Dimerization of Carboxylic Acids: Reliability of Theoretical Calculations and the Effect of Solvent

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A large number of theoretical methods, ranging from classical calculations to high-level ab initio computations, have been used to study the dimerization of formic and acetic acids in the gas phase. Analysis of the results allows us to determine the range of accuracy expected for the different theoretical methods in the study of these types of interactions. The reasons for the errors occurring at high-level ab initio theory are discussed. Finally, the effect of the solvent on the dimerization of carboxylic acids is introduced using QM-SCRF, and MC-FEP methods. The reliability of both types of calculations is discussed. Results show that polar solvents play a key role in modulating the energetics of the dimerization of carboxylic acids. Dimerization free energies in the gas phase (1 atm) are found to be around −2 to −4 kcal/mol, values which are similar to those obtained in (1 M) chloroform solution. Dimerization free energies in (1 M) water are clearly positive (around 4−5 kcal/mol).

Introduction

Interactions involving carboxylic acids are very common in molecular recognition. The unique hydrogen-bond donor−acceptor properties of neutral carboxylic acids have been exploited to design new hosts able to bind tightly and selectively with specific molecules in apolar solvents.[1] Furthermore, there is increasing evidence supporting that neutral forms of aspartic and glutamic acids exist inside proteins, playing usually a key role in the mechanism of action of proteins.[2] These findings explain the attention paid to the capabilities of carboxylic acids to establish hydrogen-bonded interactions. In particular, most interest has been focused on the dimerization of carboxylic acids, which has been studied by means of experimental[1,3] and theoretical methods.[4] These studies have been mainly conducted for small acids, especially formic and acetic.

Despite the impressive research effort devoted to this issue, there are still notable uncertainties concerning the thermodynamics of the hydrogen-bond dimerization in the gas phase and in solution. This is reflected in the dispersion of the experimental energy and free energy changes for the dimerization in the gas phase and in apolar solvents, while whether the hydrogen-bonded complex exists in polar solvents like water is still the subject of debate. On the other hand, the theoretical estimates of thermodynamic quantities have large uncertainties, it being unclear what level of theory is necessary to describe accurately the hydrogen-bond dimerization. Furthermore, most theoretical studies have not examined the role of solvation, which plays a crucial role in these processes.[3j,m,5] It seems, then, necessary to clarify the thermodynamics of the hydrogen-

bond dimerization of carboxylic acids and the influence of the solvent on this key interaction.

In this paper we report the results of a systematic theoretical study of the dimerization of formic and acetic acids in the gas phase and in aqueous and chloroform solutions. Gas-phase calculations were performed using ab initio quantum mechanical (QM), ranging from medium level to state-of-the-art calculations, and density functional (DFT) methods. Indeed, the reliability of a variety of force fields in the framework of classical techniques was also examined. Comparison with the available experimental data allowed us to determine the preciseness of the theoretical methods. Analysis of the influence of diverse factors, such as basis set extension and treatment of electron correlation, allowed us to discuss the difficulty in determining the energetics of the hydrogen-bond dimerization. Finally, Monte Carlo−free energy perturbation (MC-FEP) simulations were used in conjunction with optimized QM self-consistent reaction field (SCRF) methods to determine the solvent effect on the dimerization. The contribution of solvation is critically examined.

Methods

Gas-Phase Calculations. Geometry optimization of formic and acetic acids, both in the syn conformations, in the respective monomer and dimer structures were performed in the gas phase at different ab initio QM and DFT levels. Only the most stable double-hydrogen-bond complex (C_{2h} symmetry) was considered for the dimer, since other conformations of the dimer are expected to play a minor role in the dimerization process.[4f] The minimum energy nature of the optimized geometries was verified by frequency analysis. Following G2 theory,[6] the ab initio energies were typically corrected by addition of zero-point energy and thermal and entropic contributions using empirically scaled HF/6-31G(d) frequencies. In some cases the

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vibrational frequencies were also determined at the MP2/6-31G-(d) and MP2/6-31+G(d) levels, without and with the frozen-core approximation, respectively. The corresponding zero-point energy and thermal corrections were within ±0.1 kcal/mol from the values determined with the scaled HF/6-31G(d) frequencies, while the entropy corrections differed by ±0.8 cal/K mol. Thermal and entropic corrections were determined at the same level used to optimize the geometry in DFT calculations.

A wide range of methods and basis sets ranging from HF/6-31G(d) to G1,[7] G2(MP2),[8] and G2[6] were utilized in ab initio calculations. Three hybrid nonlocal DFT methods, B3LYP,[9] B3PW91,[9b,10] and B3P86,[9b,11] were also used in conjunction with different basis sets. In all the cases, including G1, G2(MP2), and G2, the interaction energies were corrected for basis set superposition errors (BSSE) using the counterpoise method.[12]

Classical force-field calculations were performed using the MP2/6-31+G(d) optimized geometries. Only intermolecular electrostatic and van der Waals contributions were considered. The van der Waals parameters were taken from the optimized parameters for liquid simulations (OPLS) force field.[13] Different sets of atomic charges were considered, including empirical OPLS charges and electrostatic potential-derived (ESP) atomic charges[14] obtained from the HF/6-31G(d), MP2/6-311+G(2d,p), and B3LYP/6-31G(d) wave functions.

Calculations in Solution. The free energy of dimerization in solution (ΔG_d^{sol}) was determined (see eq 1) by addition of

$$\Delta G_d^{sol} = \Delta G_d^{gas} + \Delta\Delta G_{solv} + RT \ln(1/22.4) \quad (1)$$

the best ab initio estimate of the free energy of dimerization in the gas phase (ΔG_d^{gas}) to the difference in free energy of solvation between monomers and dimer ($\Delta\Delta G_{solv}$). This latter term was computed using SCRF and MC-FEP techniques. Note that a correction term[15] ($RT \ln(1/22.4) = -1.8$ kcal/mol) is necessary to account for the change of reference state from gas phase (ideal gas) to solution (1 M state). Calculations were performed in aqueous and chloroform solutions. The MP2/6-31G(d) gas-phase optimized geometries were used in computations.

