CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200600757

Exploring the Dynamics of Calix[4]pyrrole: Effect of Solvent and Fluorine Substitution

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Abstract: Molecular dynamics simulations show that calix[4]pyrrole (CP) and octafluorocalix[4]pyrrole (8F-CP) are extremely flexible molecules. CP mainly adopts the 1,3-alternate conformation in all the solvents, although the percentage of alternative conformations increases in polar solvents, especially those with good hydrogen-bonding acceptor properties. However, in the case of 8F-CP, the cone conformation is the most populated in some solvents. Transitions between conformers are common and fast, and both CP and 8F-CP can adopt the cone conformation needed for optimum interaction with anions more easily than would be predicted on the basis of previous gas-phase calculations. Furthermore, the present studies show that when a fluoride anion is specifically placed initially in close proximity to CP and 8F-CP in their respective 1,3-alternate conformations, an extremely fast change to the cone conformation is observed in both cases. The results suggest that preorganization does not represent a major impediment to anion-binding for either CP or 8F-CP, and that ion-induced conformational changes can follow different mechanisms depending on the solvent and the chemical substituents present on the calix[4]pyrrole beta-pyrrolic positions.

Keywords: calixpyrroles · molecular dynamics · receptors · solvent effects · substituent effects

Introduction

The design of chemical receptors able to bind efficiently and with large specificity to target molecules in solution is a very active research area that touches on many fields, including biomedicine and biotechnology.[1–11] One of the most popular and versatile chemical receptors is calix[4]pyrrole (*meso*-octaalkylporphyrinogens; CP), a molecule first synthesized more than 100 years ago,[12] but which only recently has been investigated as chemical receptor for small anions.[13–24]

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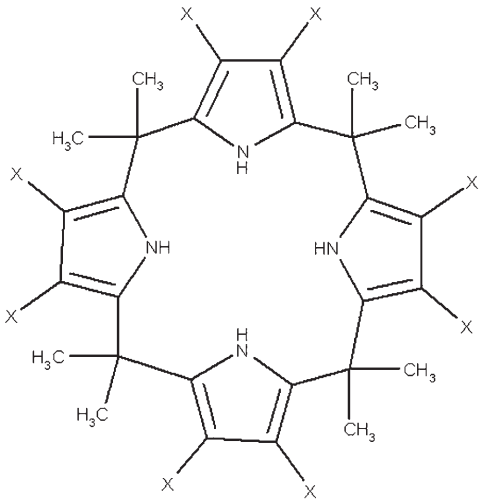
To date, a considerable number of modifications have been made to the basic CP unit. Many of them have been carried out in an effort to generate chemical sensors capable of detecting anionic analytes through changes in redox[25] or optical properties.[1,20,26–29] Such efforts have produced CP-based systems capable of effecting the colorimetric or fluorescence detection of ions in organic solvents[17,20,21,29] and biological fluids.[1] Efforts have also been devoted to the synthesis of more efficient and specific CP-type receptors. To this end, the basic CP scaffold has been modified, either by extending the size (calix[*n*]pyrrole),[30–34] or by generating double-cavity or cryptand-like derivatives.[35,36] Related work has involved the study of hybrid receptors obtained by substituting one or more of the pyrrole subunits in CP by other heterocyclic rings, such as pyridine, thiophene, and furan.[15,37–44] Attachment of substituents to CP has also been used to modify the binding properties, and has led to systems capable of binding selectively certain ions or neutral molecules.[45–56] A successful example of this latter strategy involved fluorine substitution on the beta-pyrrolic positions of the CP core; the resulting systems (Scheme 1) demonstrate enhanced affinities for small anions such as Cl^-, F^-, and $H_2PO_4^-$.[19,57,58]



CP X=H
8F-CP X=F

Scheme 1. Chemical structure of octamethylcalix[4]pyrrole (CP) and octafluorooctamethylcalix[4]pyrrole (8F-CP).

A number of studies, both theoretical and experimental, have confirmed that calix[4]pyrroles are not preorganized for anion recognition. While the cone form is the major conformation observed in 1:1 complexes with small anions,[13,15] other conformations are favored in the absence of such ligands (vide infra). Thus, the binding of CP to anionic targets (ligands) is modulated not only by the strength of ion–receptor interactions and the effect of solvent and co-solutes, but also by the energetic cost of adopting the conformation involved in ligand binding. The solvent effect on the binding of different ions to CP and its 8F-CP has been the subject of several experimental[13–15,18,19,21,59–62] and theoretical studies,[57] which indicated competition between ion solvation and ion complexation. On the other hand, in spite of considerable effort devoted to analyzing the conformational flexibility of CP,[63–65] we are far from having a detailed description of the conformational space accessible to these compounds or the effect of solvation and substitution on the conformational preferences.

