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Impact of the Solvent on the Conformational Isomerism of Calix[4]arenes: A Study Based on Continuum Solvation Models

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The influence of solvation on the conformational isomerism of calix[4]arene and *p-tert*-butylcalix[4]arene has been investigated by using the continuum model reported by Miertus, Scrocco, and Tomasi (MST). The quantum mechanical (QM) and semiclassical (SC) formalisms of the MST model have been considered for two different solvents (chloroform and water). The suitability of the QM-MST and SC-MST methods has been examined by comparison with previous results derived from classical molecular dynamics (MD) simulations with explicit solvent molecules. The application of the continuum model to the solute configurations generated by using in vacuo classical MD simulations provides a fast strategy to evaluate the effects of the solvent on the conformational preferences of calixarenes. These encouraging results allow us to propose the use of continuum models to solutes with complex molecular structures, which are traditionally studied by MD simulations.

Introduction

An understanding of many chemical process cannot be achieved without an accurate description of the solvent effects.[1−3] In the past decades, this realization has led to the development of a wide variety of computational methods, which are able to describe the effects of the solvent on molecular energies, structures, and properties. Such methods can broadly be classified into two different categories: discrete and continuum.[3−5] The discrete model considers explicitly the microscopic representation of the solvent molecules. This model is rigorous and accurate results can be expected, although serious shortcomings derived from its computational expensiveness exist. In practice, the solvated system is usually described according to one of the following three approaches:[3,4] (a) supermolecule approach (the solute and the solvent are treated quantum mechanically and, therefore, only a few molecules can be explicitly included to mimic the whole environment surrounding the solute), (b) quantum mechanics/molecular mechanics (QM/MM) approach (the solute is treated quantum mechanically and the explicit solvent molecules are simulated by using a classical force field), and (c) molecular mechanics (MM) approach (both the solute and the solvent are described by means of classical particles).

The accuracy of the results produced by each approach depends on several factors such as the size of the solute, the number of solvent molecules considered, the magnitude of the contribution due to the self-polarization between the solute and the solvent, the goodness of the fixed classical potentials, etc.

In the continuum model the solvent is represented as a structureless polarizable medium characterized by properties such as the dielectric constant and the thermal expansion coefficient.[3,5] The macroscopic continuum medium reacts against the solute charge distribution, generating a reaction field that in turn affects the solute charge distribution. Thus, the self-polarization between the solute and the solvent is accounted for properly by using QM methods. The continuum model has the obvious shortcoming that short-range interactions between solute and solvent are not well represented. This deficiency is partially removed by the combined continuum/discrete strategy,[6,7] in which the solute is surrounded by an appropriate number of explicit solvent molecules, and then this cluster, as a unique entity, is inserted in the continuum medium.

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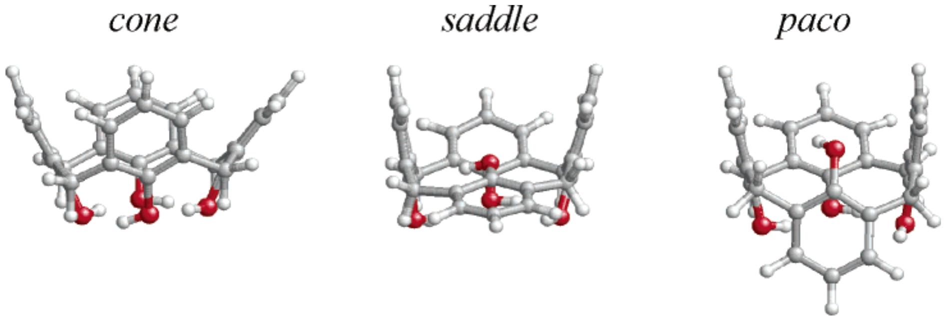
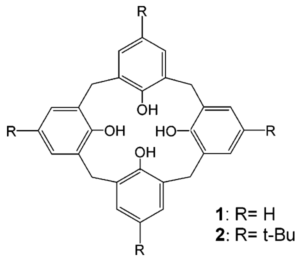


FIGURE 1. Atomistic representation of the cone, saddle, and paco conformations for **1**.

CHART 1



Complex organic molecules are the subject of intensive investigations in the field of supramolecular chemistry. Among them, calixarenes have received considerable attention because these compounds are able to bind a variety of guests.[8] Calixarenes are synthetic macrocyclic molecules built from phenolic units. The simplest representative of these macrocycles is the calix[4]arene (**1**), which only involves four phenol rings (Chart 1). Many other compounds have been prepared by introducing selective chemical modifications, the more common being at the phenolic hydroxy group, the para-position of the rings, and the methylene bridges.[9]

The conformational flexibility of **1** and its derivatives mainly arises from an oxygen-through-the-annulus rotation mechanism. The most relevant conformations are those denoted cone and partial-cone (paco), which differ in the orientation of one phenol ring with respect to the other three (Figure 1). NMR spectroscopy results indicated that, in some cases, the dynamic equilibrium between the cone and paco conformations is profoundly influenced by the polarity of the solvent.[8b,10] This conformational isomerism has been investigated by using theoretical methods in which the solvent is either neglected[9b,10c,11] or described with use of a discrete model through the MM approach,[12,13] the rates calculated with the latter method for the isomerization of calix[4]arene being in excellent agreement with experimental data.[12]