In SCRF methods $\Delta\Delta G_{solv}$ was determined as the difference between the free energies of solvation for the dimer and the monomers. Calculations were performed using the SM5.4/A version[16] of AMSOL 6.1h,[17] the AM1 and 6-31G(d) QM-optimized versions of the MST method[18] for water and chloroform,[19] and the new SCRF *quasi-classical*-MST approach (qc-MST method; see eq 2 and ref 20).

$$\Delta G_{solv} = {}^1/_2 \int \rho^0 V_\sigma \quad (2)$$

where ρ^0 stands for the gas-phase charge distribution of the solute and V_σ stands for the solvent reaction field generated by the fully polarized solute in solution. The solute charge distribution was described using atomic charges fitted to both the electrostatic potential and field.[20b,c] Let us note that, even though eq 2 is classical, the solute−solvent polarization contribution to the free energy of solvation is accounted for, as explained in detail elsewhere.[20c]

In MC-FEP simulations[21] $\Delta\Delta G_{solv}$ was determined by subtracting the reversible work spent in annihilating a monomer in the solvated dimer to the work necessary to annihilate a monomer in solution (eq 3). At this point, it is worth noting that eq 3 is formally equivalent to eq 4.

$$\Delta\Delta G_{solv} = -(\Delta G_{dimer \to monomer} - \Delta G_{monomer \to nothing}) \quad (3)$$

$$\Delta\Delta G_{solv} = \Delta G_{solv}(dimer) - 2\Delta G_{solv}(monomer) \quad (4)$$

Mutations were performed using the windowing scheme and the electrostatic decoupling approach. Simulations were initially performed for the acetic acid using OPLS parameters.[13] The electrostatic part of the simulation was carried out in 21 (water) and 11 (chloroform) double-sampling windows, whereas the van der Waals part was performed in 21 windows for the two solvents. Each window involved 2 and 3 million configurations for equilibration and averaging, respectively.

ΔG_{solv} (and $\Delta\Delta G_{solv}$) for formic acid were determined by taking advantage of the results for acetic acid by mutating the OPLS parameters from acetic to formic in both the monomer and dimer structures. Since these simulations imply only mutation of the methyl group to a hydrogen, they were carried out in just six double-sampling windows consisting of 2 million configurations for equilibration and 3 million configurations for averaging (eq 5).

$$\Delta G_{solv}^{formic} = \Delta G_{solv}^{acetic} + \Delta G_{acetic \to formic} \quad (5)$$

The values of ΔG_{solv} and $\Delta\Delta G_{solv}$ were also determined using non-OPLS partial charges. They were obtained by mutating the OPLS charges of acetic and formic acids in the monomer and dimer to the other sets of charges (eq 6; see below). These simulations were performed using six double-sampling windows, each with 2 and 3 million configurations for equilibration and averaging.

$$\Delta G_{solv}^X = \Delta G_{solv}^{OPLS} + \Delta G_{OPLS \to X} \quad (6)$$

MC-FEP calculations were performed using preferential sampling to improve the statistic around the solute. Simulations were carried out in the isothermic−isobaric ensemble ($P = 1$ atm, $T = 298$ K) using periodic boundary conditions. The range of volume movements and solute translations and rotations were adjusted to obtain around 40% acceptance. The simulation systems consisted of a single solute embedded in around 504 TIP4P[22] waters or 127 chloroform[23] molecules. In addition to the OPLS parameters, electrostatic atomic charges determined at the HF/6-31G(d), MP2/6-311+G(d,p), and B3LYP/6-31G-(d) levels were also used. The solute−solvent and solvent−solvent cutoffs were 10 and 9 Å, respectively.

Gas-phase calculations were carried out using Gaussian 94[24] and in house programs. SCRF calculations were performed using a locally modified version of MonsterGauss[25] and computer programs developed by our group. ESP charges were determined with the MOPETE/MOPFIT programs.[26] Monte Carlo calculations were performed using BOSS 3.4.[27] All calculations were done in the IBM-SP2 computer program of the Centre de Supercomputació de Catalunya (CESCA), as well as on workstations in our laboratory.

Results and Discussion

Gas-Phase Results. Formic Acid. The gas-phase dimerization energies (ΔE_d), enthalpies (ΔH_d) and free energies (ΔG_d) computed at the ab initio and DFT levels are shown in Tables 1 and 2. Ab initio calculations were carried out at different levels of theory ranging from medium-level HF/6-31G(d) to state-of-the-art MP2/aug-cc-pVTZ and G2 calculations. Inspection of Table 1 reveals the notable dependence of the results on the level of theory in QM calculations. Convergence in the results is only achieved at very high levels of theory. The uncertainties in the results are clear in the values of ΔG_d, since they are determined as the difference between two very large numbers.

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TABLE 1: Energies, Enthalpies, and Free Energies ($T = 298$ K) for the Dimerization of Formic Acid in the Gas Phase Determined by ab Initio Methods[a]

