans* χ_2 are stabilized due to the less protection of hydration of charged malonyl moiety by the methyl group of sulfide moiety. The typical example is the conformation n^-n^-t for the MNDO and AM1 calculations. The hydration free energy of the conformation n^-n^-t obtained by the AM1 method is 3.20 kcal mol⁻¹ less than that of lowest energy conformation g^+n^-e . As a result, the former conformation is more stable than the latter by 1.86 kcal mol⁻¹. However, the significant role of hydration was not found for the low energy conformations obtained by the PM3 method.

Conclusions

On the whole, the feasible conformations of malonic acid, hydrogen malonate, and malonate obtained by the three semiempirical methods and hydration shell model seem to be similar to each other. In malonic acid and malonate, two carboxyl groups are nearly perpendicular to the plane of the carbon skeleton, despite of different orientation of two carboxyl groups themselves. In particular, two carboxyl groups of hydrogen malonate are on the plane formed by carbon atoms with an intramolecular hydrogen bond. The calculated results on the geometry and conformation of three compounds are reasonably consistent with those of X-ray and spectroscopic experiments as well as the previous calculations.

The orientation of two carbonyl groups of malonyl methyl sulfide is quite similar to that of malonic acid, but different from that of its anion. Especially, the computed probable conformations of the sulfide anion by the three methods are different from each other. The role of hydration seems not to be crucial in stabilizing the overall conformations of malonic acid, hydrogen malonate, malonate, and malonyl methyl sulfide. However, the probable conformations of the unhydrated sulfide anion obtained by the MNDO and AM1 methods become less stabilized by including hydration.

In general, although the three semiempirical methods give similar results on the geometry and conformation of the compounds considered here, the AM1 method seems to be appropriate for conformational study of malonyl-CoA and its model compounds because it does not result in the formation of too strong hydrogen bonds and significant change in conformational energy from one compound to another.

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Synthesis, Structural and Electrical Characterizations of $\text{Pr}_{2-x}\text{Ba}_x\text{NiO}_{4+\delta}$ [§]

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Solid solutions of $\text{Pr}_{2-x}\text{Ba}_x\text{NiO}_{4+\delta}$ with K_2NiF_4 -type structure were prepared in air and characterized by powder X-ray diffraction, Rietveld refinements, iodometry titrations, and conductivity measurements. The range of the solid solution was $0 \leq x < 0.5$. The crystal structure changes from orthorhombic (Fmmm) for $x \leq 0.1$ to pseudo-tetragonal ($I4/mmm$) for $x \geq 0.2$. The orthorhombic structure of $x = 0.1$ transforms to tetragonal at low temperature. The bond distances obtained from the Rietveld analyses did not vary significantly with the Ba content except that of Ni-O (parallel to the c -axis) which showed an abrupt increase from $x = 0.1$ to 0.2. The excess oxygen content (δ) decreases from 0.241 to 0.03 with increasing substituted Ba contents within the solution range. The samples are all semiconductors at the temperature range $4 < T < 300$ K.

Introduction

There has been a considerable effort to the study of $\text{Ln}_{2-x}\text{A}_x\text{NiO}_4$ (Ln: rare earths, A: alkaline earths) in both synthesis and structural characterizations.¹⁻⁴ These materials have attracted interest because of their close relationship to the superconducting $\text{Ln}_{2-x}\text{A}_x\text{CuO}_4$ phases.⁵ Furthermore, the reported metal-insulator transitions in $\text{La}_{2-x}\text{Sr}_x\text{NiO}_4$ ² and the anisotropic physical properties of La_2NiO_4 ^{3,4} prompted many research groups to investigate related $\text{Ln}_{2-x}\text{A}_x\text{NiO}_4$ systems. Besides the interesting metal-insulator transitions as a function of the amount of alkaline earths substitution (x)

and/or temperature, there are very intriguing questions to the structure and composition. The ideal tetragonal ($I4/mmm$) K_2NiF_4 (or A_2BO_4) structure (Figure 1) can be slightly modified into Fmmm, Pccn, Bmab, $P4_2/nm$ phases depending on the nature of the rare earth, the alkaline earth, degree of substitution (x), and the amount of excess interstitial oxygen (δ). Table 1 summarizes the reported results on the solid solutions of $\text{Ln}_{2-x}\text{A}_x\text{NiO}_{4+\delta}$ phases for their solid solution ranges and structures. It is noticeable that among the alkaline earths strontium is the most effective in forming solid solutions and is the only one that can stabilize the K_2NiF_4 -type structures with Sm,⁸ Gd,⁸ and Y¹² which themselves alone cannot even form nickelates in this structure type.

Unsubstituted $\text{Pr}_2\text{NiO}_{4+\delta}$ has variable structures depending on the amount of the interstitial oxygen (δ). The structure is in the space group Fmmm for $\delta > 0.20$,¹³ $P4_2/nm$ for $\delta =$

[§]This paper is dedicated to professor Woon-Sun Ahn in honor of his retirement.

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