A considerable body of experimental evidence provides support for the suggestion that CP and its substituted derivatives are quite flexible. For instance, the most stable conformation in the solid state, in the gas phase, and in very apolar solvents is the 1,3-alternate form,[13,66,67] while a certain population of the 1,2-alternate conformation has been found in more polar solvents,[66] and the cone form is the major conformation in 1:1 complexes with small anions.[13,15] Theoretical studies,[65] nevertheless, suggest that the cone conformation of CP is about 16 kcal mol^{-1} less stable than the 1,3-alternate conformation, and the difference is still more than 11 kcal mol^{-1} in CH_2Cl_2. These results lead to the conclusion that conformational reorganization should represent a major impediment to ion binding in both CP and 8F-CP. Accordingly, derivatives forced to adopt the cone conformation[45–49] should have binding several orders of magnitude better than CP and 8F-CP, a result that has not received complete support from the available experimental data.[45–50]

Here we present a theoretical study on the conformational space of unbound CP. We have analyzed the accessible conformational space and the mechanisms by which conformational transitions occur. We have also explored the influence of octafluorination of the beta-pyrrolic positions and the effect of solvation on the relative population of different conformers and the transition pathways between them. We have found that conformational interconversions are more facile than previously expected and that reorganization can occur rapidly from one of several different starting states. The results detailed here thus help explain the unique anion-binding properties of CPs and provide important insights into the role that flexibility may play in modulating the recognition properties of nonrigid chemical receptors. Finally, a better understanding of these flexible macrocycles would enhance our knowledge of some interesting biochemical phenomena. For instance, chemical species similar to CP have been described as playing a crucial conformation-dependent role in several steps of porphyrin biosynthesis,[68] and their flexibility has been recently analyzed by means of molecular dynamics simulations.[69] Our results could contribute to a more detailed understanding of the obtained conclusions.

Computational Methods

Molecular dynamics: Classical molecular dynamics (MD) simulations with explicit solvent were used to explore the conformational flexibility of CP and 8F-CP. To this end, we created models of CP and 8F-CP in the

expected major conformation (1,3-alternate) immersed in pre-equilibrated cubic boxes containing molecules of dichloromethane (DCM), methanol (MeOH), dimethyl sulfoxide (DMSO), or acetonitrile (ACN). Force-field parameters for CP and 8F-CP were taken from our previous work,[57] with atomic charges obtained by averaging those determined with the RESP/6-31G(d) procedure[70] for the four conformers (charges were very similar for all the conformers). These force-field parameters were developed to study equilibrium structures but reproduce the relative energy (computed at the B3LYP/6-31G(d) level) of a range of structures of CP, including very distorted ones (see Figure 1), and this confirms that they can be safely used to analyze conformational preferences of these compounds, including the study of transition structures separating equilibrium conformations.

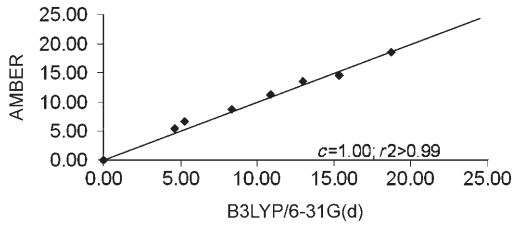


Figure 1. Comparison between QM [B3LYP/6-31G(d)] and MM[57] estimates of internal energy for CP. In each case, eight structures were randomly taken from MD samples and clustered to avoid similar structures being included in the test. The conformations from the MD were partially optimized at the B3LYP/6-31G(d) level with all the dihedral angles frozen at MD values. The energies shown are relative to the most stable structure. QM and MM agree extremely well with a slope of 1.00 and $r^2 > 0.99$ for a quite large range of relative energies.

Force-field parameters for DCM, MeOH, and DMSO were taken from the OPLS force field,[71] while those for ACN were taken from a previous parametrization study.[72] The starting systems were optimized for 4000 cycles (2000 cycles of steepest descent plus 2000 cycles of conjugated gradient), thermalized (298 K), and fully relaxed through 500 ps of MD simulations at constant pressure and temperature (1 atm, 298 K). Bond vibrational degrees of freedom were frozen using SHAKE.[73] These conditions were maintained during 10 ns of unrestrained MD simulation.