As far as we know, the continuum model has not previously been used to investigate the role of the solvent in the cone-to-paco conformational transition. This is an amazing situation since the application of this model to medium size molecules such as calix[4]arenes is computationally less expensive than the simulation of a periodic box containing many discrete solvent molecules. It should be noted that the inclusion of explicit solvent molecules implies that many configurations must be generated with molecular dynamics (MD) or Monte Carlo (MC) simulations to obtain a statistical treatment of the intermolecular interactions. Furthermore, the continuum model has successfully been employed to study the binding properties of calix[4]pyrrole,[14] a closely related compound with pyrrole rings rather than phenolic units, indicating that it provides a good description of molecules with complex architectures in solution.

The aim of this work is to investigate the isomerization of calixarenes by using the continuum model. For this purpose, the MST model,[3,15] which is an optimized version of the method developed by Miertus, Scrocco, and Tomasi,[5a,16] has been used to explore the role of the solvent in the cone-to-paco transition of **1** and *p-tert*-butylcalix[4]arene (**2**). Calculations have been performed considering the polarization effects within the QM and semiclassical (SC) frameworks of the MST model. Thus, a comparison between the results derived from QM-MST and SC-MST calculations will be valuable to check the reliability of the latter method when complex organic molecules are considered. Particular attention has been paid to the parametrization of the charges in SC-MST calculations. Furthermore, we have also studied the

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influence of the polarity of the environment by considering both chloroform and water as solvents.

Methodology and Technical Details

Generation of the Conformations. Three different conformational states (Figure 1) were considered for **1** and **2**: (i) the cone; (ii) the paco; and (iii) the saddle point, which corresponds to the transition state of the cone-to-paco transformation. It should be noted that thermal motion provides a certain degree of conformational freedom to such states. Accordingly, 100 configurations were generated for each conformational state through MD simulations with classical potentials. The force-field parameters for **1** and **2** were identical with those used in refs 12 and 13a. Simulations were performed in vacuo at 300 K, no cutoff being used for the nonbonding interactions. Configurations of the saddle point were generated by using constrained MD simulations. All calculations were performed with the GROMOS87[17] and DLPOLY_2[18] computer packages.

The MST Continuum Model. In the MST model, the solute is placed inside a molecular shape cavity embedded in the infinite dielectric medium. The free energy of solvation (ΔG_{sol}) is estimated from the addition of the electrostatic, cavitation, and van der Waals contributions.[15]

$$\Delta G_{\mathrm{sol}} = \Delta G_{\mathrm{ele}} + \Delta G_{\mathrm{cav}} + \Delta G_{\mathrm{vdW}} \tag{1}$$

The cavitation term has been computed by using Pierotti scaled particle theory[19] adapted to molecular-shaped solutes.[3,15] In eq 2, $\Delta G_{\mathrm{P},i}$ is the cavitation free energy of atom i in Pierotti's formalism, S_i is the solvent-exposed surface of atom i, S_{T} is the total solvent-exposed surface of the molecule, and N is the number of atoms.

$$\Delta G_{\mathrm{cav}} = \sum_{i=1}^{N} \frac{S_i}{S_{\mathrm{T}}} \Delta G_{\mathrm{P},i} \tag{2}$$

The van der Waals term has been evaluated by means of an empirically developed[15] linear relation with the molecular surface area,

$$\Delta G_{\mathrm{vdW}} = \sum_{i=1}^{N} \xi_i S_i \tag{3}$$

where ξ_i is the surface parameter of atom i. Specific surface parameters have been derived for different solvents.[15,20]

The electrostatic interaction between the solute and the solvent has been calculated by using the procedure originally developed by Tomasi and co-workers.[5a,16] Accordingly, the polarization of the dielectric by the solute charge distribution induces a reaction field, whose effect on the solute charge distribution is accounted for by a perturbation operator $\hat{V}_{\mathrm{R}}$ added to the gas-phase Hamiltonian in vacuo, $\hat{H}^0$:

$$\hat{H} = \hat{H}^0 + \hat{V}_{\mathrm{R}} \tag{4}$$

The perturbation operator is described in terms of a set of imaginary charges spread over the solute cavity (eq 5), which are obtained by solving the Laplace equation with suitable boundary conditions (eq 6). In eq 5, M is the total number of surface elements in which the solute/solvent boundary is divided, and $\{q_j\}$ is the set of charges (located at r_j) that represent the solvent response. In eq 6, ϵ is the solvent dielectric constant, V_{T} stands for the total (solute + solvent) electrostatic potential, and n is the unit vector normal to the surface element j. From these charges, the ΔG_{ele} can be obtained by using a QM or SC formalism.

$$\hat{V}_R = \sum_{i=1}^{M} \frac{q_i}{|r_i - r|} \tag{5}$$

$$q_j = -\frac{\epsilon - 1}{4\pi\epsilon} S_j \left(\frac{\partial V_{\mathrm{T}}}{\partial n}\right)_j \tag{6}$$

Choice of the solute/solvent interface is very important to provide reliable values of the electrostatic contribution. In the MST method the solvent-exposed surface, which is obtained upon an appropriate scaling of the atomic radii, is used to define the solute/solvent boundary. To avoid the presence of regions of dielectric medium that are too thin to accommodate a real solvent molecule, the scaling factor (κ) was specifically derived for each solvent. MC simulation indicated that the best values of κ for chloroform and water are 1.6 and 1.2,[15] respectively, which were used throughout the study.