geometry	Ψ	basis	ΔE_d	ΔH_d	ΔG_d
HF/6-31G(d)	HF/6-31G(d)	98	−12.9	−11.2	−0.9
MP2(f)/6-31G(d)	MP2(f)/6-31G(d)	98	−13.2	−11.5	−1.2
MP2(f)/6-31G(d)	MP2/6-311G(d,p)	132	−11.6	−9.9	0.4
MP2(f)/6-31G(d)	MP4/6-311G(d,p)	132	−11.3	−9.6	0.7
MP2(f)/6-31G(d)	QCISD(T)/6-311G(d,p)	132	−11.5	−9.8	0.5
MP2(f)/6-31G(d)	MP2/6-311+G(d,p)	156	−11.7	−10.0	0.3
MP2(f)/6-31G(d)	MP4/6-311+G(d,p)	156	−11.5	−9.8	0.5
MP2(f)/6-31G(d)	MP2/6-311G(2df,p)	204	−13.8	−12.1	−1.8
MP2(f)/6-31G(d)	MP4/6-311G(2df,p)	204	−13.5	−11.8	−1.5
MP2(f)/6-31G(d)	MP2/6-311+G(3df,2p)	270	−14.5	−12.8	−2.5
MP2/6-31+G(d)	MP2/6-31G(d)	98	−13.3	−11.6	−1.3
MP2/6-31+G(d)	HF/6-31G(d)	110	−12.6	−10.9	−0.6
MP2/6-31+G(d)	MP2/6-31G(d,p)	110	−13.2	−11.5	−1.2
MP2/6-31+G(d)	MP2/6-31+G(d)	122	−12.8	−11.1	−0.8
MP2/6-31+G(d)	MP2/6-311G(d,p)	132	−11.8	−10.1	0.2
MP2/6-31+G(d)	MP2/6-311++G(d,p)	160	−11.9	−10.2	0.1
MP2/6-31+G(d)	MP4/6-311G(d,p)	132	−11.5	−9.8	0.5
MP2/6-31+G(d)	QCISD(T)/6-311G(d,p)	132	−11.7	−10.0	0.3
MP2/6-31+G(d)	HF/6-311+G(2d,p)	186	−12.2	−10.5	−0.2
MP2/6-31+G(d)	MP2/6-311G(2d,p)	162	−13.3	−11.6	−1.3
MP2/6-31+G(d)	MP2/6-311G(2d,2p)	174	−13.6	−11.9	−1.6
MP2/6-31+G(d)	MP2/6-311+G(2d,p)	186	−13.4	−11.7	−1.4
MP2/6-31+G(d)	MP2/6-311G(2df,p)	204	−13.8	−12.1	−1.8
MP2/6-31+G(d)	MP2/cc-pVTZ	236	−14.2	−12.5	−2.2
MP2/6-31+G(d)	MP2/6-311+G(3df,2p)	270	−14.5	−12.8	−2.5
MP2/6-31+G(d)	MP2/6-311++G(3df,3pd)	306	−14.6	−12.9	−2.6
MP2/6-31+G(d)	MP2/aug-cc-pVTZ	368	−15.3	−13.6	−3.3
G1				−12.2	−1.9
G2(MP2)				−12.7	−2.4
G2				−12.8	−2.5

[a] In all cases the BSSE was corrected using the counterpoise method. Zero-point, thermal, and entropic terms were determined using scaled HF/6-31G(d) frequencies for all geometries following G-theory. All the values are in kcal/mol. The number of basis functions refers to the dimer.

TABLE 2: Thermodynamic Parameters ($T = 298$ K) for the Formic Acid Dimerization in the Gas Phase Determined Using Hybrid Nonlocal DFT Methods[a]

geometry	Ψ	ΔE_d	ΔH_d	ΔG_d
B3P86/6-31G(d)	B3P86/6-31G(d)	−16.5	−15.1	−3.9
B3PW91/6-31G(d)	B3PW91/6-31G(d)	−14.7	−13.3	−2.1
B3LYP/6-31G(d)	B3LYP/6-31G(d)	−15.2	−13.7	−2.6
B3P86/6-311G(2d,p)	B3P86/6-311G(2d,p)	−16.3	−15.1	−3.7
B3PW91/6-311G(2d,p)	B3PW91/6-311G(2d,p)	−14.7	−13.6	−2.3
B3LYP/6-311G(2d,p)	B3LYP/6-311G(2d,p)	−15.0	−13.7	−2.5
B3P86/6-311+G(2d,p)	B3P86/6-311+G(2d,p)	−16.3	−15.0	−3.7
B3PW91/6-311+G(2d,p)	B3PW91/6-311+G(2d,p)	−14.2	−12.9	−1.7
B3LYP/6-311+G(2d,p)	B3LYP/6-311+G(2d,p)	−14.6	−13.1	−2.0

[a] BSSE was corrected for all calculations. Thermal and entropic terms were determined using frequencies determined at each level of calculation. All the values are in kcal/mol.

Results in Table 1 show that the thermodynamic quantities are quite independent of the ab initio method used to optimize the geometries of monomer and dimer species. This is noted, for instance, in the close similarity between the values of ΔE_d (differences around 0.1−0.2 kcal/mol) determined at the same level of theory with MP2(f)/6-31G(d) and MP2/6-31+G(d) geometries (see also Table 3). Comparison of the zero-point energy, thermal and entropic corrections determined from scaled HF/6-31G(d) frequencies, or from the vibrational analysis of the MP2(f)/6-31G(d) and MP2/6-31+G(d) optimized geometries shows very close agreement (see Methods). Therefore, the thermodynamics of the dimerization is not sensibly affected by the method used to either optimize the geometry or compute frequencies.

The effect of the basis set on the energetics of dimerization

TABLE 3: Energies, Enthalpies, and Free Energies ($T = 298$ K) for the Dimerization of Acetic Acid in the Gas Phase Determined by ab Initio Methods[a]

