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# Influence of solvation on the hydrogen bond in hydrogen malonate An ab initio and semiempirical study[1]

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## Abstract

The energy difference $\Delta E_{EZ}$ in vacuo between the closed (E) and open (Z) forms of the hydrogen malonate ion was computed at the ab initio HF/6-31G(d,p), 6-311++G(d,p), DFT B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p) levels. The effects of the polar environment were simulated by attaching discrete water molecules, by the self-consistent reaction field model (SCRF) and by the combination of both approaches. These simulations were done at the HF/6-31G(d,p) level.

The SCRF approach applied to both forms of the HM tetrahydrate yields the free energy difference of –0.73 kcal mol$^{-1}$, slightly favouring the open form; this contrasts the stabilization by ~20 kcal mol$^{-1}$ of the E form in vacuo. The metric parameters of the intramolecular hydrogen bond indicate a slight weakening of the intramolecular H-bond by the influence of hydration. Calculations at the PM3 level did not reproduce the ab initio computed $\Delta E_{EZ}$ values. © 1998 Elsevier Science B.V. All rights reserved

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## 1. Introduction

The possible role of strong hydrogen bonds in the energetics of enzyme reactions has given rise to heated discussions [1–6]. This has renewed the interest in the medium effects upon the properties of such hydrogen bonds, particularly on the stability in the aqueous environment [7]. In view of the difficulties with direct experimental characterization of H-bonded systems in aqueous solutions, adequate theoretical model studies may contribute to the issue.

Hydrogen malonate (HM) appears to be a suitable

object for investigating the effects of solvation on the stability of the intramolecular H-bond. The flexibility of the carbon skeleton makes HM a more adequate model for the intermolecularly bonded systems than the constrained systems such as hydrogen maleate [8]. Previous calculations of the difference between the in vacuo energies of the cyclic form E and the open form Z ($\Delta E_{EZ}$) that reflects the strength of the intramolecular H-bond in HM, show it to be on the strong side ($\Delta E_{EZ} = 22.4$ kcal mol$^{-1}$ at the 6-31G(d,p) level); the classical proton transfer barrier is estimated to be ~1 kcal mol$^{-1}$. The exact value depends on the level of calculation but it is definitely below the zeroth vibrational level [9]. The proton transfer dynamics in HM in aqueous solution have been studied by quantum dynamical simulations [10,11].

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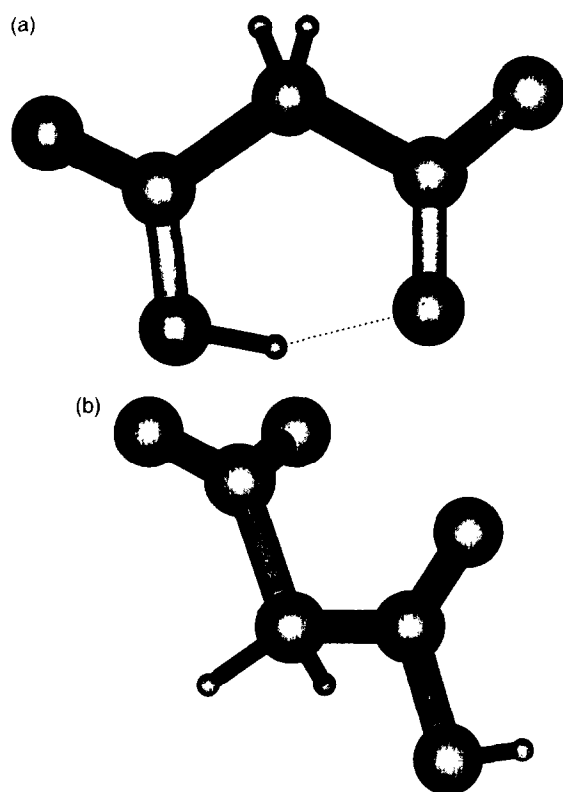[1] Dedicated to Professor Lucjan Sobczyk on the occasion of his 70th birthday.