Quantum Mechanical Formalism of the MST Model (QM-MST). If a QM formalism is used, the electrostatic contribution is determined as follows:

$$\Delta G_{\mathrm{ele}} = \left\langle \psi^{\mathrm{sol}} \middle| \hat{H}^0 + \frac{1}{2}\hat{V}_{\mathrm{R}} \middle| \psi^{\mathrm{sol}} \right\rangle - \langle \psi^0 | \hat{H}^0 | \psi^0 \rangle \tag{7}$$

where ψ is the solute wave function, and indices "0" and "sol" represent gas-phase and solvent environments, respectively. QM-MST calculations were performed by using the optimized versions developed for the semiempirical AM1 wave function,[21] which are implemented in the modified version of the MOPAC[22] program.

Semiclassical Formalism of the MST Model (SC-MST). In the classical framework ΔG_{ele} adopts the expression indicated in eq 8, where $\{Q_i\}$ and $\{q_k\}$ correspond to the sets of partial charges that represent the charge distribution of the solute and the solvent reaction field, and where r_i and r_k stand for the position vectors of the solute and solvent charges, respectively.

$$\Delta G_{\mathrm{ele}} = \frac{1}{2} \sum_{i=1}^{N} \sum_{k=1}^{M} \frac{Q_i q_k}{|r_i - r_k|} \tag{8}$$

To account for the contribution arising from the solute–solvent polarization effects, which are neglected in eq 8, ΔG_{ele} can be expressed as:[23]

$$\Delta G_{\mathrm{ele}} = \frac{1}{2} \sum_{i=1}^{N} \sum_{k=1}^{M} \frac{Q_i^0 q_k(Q_i^{\mathrm{sol}})}{|r_i - r_k|} \tag{9}$$

where $\{Q_i^0\}$ and $\{Q_i^{\mathrm{sol}}\}$ are the charge distributions of the solute in the gas phase and in solution, respectively, and $\{q_k(Q_i^{\mathrm{sol}})\}$is the solvent reaction field computed from the charges that represent the fully relaxed charge distribution of the solute in solution. In the SC-MST procedure the electrostatic interaction between the solute and the solvent is evaluated by using eq 9 rather than eq 7.[23]

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Obviously, the reliability of the SC-MST procedure largely depends on $\{Q_i^0\}$ and $\{Q_i^{\mathrm{sol}}\}$. In the present study electrostatic potential-derived charges centered at the nuclei were computed at the ab initio HF/6-31G(d) level[24] by using the Gaussian 98 computer program.[25] The influence of the strategy used to derive $\{Q_i^0\}$ and $\{Q_i^{\mathrm{sol}}\}$ was examined considering three different approaches:

Approach-1 (A1). Charges were computed only for the cone, which is the most stable conformation of both **1** and **2**, the electrostatic parameters for the paco and saddle being directly transferred from those of the cone. Furthermore, the four chemically equivalent fragments contained in the compounds under study (each fragment contains a phenolic ring and a methylene bridge) were constrained to have identical site charges. This approach closely follows the standard practice in MM of assigning identical charges to equivalent groups.

Approach-2 (A2). The dependence of the charges upon the conformation was taken into account. A specific set of atomic charges was computed for each of the three conformational states by using the procedure described above. However, chemically equivalent fragments were still required to have identical site charges within each state.

Approach-3 (A3). A set of parameters was developed for each conformation like above (A2), but no constraint was applied in the parametrization. Thus, each phenol was allowed to have its own set of atomic charges. For the paco and saddle large differences were found between the charges of the rotated phenolic unit and the other three, even although some differences were also detected among the latter.

For the three approaches, we included the effects produced by small thermal atomic motions on electrostatic parameters by evaluating the charges on several representative configurations of each conformation, and weighting them according to Boltzmann's distribution.[26]

Results and Discussion

Quantum Mechanical Calculations. The ΔG_{sol} values were computed for the cone, saddle, and paco conformations of **1** and **2** by using QM-MST calculations. A set of 100 configurations, which were generated through MD simulations in a vacuum, was considered for each conformational state. Results are displayed in Tables 1 and 2, which also show the effect of the solvent on the isomerization barrier [$\Delta\Delta G_{\mathrm{sol}}$(cone-saddle)] and on the reaction equilibrium between between cone and paco [$\Delta\Delta G_{\mathrm{sol}}$(cone-paco)].

The solvation of both **1** and **2** is more favorable in chloroform than in water. Thus, the free energy to transfer such compounds in the cone conformation from water to the organic solvent is −12.3 and −26.6 kcal/mol, respectively. Similar values are predicted for the saddle (−10.6 and −26.2 kcal/mol, respectively) and paco (−10.6 and −25.4 kcal/mol, respectively) conformations.