geometry	Ψ	basis	ΔE_d	ΔH_d	ΔG_d
HF/6-31G(d)	HF/6-31G(d)	136	−13.1	−11.5	−1.3
HF/6-31G(d)	HF/6-311++G(d,p)	232	−12.5	−10.8	−0.7
HF/6-31G(d)	MP2/6-311++G(d,p)	232	−12.6	−11.0	−0.8
MP2(f)/6-31G(d)	MP2(f)/6-31G(d)	136	−13.3	−11.7	−1.5
MP2/6-31+G(d)	HF/6-31+G(d)	168	−12.8	−11.2	−1.0
MP2/6-31+G(d)	MP2/6-31+G(d)	168	−13.3	−11.7	−1.5
MP2/6-31+G(d)	MP4/6-31+G(d)	168	−13.0	−11.4	−1.1
MP2/6-31+G(d)	QCISD(T)/6-31+G(d)	168	−13.1	−11.5	−1.3
MP2/6-31+G(d)	MP2/6-311+G(d)	200	−12.3	−10.6	−0.5
MP2/6-31+G(d)	MP2/6-311++G(d,p)	232	−12.5	−10.9	−0.7
MP2/6-31+G(d)	MP4/6-311+G(d)	200	−11.9	−10.2	0.1
MP2/6-31+G(d)	MP2/cc-pVTZ	352	−14.7	−13.1	−2.9
MP2/6-31+G(d)	HF/6-311+G(2d,p)	264	−12.5	−10.9	−0.7
MP2/6-31+G(d)	MP2/6-311G(2d,p)	232	−13.7	−12.1	−1.9
MP2/6-31+G(d)	MP2/6-311+G(2d,p)	264	−14.0	−12.4	−2.2
MP2/6-31+G(d)	MP2/6-311+G(3df,2p)	384	−15.0	−13.4	−3.2
MP2/6-31+G(d)	MP2/6-311++G(3df,3pd)		−15.1	−13.5	−3.3
MP2/6-31+G(d)	MP2/aug-cc-pVTZ		−15.8	−14.2	−4.0
G2				−13.4	−3.2

[a] In all cases the BSSE was corrected using the counterpoise method. Zero-point, thermal, and entropic terms were determined using scaled HF/6-31G(d) frequencies for all geometries following G-theory. MP2/6-311++G(3df,3pd), MP2/aug-cc-pVTZ, and G2 values were estimated from results for formic acid (see text). All the values are in kcal/mol.

is much larger than that of electronic correlation. Thus, the change from MP2 to MP4(SDTQ) or QCISD(T) levels leads, in general, to small changes (typically around 0.3 kcal/mol) in the free energy of dimerization, suggesting a good convergence regarding the contribution of electron correlation. On the contrary, expansion of the basis set changes ΔG_d by more than 4 kcal/mol, and very large basis sets are required to achieve reasonable convergence. In general, the values of ΔG_d become more negative as the basis is enlarged. For instance, ΔG_d amounts to +0.5, −1.8, and −3.3 kcal/mol for the 6-311G-(d,p), 6-311G(2df,p), and aug-cc-pVTZ basis[28,29] (132, 204, and 368 basis functions, respectively). Addition of polarization functions over heavy atoms has remarkable influence on the results. Thus, extension from one to two sets of d-orbitals reduces ΔG_d by around 2 kcal/mol, and inclusion of a third set of d-orbitals plus a set of f-orbitals further decreases ΔG_d by 1 kcal/mol. However, polarization functions over the hydrogens have little effect on the results. Thus, at the MP2 level the addition of a set of p-orbitals to the 6-31G(d) and 6-311G(2d,p) basis changes ΔG_d by 0.1 and 0.3 kcal/mol, while expanding the basis from 6 to 311+G(3df,2p) to 6-311++G(3df,3pd) leads to a variation in ΔG_d of only 0.1 kcal/mol. Diffuse functions have also a moderate effect in Pople's basis, which is slightly remarkable for a small basis and clearly negligible for large basis sets. Thus, at the MP2 level, addition of a set of diffuse functions to the 6-31G(d) basis changes ΔG_d by 0.5 kcal/mol, but addition of such a set to the 6-311G(2d,p) basis varies ΔG_d by only 0.2 kcal/mol. As expected, a notable improvement is found in Dunning's basis sets upon inclusion of large sets of polarization functions (compare cc-pVTZ and aug-cc-pVTZ results in Table 1).

The thermodynamic quantities determined from DFT calculations (see Table 2) are generally more negative than the ab initio values. Indeed, the DFT results are rather less sensitive to basis set extension, as noted in the similarity of the values determined with the 6-31G(d) and 6-311+G(2d,p) basis. The entropy term in DFT computations amounts to around 37 cal/K mol, only slightly larger than the ab initio value. Finally, as expected from the values of ΔH_d, the free energy of dimerization is in

general more negative than the MP2 results estimated with the same basis, the difference MP2-DFT being slightly reduced for the largest basis. The B3P86 functional provides the most negative values of ΔG_d, while both B3PW91 and B3LYP functionals give similar results.

Several theoretical studies focused on the dimerization of formic acid have been reported.[4] Since most of them were performed with low- or medium-level calculations, there are notable uncertainties in the energetics of the dimerization. To our knowledge, the highest level computations were performed by Neuheuser et al.,[4c] who estimated ΔH_d to be −13.1 kcal/mol at the MP2/VQZ2PP//MP2/TZ2P level, and by Kim,[4h] who determined a value of −14.2 kcal/mol for ΔH_d using G2 theory without BSSE correction. This latter study also provided, to the best of our knowledge, the best DFT estimate of ΔE_d, −15.7 kcal/mol, determined at the B3LYP/aug-cc-pVDZ level. As expected, these values agree well with our best ab initio and DFT estimates.

A large number of experimental thermodynamic data for the dimerization of formic acid are available.[3] With only one exception,[3i] where ΔH_d was reported to be −11.7 kcal/mol, the experimental enthalpy is around −14.5 (±0.5) kcal/mol (average and standard deviation of experimental results; ref 3a,b,e−h,o,n). This average value agrees reasonably well with our best estimates: −13.6 (MP2/aug-cc-pVTZ), −12.9 (MP2/6-311++G-(3df,3pd), and −12.8 (G2) kcal/mol. However, it is clear that these estimates are too small (in absolute terms) compared to the experimental values, the difference ranging from 0.9 to 1.7 kcal/mol. Such an underestimation is even higher for lower level calculations, the deviation being larger than 5 kcal/mol at the MP4/6-311G(d,p) level. The DFT results agree better with experimental data, especially when the 6-31G(d) basis set is used, the error ranging from 0.6 kcal/mol (B3P86) to 1.2 kcal/mol (B3LYP).