Fig. 1. Optimized HF/6-31G(d,p) structures of hydrogen malonate isomers: (a) closed (Z), (b) open (E). For the E isomer the constraint of dihedral angle $OH-C-CH_2-O) = 180°$ was applied. Figs. 1–3 were plotted using the program MOLDEN written by G. Schaftenaar, Department of Chemistry, University of Nijmegen, The Netherlands.

The persistence of the intramolecular H-bond in dimethylsulfoxide (DMSO) solutions of various HM salts has been inferred from ^{13}C-NMR studies by Kidrič et al. [12]. However, infrared [13] and Raman spectroscopic investigations [14] of aqueous solutions indicate that in this solvent the intramolecular H-bond does not persist. This is in contrast to the ionization properties of malonic acid; the fairly high ratio of the first and second dissociation constants is attributed to the stabilization of the half ionized acid by intramolecular H-bonding [15,16]. Apparently, the presence of minor proportions of the E form cannot be detected by the optical methods. In solids, both the E and Z forms of acid salts were observed [17] depending on the cation. Remarkably, the E form of the potassium salt was obtained by crystallization from

DMSO while crystals containing the Z form were obtained from the aqueous solution; however, this crystal form is unstable.

The purpose of this work is the modelling of the effect of polar, particularly the aqueous environment, on the relative stabilities of the E and Z isomers of HM (Fig. 1(a) and 1(b)). This was done by calculating the total energies of both isolated isomers by the ab initio and hybrid HF-DFT schemes using the 6-31G(d,p) and 6-311++G(d,p) basis sets in the ab initio and B3LYP approximations. Since the comparative calculations showed the HF/6-31G(d,p) level to yield acceptable results, we adopted it for the subsequent calculations on the mono- and tetrahydrated HM supermolecules and of the free energies of solvation by the SCRF method of Tomasi et al. [18]. Hydration in the supermolecular approach strongly reduces the difference between the total energies ($\Delta E_{EZ}$) of the conformers, that is still favouring the E form, while the free energies of hydration differ by only 0.73 kcal mol$^{-1}$, in favour of the Z form.

## 2. Computational

The ab initio and DFT calculations were carried out by the GAUSSIAN 94 suite of programs [19] implemented on the Silicon Graphics Power Challenge parallel computer using the standard 6-31G(d,p) and 6-311++G(d,p) basis sets within the ab initio and DFT schemes. The program package also includes the SCRF method of Miertuš et al. [18]; the solute cavity is composed of interlocking spheres. In our study, the radii of the atomic spheres were van der Waals radii multiplied by 1.2 for all atoms and the original polarizable continuum model (PCM) version was used. The solvent permittivities were 78.3 and 20, which corresponds to bulk water and the protein interior, respectively. The full geometry optimization was carried out in vacuo for the isolated E isomer and the supermolecules. A partial geometry optimization of the Z isomer was performed under the constraint of the dihedral angle $(OH-C-CH_2-O)$ to 180°. For the PM3 calculations, the program package AMPAC 5.0, Semichem Inc. [20] was used, which includes the SCRF method of Cramer and Truhlar [21,22]; the PM3 SM3 algorithm was used.

Table 1
Total energies and selected metric parameters of the two conformers of hydrogen malonate. In vacuo calculations by ab initio and DFT methods

| Method/basis set | E(open) [a] | E(closed) [a] | $\Delta E$ [b] | $d$(O...O) [c] | $d$(OH) [d] |
|---|---|---|---|---|---|
| HF/6-31G(d,p) | – 414.853 062 | – 414.888 185 | 22.04 | 2.480 | 0.994 |
| B3LYP/6-31G(d,p) | – 417.079 020 | – 417.119 016 | 25.10 | 2.404 | 1.131 |
| HF/6-311++G(d,p) | – 414.987 212 | – 415.014 119 | 16.88 | 2.500 | 0.986 |
| B3LYP/6-311++G(d,p) | – 417.239 930 | – 417.272 918 | 20.70 | 2.430 | 1.082 |

[a] In a.u.
[b] E(open) and E(closed) in kcal mol$^{-1}$.
[c] Distance between the proton donating and accepting oxygens in Å in the closed form.
[d] Distance between hydrogen and the nearer oxygen in Å in the closed form.