TABLE 1. Free Energies of Solvation (ΔG_{sol}, in kcal/mol) in Chloroform and Water Computed for the Cone, Saddle, and Paco Conformational States of 1[a] (see Chart 1) by Using Different Formalisms of the MST Model and the Influence of the Solvent on the Conformational Isomerism of This Compound Expressed in Terms of $\Delta\Delta G_{\mathrm{sol}}$

		QM	SC(A1)	SC(A2)	SC(A3)
chloroform	ΔG_{sol}(cone)	−21.6	−22.2	−22.2	−22.8
	ΔG_{sol}(saddle)	−21.6	−24.4	−23.4	−22.7
	ΔG_{sol}(paco)	−21.3	−25.0	−23.7	−22.8
	$\Delta\Delta G_{\mathrm{sol}}$(cone-saddle)	0.0	−2.2	−1.2	0.1
	$\Delta\Delta G_{\mathrm{sol}}$(cone-paco)	0.3	−2.8	−1.5	0.0
water	ΔG_{sol}(cone)	−9.3	−14.1	−14.1	−14.8
	ΔG_{sol}(saddle)	−11.0	−18.9	−16.6	−16.1
	ΔG_{sol}(paco)	−10.7	−20.5	−17.7	−16.2
	$\Delta\Delta G_{\mathrm{sol}}$(cone-saddle)	−1.7	−4.8	−2.5	−1.3
	$\Delta\Delta G_{\mathrm{sol}}$(cone-paco)	−1.4	−6.4	−3.6	−1.4

[a] A set of 100 configurations were considered for each conformational state. [b] MST: Miertus, Scrocco, and Tomasi solvation model. QM: quantum mechanical at the semiempirical AM1 level. SC(A1): semiclassical-approximation 1. SC(A2): semiclassical-aproximation 2. SC(A3): semiclassical-approximation 3. For a more detailed description of the methods used to evaluate the ΔG_{sol} see the Methods section.

TABLE 2. Free Energies of Solvation (ΔG_{sol}, in kcal/mol) in Chloroform and Water Computed for the Cone, Saddle, and Paco Conformational States of 2[a] (see Chart 1) by Using Different Formalisms of the PCM Model and the Influence of the Solvent on the Conformational Isomerism of This Compound Expressed in Terms of $\Delta\Delta G_{\mathrm{sol}}$

		QM	SC(A1)	SC(A2)	SC(A3)
chloroform	ΔG_{sol}(cone)	−35.9	−36.2	−36.2	−38.3
	ΔG_{sol}(saddle)	−37.1	−38.7	−37.8	−39.1
	ΔG_{sol}(paco)	−36.2	−41.3	−39.8	−38.8
	$\Delta\Delta G_{\mathrm{sol}}$(cone-saddle)	−1.2	−2.5	−1.6	−0.8
	$\Delta\Delta G_{\mathrm{sol}}$(cone-paco)	−0.3	−5.1	−3.6	−0.5
water	ΔG_{sol}(cone)	−9.3	−11.3	−11.3	−10.7
	ΔG_{sol}(saddle)	−10.9	−17.7	−14.4	−13.1
	ΔG_{sol}(paco)	−10.8	−19.1	−15.2	−12.4
	$\Delta\Delta G_{\mathrm{sol}}$(cone-saddle)	−1.6	−6.4	−3.1	−2.4
	$\Delta\Delta G_{\mathrm{sol}}$(cone-paco)	−1.7	−7.8	−3.9	−1.7

[a] A set of 100 configurations, which were generated by using molecular dynamics simulations, were considered for each conformational state. [b] MST: Miertus, Scrocco, and Tomasi solvation model. QM: quantum mechanical at the semiempirical AM1 level. SC(A1): semiclassical-approximation 1. SC(A2): semiclassical-aproximation 2. SC(A3): semiclassical-approximation 3. For a more detailed description of the methods used to evaluate the ΔG_{sol} see the Methods section.

On the other hand, QM-MST calculations indicate that the influence of the organic solvent on the isomerization barrier is negligible for **1** and small for **2**. Thus, the $\Delta\Delta G_{\mathrm{sol}}$(cone-saddle) predicted in chloroform solution for **1** is 0.0 kcal/mol, which is good agreement with the value previously estimated by using a discrete solvation model through MD simulations (0.7 kcal/mol).[12a] Accordingly, the interactions between the solute and the bulk solvent are predicted to be similar for these two confomational states.

The value provided in Table 2 for **2** (−1.2 kcal/mol) indicates that the interactions of bulk chloroform with *tert*-butyl substituents are slightly more favorable for the saddle than for the cone. This feature was not fully

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supported by MD simulations, the estimations provided by different sampling schemes being 0.0 (windows umbrella sampling) and 0.3 kcal/mol (combined coupling parameter-umbrella sampling).[12c] However, the deviation between QM-MST and MD (1.2−1.5 kcal/mol) is within the error currently accepted when very different models are compared.[27] The solvent-induced barriers decrease to −1.7 and −1.6 kcal/mol for **1** and **2**, respectively, when the environment is bulk water. The variation of the barrier with the polarity of the environment is consistent with the features detected by Kollman and co-workers[13b] using MD simulations, and indicates that the hydration of the cone is worse than that of the saddle.