Experimental values of the entropic contribution are difficult and likely contain significant uncertainties. However, the available data point out an entropy difference of 37−39 cal/K mol,[3e,n,o] which agrees with the DFT estimates (37 cal/K mol) and are close to the scaled HF/6-31G(d) value (35 cal/K mol). Accordingly, ΔG_d at 298 K is estimated to be around −3.2 kcal/mol, with an expected error of ±0.8 kcal/mol. Within this range of error, this value compares with our best theoretical estimates: −3.3 kcal/mol (MP2/aug-cc-pVTZ), −2.6 MP2/6-311++G(3df,3pd), and −2.5 (G2) kcal/mol. As expected, the agreement is worse when medium-sized basis sets are used, since even positive values of ΔG_d are obtained. DFT calculations provide good estimates of ΔG_d, especially when the 6-31G-(d) basis set is used, while surprisingly the results are slightly worse when large basis sets are used. As expected from the ΔH_d values, B3LYP and B3PW91 give too small (in absolute terms) values, while the B3P86 results overestimate the experimental values.

Acetic Acid. Extension of the preceding study to the acetic acid allowed us to explore whether the trends mentioned above are applicable to other carboxylic acids. The gas-phase dimerization energies, enthalpies, and free energies for acetic acid using ab initio and DFT methods are given in Tables 3 and 4.

Results in Table 3 reflect the same trends noted before for the dimerization of formic acid. Clearly, the effect of electron correlation is moderate, while the basis set extension leads to dramatic changes in the energetics. Increasing the polarization functions on heavy atoms seems to be necessary to obtain reasonable results, while polarization on hydrogens or addition of diffuse functions is sensibly less relevant. Comparison of

TABLE 4: Energies, Enthalpies, and Free Energies ($T = 298$ K) for the Dimerization of Acetic Acid in the Gas Phase Determined by Hybrid Nonlocal DFT Methods[a]

geometry	Ψ	ΔE_d	ΔH_d	ΔG_d
B3P86/6-31G(d)	B3P86/6-31G(d)	−16.9	−15.6	−4.4
B3PW91/6-31G(d)	B3PW91/6-31G(d)	−15.1	−13.7	−2.5
B3LYP/6-31G(d)	B3LYP/6-31G(d)	−15.6	−14.1	−3.0
B3P86/6-311+G(2d,p)	B3P86/6-311+G(2d,p)	−16.8	−15.7	−4.4
B3PW91/6-311+G(2d,p)	B3PW91/6-311+G(2d,p)	−14.7	−13.5	−2.3
B3LYP/6-311+G(2d,p)	B3LYP/6-311+G(2d,p)	−15.1	−13.6	−2.4

[a] In all cases the BSSE was corrected using the counterpoise method. Zero-point, thermal, and entropic terms were determined using frequencies determined at each level of calculation. All the values are in kcal/mol.

the results in Tables 1 and 3 shows that the thermodynamic quantities for dimerization of acetic acid are always more negative than for formic acid. This finding, which is also found experimentally (see below), stems from the polarizing effect of the methyl group. The difference between the free energy of dimerization of the two acids is quite constant at all the calculational levels, provided the basis set is larger than the 6-31G(d) one, it being estimated to be 0.7 ± 0.1 kcal/mol. This allowed us to obtain indirect values at the G2, MP2/aug-cc-pVTZ and MP2/6-311++G(3df,3pd) levels of theory (see Table 3), which are not affordable for the acetic acid dimerization with current computational resources.

As noted for the formic acid dimerization, DFT results are little affected by the basis set. Indeed, they compare well with the highest level ab initio values. The B3P86 functional provides the most negative dimerization energies, while B3PW91 and B3LYP functionals give similar results. The dimerization entropy is slightly larger (around 3 cal/K mol) than the value determined from scaled HF/6-31G(d) frequencies. Finally, the dimerization free energy at the B3P86 level is more negative than the highest level ab initio values, while the B3LYP and B3PW91 results are lower (in absolute values) than the ab initio ones.

Experimental enthalpies of dimerization for acetic acid ranges between −14.2 and −15.3 kcal/mol,[3b,e−g,o] the average value being −14.8 ± 0.4 kcal/mol, which is 0.3 kcal/mol more negative than the average value for formic acid. Data for the dimerization entropy are more scarce, but the available values[3e,f,o] are close to −35.8 ± 0.3 cal/K mol, which is around 1 cal/K mol lower than for formic acid. The free energy of dimerization at 298 K is, therefore, expected to be −4.1 ± 0.4 kcal/mol, around 0.9 kcal/mol more negative than for dimerization of formic acid. Our best QM estimates of ΔH_d are close to the experimental values. Indeed, the ΔS_d determined from scaled-HF/6-31G(d) frequencies is only around 1 cal/K mol less negative than the experimental value. Finally, this agreement between high-level QM data and experimental results is also reflected in the free energy of dimerization, as stated from inspection of the highest level ab initio results provided a very large basis is used (see Table 3). The DFT values of ΔH_d are also reasonable, while the dimerization entropy differences are 1−2 cal/K mol more negative than the experimental values. The best DFT estimate of ΔG_d is provided by the B3P86 functional, while B3LYP and B3PW91 underestimate the stability of the acetic dimer.

In summary, it is worth noting that the trends found for dimerization of either acetic or formic acids are very similar. This suggests that most of the methodological considerations inferred from the study of formic acid dimerization can likely be applicable to other dimerization processes, at least of related carboxylic acids.