## 3. Results and discussion

### 3.1. Total energies of the isolated conformers and supermolecules

The computed energy differences $\Delta E_{EZ}$ between the open and closed forms and the essential metric parameters are reported in Table 1. The ab initio
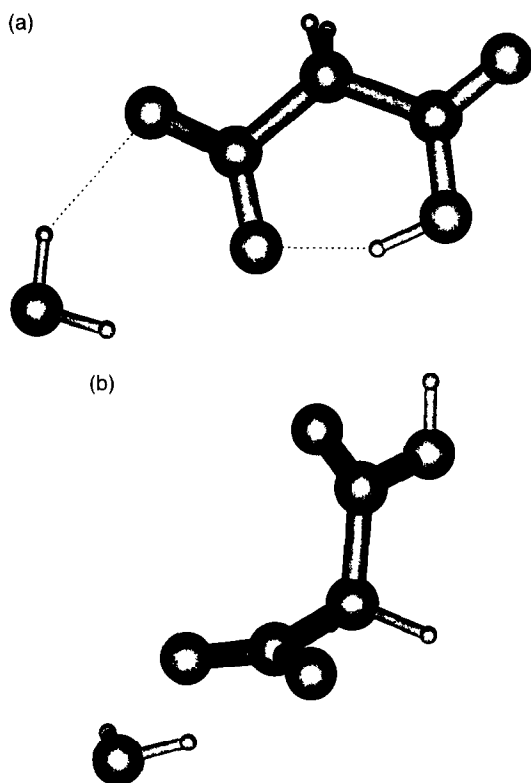


Fig. 2. Structures of hydrogen malonate conformers complexed with one water molecule: (a) closed, (b) open. Computed as for Fig. 1.

computed values are $\sim 10$ kcal mol$^{-1}$ less than the value computed at comparable level for the intermolecularly bonded hydrogen diformate with $C_{2h}$ symmetry [23]. The conformational energy difference $\Delta E_{EZ}$ is not simply equal to the energy of the intramolecular H-bond in HM. The latter is not linear (Fig. 1), in contrast with the intermolecular H-bond in hydrogen diformate. Part of the difference between the H-bond energy of the latter and $\Delta E_{EZ}$ of HM is due to the substantial deformation of the heavy atom skeleton in the E form: the angle at the methylene carbon is $\sim 117°$. Moreover, the geometry of the E form adopted as the reference for the non-H-bonded form of HM results from the optimization with the necessary, but somewhat arbitrary constraint.

The single water molecule was placed in the ab initio calculation to form double H-bonded, cyclic structures (Fig. 2). These correspond to the global minimum of the formate–water complex [24] which is stabilized by $- 20.5$ kcal mol$^{-1}$. The monohydrated, optimized Z form of HM is $\sim 6$ kcal mol$^{-1}$ less stable than the E form (Table 2).

The potential energy hypersurface of the HM tetrahydrates was explored by the PM3 method. Several secondary minima were identified besides the global one which corresponds to that resulting from the direct ab-initio energy minimizations (Fig. 3). The geometry optimization under the SCRF might change the relative depth of the minima but this is not expected to influence to any major degree the final conclusion concerning the similarity of $\Delta G$ of both isomers. The attachment of four water molecules is considerably more efficient in lowering $\Delta E_{EZ}$ of the free supermolecules. The $\Delta E_{EZ}$ of the tetrahydrates amounts to only 10% of the value (Table 2) of the non-hydrated HM isomers.
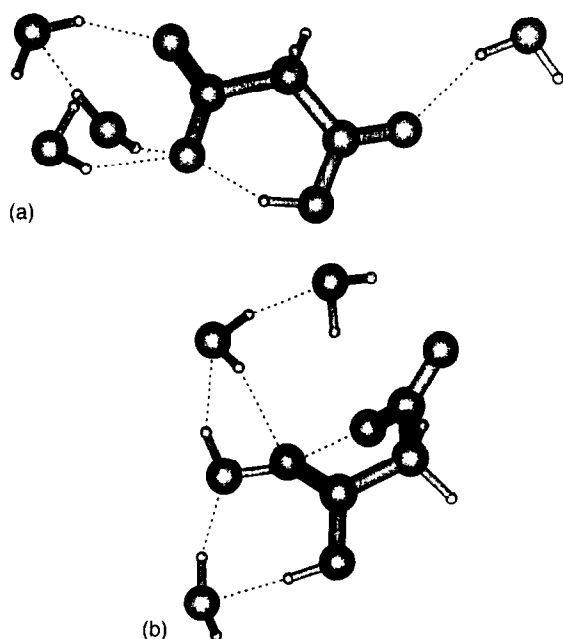
Fig. 3. Structures of hydrogen malonate conformers complexed with four water molecules: (a) closed (Z), (b) open (E). Computed as for Fig. 1.