The $\Delta\Delta G_{\mathrm{sol}}$(cone-paco) predicted in chloroform solution for **1** and **2** is 0.3 and −0.3 kcal/mol, respectively. Thus, the solvation predicted by QM-MST is similar for the two conformations even when the phenol ring is substituted in the para position by the *tert*-butyl group. The values derived from MD simulations were 1.3 and 1.6 kcal/mol for **1** and **2**, respectively. Again, the differences between the results provided by continuum and discrete models are within an acceptable interval. On the other hand, the paco conformation is clearly better hydrated than the cone in all cases, as was also predicted by MD simulations.[13a]

It is interesting to examine the influence of the number of configurations considered for each conformational state on ΔG_{sol}. Figure 2 shows the values of the ΔG_{sol} in aqueous solution for the configurations generated to represent the saddle conformation of **1**. Each point corresponds to one of the 100 configurations generated by MD simulations whereas the solid line displays the final weighted average. It is worth noting that ΔG_{sol} ranges from −8.4 to −11.6 kcal/mol indicating that this thermodynamic parameter is considerably affected by small atomic displacements. Thus, to predict free energy differences associated with conformational changes, a significant number of configurations must be used to represent each conformational state of flexible molecules. In this case the mean ΔG_{sol} values are converged after ∼30 configurations.

Similar results were obtained for the cone and paco conformations of **1** and for **2**, the ΔG_{sol} values ranging in these cases (in absolute values) from 7.8 to 10.1 kcal/mol (cone, **1**), 8.4−11.2 kcal/mol (paco, **1**), 7.0−10.1 kcal/mol (cone, **2**), 7.7−11.2 kcal/mol (paco, **2**), and 9.3−11.7 kcal/mol (saddle, **2**). These variations are smaller (typically 50% less) in chloroform solution. It should be noted that the influence of the solvent on the internal degrees of freedom of the solute is usually accounted for by discrete methods based on MM. However, these simulations are computationally very demanding, since most of the computer time is spent on sampling the solvent configurational space. The combination of the continuum approach to represent the solvent with the solute configurations generated by MD simulations in vacuo provides a useful alternative to discrete methods to represent flexible molecules in solution.

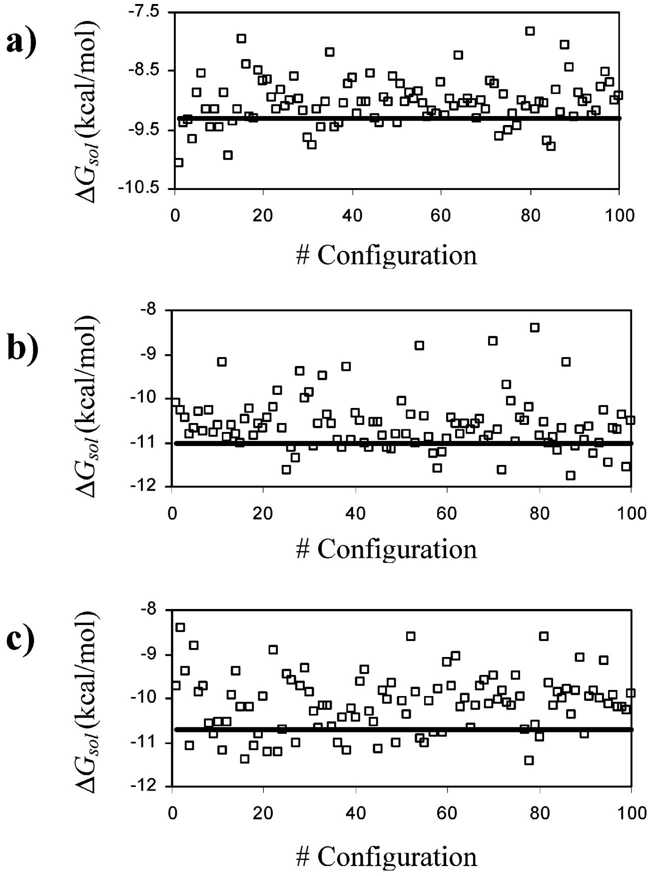

FIGURE 2. ΔG_{sol} in aqueous solution calculated by using the QM-MST method for 100 configurations of the cone (a), saddle (b), and paco (c) conformational states of **1**. The solid line corresponds to the final weighted average value.

TABLE 3. Mean Unsigned Difference (in kcal/mol) between the Free Energies of Solvation Determined from QM-MST and SC-MST Calculations on the Three Conformational States of 1 and 2

method MST	chloroform	water
SC(A1)	2.3	6.6
SC(A2)	1.6	4.5
SC(A3)	1.8	3.5

Semiclassical Calculations. ΔG_{sol} values derived from SC(A1)-, SC(A2)-, and SC(A3)-MST calculations are included in Tables 1 and 2. It is worth noting that the reliability of the SC-MST results strongly depends on the quality of the atomic charges used to describe the QM electronic distribution of the solute. The influence of the electrostatic parameters on the ΔG_{sol} values predicted by this method has been examined by computing the mean unsigned difference with respect to the QM-MST results (Table 3).