TABLE 5: Classical Estimates of the Electrostatic (ΔE_d(ele)) and Total Dimerization Energy (ΔE_d)[a]

dimer	charges	ΔE_d(ele)	ΔE_d	ΔH_d[c]
formic	OPLS[b]	−15.6	−15.2	−13.5
	ESP(HF/6-31G(d))	−17.5	−17.1	−15.4
	ESP(B3LYP/6-31G(d)	−14.0	−13.6	−11.9
	ESP(MP2/6-311+G(2d,p))	−14.5	−14.1	−12.4
acetic	OPLS	−15.7	−15.4	−13.8
	ESP(HF/6-31G(d))	−18.0	−17.7	−16.1
	ESP(B3LYP/6-31G(d)	−14.5	−14.3	−12.7
	ESP(MP2/6-311+G(2d,p))	−14.9	−14.6	−13.0

[a] OPLS van der Waals parameters were used in all cases. [b] OPLS charges for formic taken from acetic acid. [c] Zero-point and thermal corrections from scaled HF/6-31G(d) frequencies (Tables 1−3). All the values are in kcal/mol.

Finally, let us explore the reliability of classical force-field calculations. To verify this, the dimerization energies were computed by force-field-derived techniques (see Methods). The results in Table 5 stress the electrostatic nature of the interaction, since the van der Waals term accounts only for 0.4 kcal/mol of the total interaction energy. The results show the excellent accuracy of the classical interaction energies for the hydrogen-bond dimer of carboxylics acids. Thus, the results determined with OPLS parameters agree very well with results derived from the highest level calculations and with the experimental data. It is also remarkable that the classical energy values obtained by using ESP charges are generally better than those obtained from the corresponding QM calculation.

Results in Solution. A total of 32 MC-FEP simulations were performed to determine the effect of water and chloroform on the hydrogen-bond dimerization. The free energy changes, as well as the hysteresis and standard errors, are shown in Figures 1 and 2. Processing these results with the appropriate thermodynamic cycles (eqs 3−6) allowed us to determine the free energy of solvation of monomer and dimers (ΔG_{sol}) and the solvation contribution to the dimerization ($\Delta\Delta G_{sol}$). The results are shown in Table 6, which also reports the available experimental data for comparison. The corresponding SCRF results are given in Table 7.

MC-FEP estimates of ΔG_{sol} for acetic acid in aqueous solution range from −5.4 to −8.0 kcal/mol depending on the set of charges. This range of values is similar to that found in SCRF results (from −5.6 to −7.3 kcal/mol), depending on the formalism used to account for solvent effects. The experimental value of ΔG_{sol} is −6.7 kcal/mol, which lies within the range of theoretical values. The agreement with theoretical estimates is especially good for the MC-FEP(OPLS) and 6-31G(d)/MST results. The ΔG_{sol} of formic acid is slightly more negative than for acetic acid, the largest difference being 0.5 kcal/mol. Accordingly, attachment of the methyl group to formic acid does not lead to a substantial change in the hydration of this compound.

Solvation of acetic acid in chloroform is less favorable than in aqueous solution. The MC-FEP values range between −3.6 and −3.9 kcal/mol. As expected, the origin of partial charges has little influence on ΔG_{sol}, due to the reduced importance of solute−solvent electrostatic interactions in chloroform solution. The SCRF results vary between −4.0 and −5.3 kcal/mol, which are on average slightly more negative than the MC-FEP values. The experimental value of the free energy of solvation in chloroform, as estimated from the hydration free energy and water/chloroform partition coefficient,[30] is −4.5 kcal/mol, which agrees with SCRF values and is close to MC-FEP estimates. Solvation of formic acid is around 0.7 kcal/mol less negative
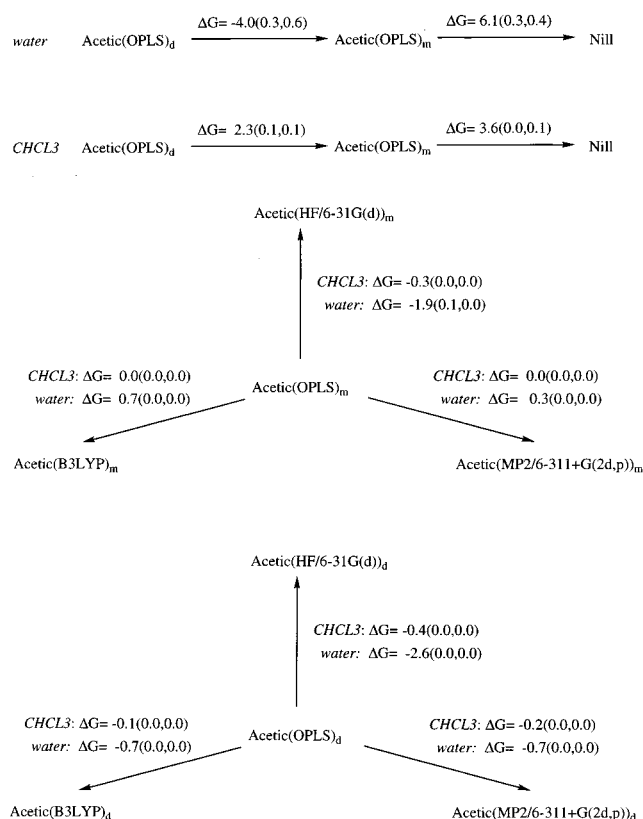

Figure 1. FEP mutations performed for the acetic acid. The numbers in parentheses correspond to the standardard deviation in the averages and to the hysteresis error. All the values are in kcal/mol.

than for acetic acid according to MC-FEP and MST calculations, this difference being slightly larger (1.4 kcal/mol) according to AMSOL results. Therefore, the presence of the methyl group leads to an important change in the preferential solvation of formic and acetic acids between aqueous and chloroform solutions. Note that this effect would alter the partitioning of these compounds in aqueous and organic phases (around 0.4− 0.5 log *P*(water/chloroform) units from MC-FEP and SCRF data), even when the intrinsic (gas phase) hydrophilicity of the carboxylic acid is not altered by the presence of a methyl group.