## 3.2. Free energies of solvation

The free energy of hydration, calculated by the SCRF method of Tomasi et al. [18] with $\epsilon = 78.3$ is more negative for the Z form (Table 2). SCRF applied to the tetrahydrate thus makes this Z form slightly more stable in terms of $\Delta G$. This is in harmony, at least qualitatively, with the acid ionization properties of malonic acid [15,16]. In order to check the effect of

non-aqueous, polar media on the relative stability of the HM conformers, we carried out the SCRF calculation at $\epsilon = 20$. The resulting $\Delta G = 7.03$ kcal mol$^{-1}$ is only slightly above the value of 6.23 kcal mol$^{-1}$ obtained at $\epsilon = 78.3$. This result has a bearing on the discussion of the possible role of strong H-bonds in stabilizing the transition states in enzyme reactions.

## 3.3. Effect of solvation on the intramolecular H-bond

Simulation of the hydration by the attachment of explicit water molecules not only reduces $\Delta E_{EZ}$ but also affects the metric parameters of the intramolecular H-bond in the E form. The O–H bond length decreases from 0.994 Å to 0.982 Å. The O...O distance increases from 2.480 Å to 2.512 Å indicating a weakening of the intramolecular H-bond. It then appeared interesting to also examine the effect of SCRF in this context. The results of the pointwise energy calculation for fixed O...O distances are summarized in Fig. 4. The energy dependence of the isolated HM is shown for comparison. The minimum at about 2.55 Å is close to the value obtained by energy minimization of the HM tetrahydrate.

## 3.4. Comments on the methods of computation

In commenting on the reliability of the approaches employed, we first consider the effect of the level of calculation on the in vacuo conformational energies and energy differences $\Delta E_{EZ}$ (Tables 1 and 2). The difference between the two basis sets is rather large in both the ab initio and DFT methods. However, it is

Table 2
Relative and free energies (in kcal mol$^{-1}$) of solvation of hydrogen malonate

| Species | Form [a] | $\Delta E_{EZ}$ [b] HF/6-31G(d,p) | $\Delta G_{EZ}$ [c] HF/6-31G(d,p)// SCRF | $\Delta G_{hydr}$ HF/6-31G(d,p)// SCRF | $\Delta H_{EZ}^d$ PM3 in vacuo | $\Delta G_{EZ}$ [c] PM3-SM3 | $\Delta G_{hydr}$ PM3-SM3 |
|---|---|---|---|---|---|---|---|
| Isolated | E | 0.0 | 0.0 | − 64.68 | 0.0 | 0.0 | − 65.15 |
| ion | Z | 22.04 | 7.92 | − 78.81 | 13.07 | 3.08 | − 77.52 |
| Monohydrate | E | 0.0 | 0.0 | − 59.75 | – | – | – |
| | Z | 16.25 | 7.56 | − 68.44 | – | – | – |
| Tetrahydrate | E | 0.0 | 0.0 | − 57.99 | 0.0 | 0.0 | − 54.99 |
| | Z | 2.29 | − 0.73 | − 61.00 | 8.46 | 6.08 | − 57.33 |