The poor results provided by the SC(A1)-MST method, which involves many of the approximations typically applied in classical MM, are surprising and even disturbing. The mean unsigned differences are 2.3 and 6.6 kcal/mol in chloroform and aqueous solution, respectively, which arise from the unsatisfactory description of the ΔG_{sol} for the paco and saddle conformations. Furthermore, the influence of the solvent in the $\Delta\Delta G_{\mathrm{sol}}$(cone-saddle) barrier was overestimated by 2.2 and 1.3 kcal/

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mol (in absolute value) for **1** and **2**, respectively, in chloroform solution, and by 3.1 and 4.8 kcal/mol in aqueous solution. The error is even larger in the difference $\Delta\Delta G_{\mathrm{sol}}$(cone-paco): 3.1 and 4.8 kcal/mol for **1** and **2**, respectively, in chloroform solution, and 5.0 and 6.1 kcal/mol in aqueous solution. These results clearly indicate that the atom-centered charges derived from the cone conformation are not able to represent the QM electronic distribution of the saddle and paco states. This deficiency could be avoided by deriving explicit charge models for each conformation, as was described in the Methods section (Approximation 2).

Results provided by the SC(A2)-MST formalism indicate a significant improvement with respect to those obtained with the SC(A1)-MST one. As is reflected in Table 3, the mean unsigned difference decreases by about 30% in both chloroform and water. Furthermore, the $\Delta\Delta G_{\mathrm{sol}}$ values predicted by the former method are smaller than those computed by using the latter one by about a half. This reduction is similar for the two solutes, indicating that for solutes with complex electron distributions, like calixarenes, the electrostatic parameters cannot be transferred routinely among different conformations. Despite this notable improvement, a detailed inspection of Tables 1 and 2 shows that the conformationally dependent charges still produce significant errors, the $\Delta\Delta G_{\mathrm{sol}}$ values computed with the SC(A2)-MST method being approximately twice as large as those predicted by QM-MST. This feature motivated the investigation of a new model in which the electrostatic parameters are accurately obtained (Approximation 3) not only for each conformation but also for each fragment of the molecule.

The $\Delta\Delta G_{\mathrm{sol}}$ values obtained for **1** and **2** with use of the SC(A3)-MST formalism are in excellent agreement with those produced by the QM-MST method. Thus, although the ΔG_{sol} values obtained with the SC(A3)-MST and SC(A2)-MST methods present similar unsigned differences with respect to the QM-MST ones, a marked improvement is achieved by the latter approximation in the relative values. This is specially notable for **1**, where the largest difference with respect to the $\Delta\Delta G_{\mathrm{sol}}$ values predicted by QM-MST is 0.4 kcal/mol. Accordingly, the electrostatic charges directly derived from the fitting between the quantum and classical molecular electrostatic produces a drastic increase in the quality of the results.

The systematic overestimation of the ΔG_{sol} values produced by SC(A2)-MST and SC(A3)-MST calculations is attributed to the use of an atom-centered charge model since all the other simplifications typically used in the parametrization of electrostatic charges have been omitted, especially in the latter approximation. An atom-centered model involves a drastic simplification of the description of the molecular charge distribution, which can often provide a sufficiently accurate representation of the molecular systems. Nevertheless, in this case a more precise representation of the charge distribution is needed. Accordingly, more sophisticated models, like the multicentric ones,[28] should be employed to obtain a better quantitative agreement between SC- and QM-MST results.

Analysis of the Reliability of the MST Method. Inspection of the literature reveals that experimental ΔG_{sol} values for **1** and **2** are not available. The experimental measurement of this thermodynamic parameter is precluded in many cases by the technical difficulties of obtaining equilibrium constants for large exothermic reactions such as the solvation of a solute. As a consequence, the ΔG_{sol} values for important bioorganic systems, like for instance the nucleic acid bases and some amino acids, remain unknown, making the theoretical methods powerful tools to provide new insights into the solution-phase properties of such compounds. However, to make quantitative predictions, it is necessary to be able to calculate ΔG_{sol} to high accuracy and this is the subject of this section. QM and SC calculations have been performed to calibrate the reliability of ΔG_{sol} values provided by MST for complex molecules such as calixarenes.

TABLE 4. Free Energies of Solvation (ΔG_{sol}, in kcal/mol) in Chloroform (first line) and Water (second line) Determined from QM-MST and SC-MST Calculations on Selected Model Compounds and a Statistical Comparison between the Theoretical and Experimental Values

compd	exptl[a]	QM-MST	SC-MST
water	−2.0	−2.7	−3.6
	−6.3	−6.1	−7.2
methanol	−3.4	−3.0	−3.5
	−5.1	−3.6	−4.1
dimethyl ether		−3.4	−3.6
	−1.9	−2.0	−2.5
diethyl ether	−4.3	−4.4	−4.4
	−1.8	−2.5	−3.4
benzene	−4.6	−5.9	−3.8
	−0.9	−1.6	−1.8
phenol	−7.1	−7.2	−8.0
	−6.6	−4.6	−6.4
toluene	−5.4	−6.5	−6.7
	−0.9	−1.9	−1.6
ethylbenzene	−5.8	−7.1	−7.3
	−0.8	−2.0	−1.5
p-cresol	−7.6	−7.7	−7.9
	−6.1	−6.3	−6.8
rms[b]		0.9	1.1
		1.1	0.9
mud (msd)[c]		0.6 (−0.5)	0.8 (−0.6)
		0.8 (0.0)	0.8 (−0.5)

[a] The experimental values are displayed in the second column. [b] rms: root-mean-square deviation (kcal/mol). [c] mud: mean unsigned deviation (kcal/mol). msd: mean signed deviation (kcal/mol).