The dimers of acetic and formic acid are less well solvated than the corresponding monomers, which can be explained by the dipole annihilation of the monomers in the complex and by the loss of hydrogen-bonding capabilities upon dimerization. In fact, in aqueous solution the solvation contribution to the dimerization is very unfavorable, the MC-FEP and SCRF estimates ranging typically between 8 and 10 kcal/mol. The average MC-FEP value of $\Delta\Delta G_{solv}$ in water is 9.9 and 9.6 kcal/mol for formic and acetic acids, which is similar to the average SCRF results, 9.3 and 8.9 kcal/mol, respectively. The agreement between MC-FEP and SCRF results is very remarkable considering the large magnitude of the number and gives confidence to the theoretical estimates of the hydration effect.

Chloroform has a less, but still significant, perturbing effect on the dimerization. MC-FEP calculations suggest average $\Delta\Delta G_{solv}$ values of 1.0 (formic acid) and 1.3 (acetic acid) kcal/mol, while SCRF calculations give slightly more positive values: 2.9 (formic acid) and 2.4 (acetic acid) kcal/mol. The average value for the eight available theoretical estimates is 2.0 (formic) and 1.9 (acetic acid) kcal/mol.

Despite the numerical uncertainties, both MC-FEP and optimized SCRF methods give, in general, a reliable representation of the solvent effect on the hydrogen-bond dimerization of
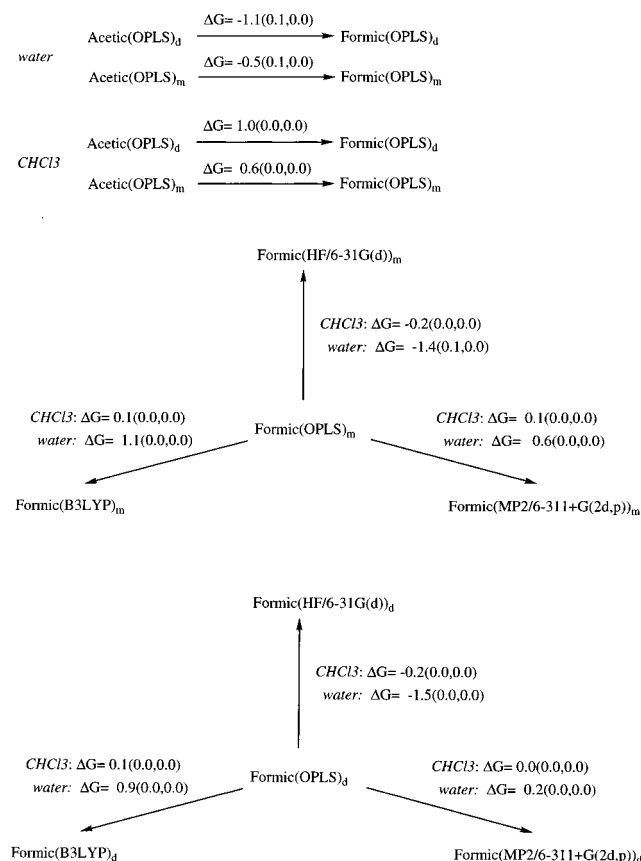
Figure 2. FEP mutations performed for the formic acid. The numbers in parentheses correspond to the standardard deviation in the averages and to the hysteresis error. All the values are in kcal/mol.

TABLE 6: Different FEP Estimates of the Free Energies of Solvation in Water and Chloroform of the Monomer ($\Delta G_{solv}^{(m)}$) and Dimer ($\Delta G_{solv}^{(d)}$) of Acetic and Formic Acids[a]

molecule	solvent	charges	$\Delta G_{solv}^{(m)}$	$\Delta G_{solv}^{(d)}$	$\Delta\Delta G_{solv}$
acetic	water	OPLS	−6.1	−2.1	10.1
		B3LYP	−5.4	−2.4	8.4
		HF/6-31G(d)	−8.0	−4.7	11.3
		MP2/6-311+G(2d,p)	−5.8	−2.9	8.7
		experimental	−6.7		
acetic	chloroform	OPLS	−3.6	−5.9	1.3
		B3LYP	−3.6	−6.0	1.2
		HF/6-31G(d)	−3.9	−6.3	1.5
		MP2/6-311+G(2d,p)	−3.6	−6.1	1.1
		experimental	−4.5	1.7	
formic	water	OPLS	−6.6	−3.2	10.0
		B3LYP	−5.5	−2.3	8.7
		HF/6-31G(d)	−8.0	−4.7	11.3
		MP2/6-311+G(2d,p)	−6.0	−3.0	9.0
formic	chloroform	OPLS	−3.0	−4.9	1.1
		B3LYP	−2.9	−4.8	0.9
		HF/6-31G(d)	−3.2	−5.1	1.3
		MP2/6-311+G(2d,p)	−2.9	−4.9	0.9

[a] The solvation contribution to the dimerization process ($\Delta\Delta G_{solv}$) is also displayed. All the values are in kcal/mol. OPLS values for formic acids are only approximate, since charges for formic acid were transferred from acetic acid. Experimental $\Delta G_{solv}^{(m)}$ from ref 28. Experimental $\Delta\Delta G_{solv}$ from association constants in gas phase and chloroform in refs 1a and 3c,d.

carboxylic acids. At this point, it is fair to remark the good performance of SCRF calculations, which is at least comparable to that obtained from much more expensive MC-FEP calculations. In this respect, the good quality of the qc-MST method is encouraging considering that this type of calculation is very fast, since it does not imply to perform QM calculations on the