[a] E, closed by intramolecular H-bond; Z, open.
[b] $\Delta E_{EZ} = E_E - E_Z$, in vacuo.
[c] $\Delta G_{EZ} = \Delta G_E - \Delta G_Z$.
[d] $\Delta H_E - \Delta H_Z$.
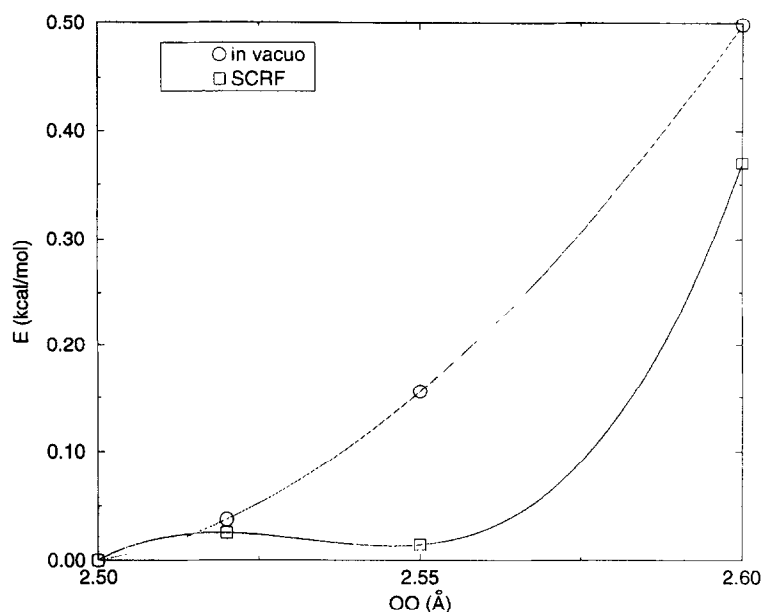
Fig. 4. Dependence of the total and free energies of the E form of hydrogen malonate on $R_{O\ O}$. Circles, free ion; squares, solvated (SCRF model).

comforting that the HF/6-31G(d,p) result is quite close to that obtained in the B3LYP/6-311++G(d,p) approximation. This is another confirmation of the well known, positive experience with the former theory in the treatment of H-bonded systems [25]. Hence, the use of the HF(6-31G(d,p) level for the further computations is justified. The success of this basis set at the HF level is due to the accidental cancellation of simplifications that also include the omission of the correlation energy. The size of the barrier for the proton transfer is very sensitive to correlation effects, but in the present context this barrier is not involved and with a conformational energy difference of ~20 kcal mol$^{-1}$ the correlation effects should not be crucial [26]. It is worth noting that the description of intramolecular H-bonding is, in general, still a difficult problem [27].

The PM3 method underestimates the strength of the intramolecular H-bond. This was also observed with other strong intramolecular H-bonds [28]. However, we expected that the method will perform better with hydration using discrete water molecules since $\Delta H$ of formation of the formate–water complex is comparable to the ab initio calculated value [29].

Methods of modelling the effects of hydration on molecular structure have been intensively developed

and discussed in the last two decades (for reviews, see Refs. [30–34]). The advantages of combined approaches — quantum mechanical treatment of at least the first hydration shell supplemented with the classical treatment of the dielectric continuum — have already been emphasized by Claverie et al. [35] and, more recently, by Rivail et al. [36].

Refinements of Tomasi's original version of the SCRF method have been proposed subsequently (Refs. [26,37] and references cited therein). Most of them are concerned with the parametrization of the solvent cavity and the compensation of the long range electrostatic effects of anions. The increase of the van der Waals radii proposed by Orozco et al. [38] proved to yield reasonable results of free energies of hydration; the inclusion of a first larger energy of hydration should reduce the long range effects of the net negative charge.

## 4. Conclusions

The ab initio and DFT calculations of the energies of the tetrahydrated conformers of HM immersed in the continuum dielectric as modeled by Tomasi's SCRF method slightly favour the open,

non-hydrogen-bonded Z form. This is in accord, at least qualitatively, with experimental evidence, particularly the ionization properties of HM. To obtain more precise results that could be compared with quantitative experimental data such as $pK_a$ values, more advanced methods, e.g. hybrid QM/MM and thermal averaging, using molecular dynamics or Monte Carlo, should be engaged. Differences in entropy due to the larger flexibility of the Z form should also somehow contribute to lowering $\Delta G$ of this form. Attempts at using the PM3 method in conjunction with the SCRF model of Cramer and Truhlar [21,22] have failed because of the inadequacy of the basic method for treating H-bonding in this system and despite the good quality of the SCRF calculation.

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