Table 4 compares the experimental and predicted ΔG_{sol} in chloroform and water for a few small model compounds that are closely related to the investigated calixarenes. As expected, the performance of the MST method is very consistent in both chloroform and aqueous solutions.

In chloroform solution the largest error between the QM-MST and experimental ΔG_{sol} values is 1.3 kcal/mol and the mean unsigned deviation is 0.6 kcal/mol, whereas in aqueous solution these values are 2.0 and 0.8 kcal/mol, respectively. The rms deviation between QM-MST and experimental values is 0.9 and 1.1 kcal/mol for solvation in chloroform and water, respectively. Analysis of the ΔG_{sol} determined from SC-MST calculations provides similar statistical parameters. Inspection of the mean signed deviation indicates that both the QM and

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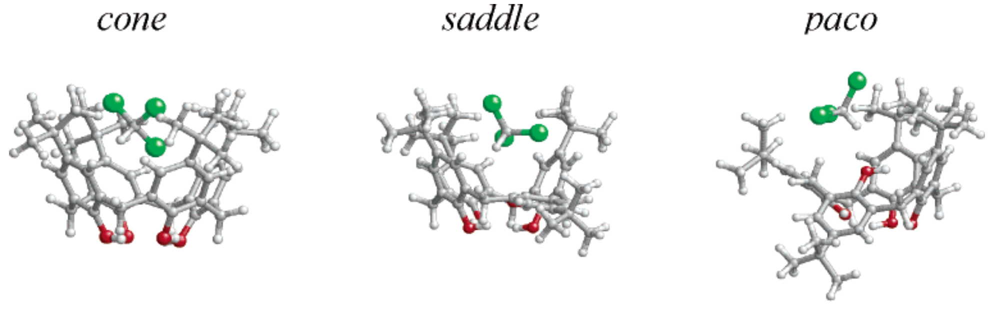

FIGURE 3. Atomistic representation of the cone, saddle, and paco conformations for **2**. The chloroform molecule trapped inside the cavity is also displayed.

SC formalisms of the MST model tend to slightly overestimate the ΔG_{sol}. Overall, there is excellent agreement between experimental and theoretical ΔG_{sol} in the two solvents for the series of selected model compounds.

On the other hand, the omission of specific solute–solvent interactions could limit the usefulness of continuum models for organic solutes with complex molecular structures. This situation is specially important for **2**, whose cavity is large enough to capture a chloroform molecule.[12c,29] Thus, a very accurate description of the solute/solvent interface is required to account for the influence on ΔG_{sol} of the solvent molecule trapped in the cavity of the solute. It should be emphasized that discrete models are able to represent this situation satisfactorily.[12c]

The reliability of the MST model to study the solvation of organic solutes with complex molecular structures has been demonstrated in recent studies involving calixpyrroles[14a] and rotaxanes.[30] However, we gave put the model further to test by comparing the ΔG_{sol} predicted by all-continuum QM-MST calculations with that obtained through a discrete/QM-MST model,[31] in which the captured chloroform is explicitly represented. SC calculations were not performed to avoid the influence of the electrostatic parametrization on this analysis. A set of 25 configurations was selected for each conformational state of **2** from MD trajectories in chloroform solution, with a solvent molecule inside the molecular cavity in all selected configurations.[12c] This situation is illustrated in Figure 3, which shows a representative configuration of the cone, saddle, and paco.

The ΔG_{sol} for **2** with one explicit chloroform molecule (ΔG_{sol}^{E-CHL}) was computed as the sum of the gas-phase binding energy (ΔE_{gp}) between the solute and the explicit chloroform molecule, which for consistency was computed at the semiempirical AM1 level,[21] and the ΔG_{sol} computed for the complex $\mathbf{2}\cdot\mathrm{CHCl_3}$, using the QM-MST method:[31]

$$\Delta G_{sol}^{E-CHL} = \Delta E_{gp} + \Delta G_{sol}(\mathbf{2}\cdot\mathrm{CHCl_3}) \qquad (10)$$

TABLE 5. Free Energies of Solvation[a] (in kcal/mol) in Chloroform Computed for the Cone, Saddle, and Paco Conformational States of 2 by Using Discrete/Continuum and All Continuum Calculations

	cone	saddle	paco
ΔG_{sol}^{E-CHL}	−36.4	−38.2	−37.2
$\Delta G_{sol}^{D/MST}$	−32.7	−34.9	−33.5
$\Delta G_{sol}(\mathbf{2})$	−35.9	−37.1	−36.2
$\Delta G_{sol}^{D/MST} - \Delta G_{sol}(\mathbf{2})$	3.2 ± 1.1	2.2 ± 0.9	2.7 ± 1.2

[a] ΔG_{sol}^{E-CHL} corresponds to the free energy of solvation of the complex $\mathbf{2}\cdot\mathrm{CHCl_3}$ estimated by using eq 10. $\Delta G_{sol}^{D/MST}$ is the free energy of solvation of **2** obtained by using the formalism indicated in eq 11 for discrete/continuum models. $\Delta G_{sol}(\mathbf{2})$ is the free energy of solvation of **2** obtained by using all continuum calculations. In all cases the QM-MST continuum method was used.