TABLE 7: Different SCRF Estimates of the Free Energies of Solvation in Water and Chloroform of the Monomer ($\Delta G_{solv}^{(m)}$) and Dimer ($\Delta G_{solv}^{(d)}$) of Acetic and Formic Acids[a]

molecule	solvent	SCRF	$\Delta G_{sol}^{(m)}$	$\Delta G_{solv}^{(d)}$	$\Delta\Delta G_{solv}$
acetic	water	AM1/MST	−5.9	−3.9	7.9
		AMSOL	−5.6	−3.7	7.5
		6-31G(d)/MST	−6.5	−3.9	9.1
		qc-6-31G(d)/MST	−7.3	−3.7	10.9
		experimental	−6.7		
acetic	chloroform	AM1/MST	−5.0	−8.1	1.9
		AMSOL	−4.0	−5.7	2.3
		6-31G(d)/MST	−5.2	−7.8	2.6
		qc-6-31G(d)/MST	−5.3	−7.8	2.8
		experimental	−4.5		1.7
formic	water	AM1/MST	−6.2	−3.9	8.5
		AMSOL	−5.6	−3.2	8.0
		6-31G(d)/MST	−6.6	−3.8	9.4
		qc-6-31G(d)/MST	−7.5	−3.9	11.1
formic	chloroform	AM1/MST	−4.4	−6.7	2.1
		AMSOL	−2.6	−2.6	2.6
		6-31G(d)/MST	−4.6	−6.1	3.1
		qc-6-31G(d)/MST	−4.7	−5.8	3.6

[a] The solvation contribution to the dimerization ($\Delta\Delta G_{solv}$) is also displayed. All the values are in kcal/mol.

TABLE 8: Estimates of the Free Energy of Dimerization for Formic and Acetic Acids in Aqueous and Chloroform Solutions[a]

molecule	gas-phase level	solvent	ΔG_d
formic	G2	water	+5.3
formic	MP2/aug-cc-pVTZ	water	+4.5
formic	G2	chloroform	−2.3
formic	MP2/aug-cc-pVTZ	chloroform	−3.1
acetic	G2	water	+4.3
acetic	MP2/aug-cc-pVTZ	water	+3.5
acetic	G2	chloroform	−3.1
acetic	MP2/aug-cc-pVTZ	chloroform	−3.9
acetic	experimental	chloroform	−2.4

[a] Two high-level QM methods were used to compute the gas-phase contribution. The solvation contribution was introduced as the average of the eight diffrent theoretical estimates obtained. Experimental result from refs 1a and 3c,d. Theoretical results are corrected for the change of reference state (−1.8 kcal/mol; see Methods). All values are in kcal/mol.

dimers, nor to carry out large molecular dynamics or Monte Carlo simulations.

The whole of results in Tables 6 and 7 strongly suggests that, irrespective of the methodology utilized (FEP or SCRF), the current state-of-the-art methods to represent solvation provide results of very high quality. Actually, comparison of Tables 1−4 and 7 with experimental data suggests that the accuracy of FEP and SCRF methods to treat solvent contributions is larger than that of the highest level ab initio methods to reproduce gas-phase interactions. In fact, the largest source of uncertainty in the calculation of the hydrogen-bond dimerization of carboxylic acids (and likely related species) in solution lies in the representation of the intrinsic interaction between monomers rather than in the solvent contribution.

Combination of the highest level gas-phase ab initio data (G2 and MP2/aug-cc-pVTZ) with the average of SCRF and FEP results (see eq 1) allowed us to estimate the free energy change for the hydrogen-bond dimerization of formic and acetic acids in chloroform and aqueous solutions (see Table 8). In general, dimerization of acetic acid is easier than that of formic acid, which largely stems from the gas-phase contribution. The dimerization free energies are negative (values between −2 and 4 kcal/mol) in chloroform, supporting the stability of the double H-bond dimer in 1 M chloroform. Note that −1.8 kcal/mol of

these dimerization free energies are due to the change of reference state from ideal gas conditions (1 atm) to 1 M solution (see eq 1).

It must be emphasized that theoretical estimates of dimerization free energy values should be taken with caution, since they are based on the assumption that the intrinsic entropic contribution to binding in gas phase and solution is the same, which is probably only a rough approximation.[31] However, despite this and other numerical uncertainties, the agreement of dimerization free energy in chloroform of acetic acid with experimental estimate (around −2.4 kcal/mol) is quite reasonable considering the large number of calculations necessary to determine the theoretical value.

It is clear that according to our calculations the hydrogen-bond dimerization of formic and acetic acids, which occurs easily in the gas phase and chloroform, does not happen in aqueous solution. The estimated free energy of dimerization is so large (around 4−5 kcal/mol) that no error in the calculations can be assumed to justify a significative change in the results. However, experimental studies of acetic acid dimerization in water have suggested free energy values ranging between 0.0 and 1.7 kcal/mol,[1a,3c,d] which are far from present theoretical results. This apparent disagreement suggests that the dimers detected experimentally in aqueous solutions cannot correspond to the double-hydrogen-bond dimer found in the gas phase or apolar solvents and considered in this study. Previous Monte Carlo studies on *N*-methylacetamide[32] suggested that the association of two *N*-methylacetamide molecules in water occurs via stacking interactions rather than through double-hydrogen-bond interactions. A similar situation is suggested here for carboxylic acids. Further work will be focused on the determination of the characteristics of possible carboxylic acid dimers in aqueous solutions.

Conclusions

High-level ab initio methods are able to reproduce quantitatively the thermodynamics of carboxylic acid dimerization in the gas phase. However, such an accuracy is obtained only at the highest level of ab initio theory. Correlation effects are not very important for the determination of dimerization energies, but very large and flexible basis sets, including a large number of polarization functions, are necessary to estimate accurately the energetics of this process. Medium-sized basis sets lead to quantitatively, and even qualitatively, incorrect results.

DFT methods provide a reasonably precise representation of the dimerization process in the gas phase, even when medium-sized basis sets are used. Classical calculations also provide estimates of the dimerization energy which are very accurate.

Calculations suggest that dimerization of acetic acid is slightly more favorable than that of formic acid, which should be related to the inductive and polarizable characteristics of the methyl group.

The hydrogen-bond dimerization of carboxylic acids is not favored in aqueous solution due to the very large disturbing effect of water solvation. This conclusion seems to be clearly out of the possible range of error of our calculations. It is suggested that carboxylic acid dimerization in water, if it occurs, takes place through other type of interactions.

Dimerization in 1 M chlroform solution is favorable for both acetic and formic acids. It is suggested that double H-bond structure is the principal component of carboxylic acid dimers in these apolar solvent.

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