Ideally, ΔG_{sol}^{E-CHL} should be identical with the sum of the ΔG_{sol} values computed for the chloroform molecule and for **2** with use of the all-continuum model. Therefore, the ΔG_{sol} for **2** provided by the combined discrete/QM-MST model ($\Delta G_{sol}^{D/MST}$) can be determined as:

$$\Delta G_{sol}^{D/MST} = \Delta G_{sol}^{E-CHL} - \Delta G_{sol}(\mathrm{CHCl_3}) \qquad (11)$$

Obviously, the differences between $\Delta G_{sol}^{D/MST}$ and the ΔG_{sol} obtained by using the same conditions in the all-continuum model allow one to estimate the accuracy of the latter to describe the solvation of **2**. Table 5 shows the values of ΔG_{sol}^{E-CHL} and $\Delta G_{sol}^{D/MST}$ for the three conformational states of **2**. Inspection of the ΔG_{sol}^{E-CHL} estimations reveals that the chloroform molecule trapped inside the cavity does not alter the solvation order of the three conformational states. Thus, the interaction between the $\mathbf{2}\cdot\mathrm{CHCl_3}$ complex and the bulk chloroform increases as follows: saddle > paco > cone. Furthermore, the $\Delta\Delta G_{sol}^{E-CHL}$(cone-saddle) and $\Delta\Delta G_{sol}^{E-CHL}$(cone-paco) values are −1.8 and −0.8 kcal/mol, respectively, which are very similar to the values obtained without including any explicit solvent molecule.

A similar qualitative agreement is reflected by the values of $\Delta G_{sol}^{D/MST}$ estimated for the cone, saddle, and paco conformations. However, the $\Delta G_{sol}^{D/MST}$ values are underestimated by about 3 kcal/mol with respect to the ΔG_{sol} obtained by using the all continuum model, although relative values present a noticeable agreement. This systematic failure is probably due to an overestimation of the ΔG_{sol} predicted by QM-MST for the chloroform molecule (eq 11). Thus, the excellent agreement found between $\Delta\Delta G_{sol}^{D/MST}$ and $\Delta\Delta G_{sol}$ values allows us to conclude that the MST continuum model provides a satisfactory description of the molecular cavity, i.e. no explicit solvent molecule is required.

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Conclusions

The results presented in this article allow us to conclude that the MST continuum model is able to provide, at least qualitatively, a reliable description of the role of the solvent on the conformational isomerism of complex solutes such as calixarenes. Support to this conclusion comes from the comparison between the results obtained in the present work for different frameworks of the MST model with those reported in previous studies where the discrete solvation model was employed through classical MD simulations. It has been shown that the effects of the solvent on the conformational preferences of calixarenes are satisfactorily reproduced by using a combined approach in which the configurational space of the solute is sampled through in vacuo MD simulations and the bulk solvent is represented with an implicit continuum model. From a practical point of view, this appears to be an efficient approach that requires less computer power than conventional MD simulations with their explicit description of solvent particles. The strategy was tested with two representative calixarenes, **1** and **2**, and using two different solvents. It is very encouraging that the application of the QM-MST method to the configurations generated in vacuo correctly reproduces the tendencies previously predicted by MD simulations in solution.

The performance of the SC-MST method has been examined. Particular attention has been paid to the parametrization of the atomic charges required to evaluate the electrostatic contribution to ΔG_{sol}. The results reveal that the SC-MST method is an inexpensive procedure to investigate solvation effects when suitable atomic charges are used. Thus, the accuracy of the results clearly depends on the quality of the electrostatic parameters. The results presented here indicate that the method works well when standard molecular electrostatic potential-derived charges are directly used, i.e. avoiding the approximations usually employed in the MM calculations. Furthermore, better results should be obtained by improving the charge representation, e.g. by using atomic dipoles or multicentric charges.

Finally, it should be mentioned that although the results presented in this study give confidence in the suitability of the inexpensive MST continuum model to account for solvation effects on the conformational preferences of calixarenes, the method would present a potential limitation. This is the lack of information about solvent molecules plays a relevant structural or dynamical role. In these cases MD with explicit solvent molecules is usually the most appropriate procedure.[12] However, in some cases these deficiencies can be alternatively corrected by introducing discrete solvent molecules into the continuum calculation with little increase in computer expense. In this way both macroscopic and microscopic solvation effects are taken into account. In summary, each strategy has its strengths and shortcomings, and the judicious selection of the appropriate method to be used in the study of a particular problem is probably the most important decision for the study of a chemical process in solution.

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Supporting Information Available: *Z*-matrix for the cone, paco, and saddle conformations of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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