Additional trajectories were performed to analyze the possibility of 1,3-alternate→cone transitions in the presence of bound anions. These calculations were performed for CP and 8F-CP by selecting one 1,3-alternate snapshot and placing a fluoride anion within binding distance of two of the pyrrole hydrogen atoms. The force-field parameters for fluoride anion were those used in our previous work on the same system.[57] The systems were then optimized, thermalized, and equilibrated, and the trajectories were followed for 10 ns as described before. In all cases, the 1,3-alternate→cone transitions occurred less than 1 ns after initiating the process of trajectory monitoring, and in many cases already during the initial thermalization or equilibration process.

Analysis of the trajectories: All conformers sampled along the trajectories were clustered into one of four families, namely, 1,3-alternate, 1,2-alternate, partial cone, and cone (Figure 2), according to the relative orientation of the pyrrole rings.[74] The snapshots collected in the four regions were then averaged (considering symmetry constraints) to derive representative conformations for the four major conformers of both CP and 8F-CP. These structures were then used in CMIP[75] calculations to determine the ability of CP and 8F-CP to interact with small anions by using a probe with net charge of −1 and the van der Waals parameters of oxygen. To this end, the receptor was immersed in a cubic grid of 46.656 Å^3 with a node spacing of 0.3 Å, which gives rise to a final number of grid points on the order of 1.73×10^6. An iterative solution to the Poisson–Boltzmann equation was used to derive electrostatic potentials with a dielectric constant of 1 for the receptor and dielectric constants of 8.93 (DCM) and 80 (water), which correspond to limits of low and high dielectric response. Only data at high dielectric constant are shown, but the others are available on request to the authors.

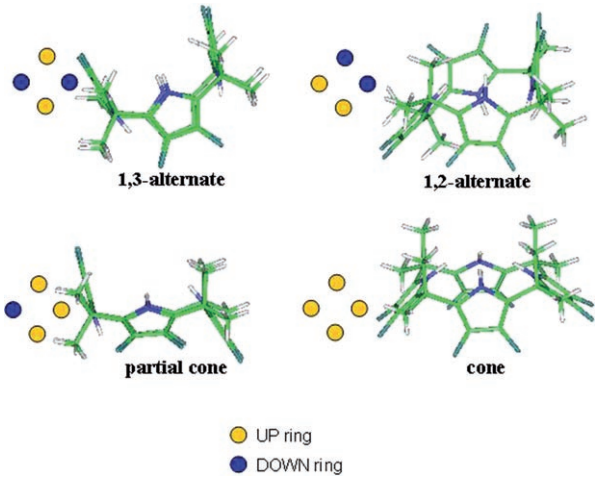


Figure 2. Conformations adopted by the receptor. Colored circles indicate the position of each ring relative to the plane that better fits the *meso*-carbon atoms.

The internal energy corresponding to each conformation was determined by averaging it within a given family. The intramolecular terms were determined by using the same force field considered in the simulations, while two methods were used to determine the solvation contribution: 1) Generalized Born (GB) model[76] as implemented in AMBER6 code;[77] and 2) The discrete linear response theory (LRT).[78]

Computational details: Pre-equilibration of solvent boxes (see above) was performed using the BOSS4.2 computer program.[79] Solvent boxes were equilibrated for 10^7 configurations at constant pressure and temperature (1 atm, 298 K) using a residue-based cutoff of 10 Å. MD were carried out using AMBER6.0 computer program.[77] Poisson–Boltzman calculations were performed with the CMIP program,[75] and quantum mechanical calculations were carried out with Gaussian 98.[80]

Results and Discussion

Both CP and 8F-CP are very flexible and conformational transitions occur on the nanosecond timescale (see Figure 3), which suggests that a 10 ns trajectory is long enough to sample the accessible conformational space. For CP the 1,3-alternate conformation is the most populated in all the solvents (between 61% in DMSO and 80% in DCM; see Figure 4). In general, the population of the 1,3-alternate conformer decreases as the polarity of the solvent increases, although for MeOH the population is greater than expected based on its dielectric constant; this indicates that unfavorable interactions between the polar hydrogen atom of MeOH and the pyrrole hydrogen atoms hinders solvation, while the good hydrogen-bond acceptor properties of DMSO explains why it solvates the cone conformation so well to form host–guest-like complexes (see selected structures of strong solute–solvent interactions for CP and 8F-CP in Figures S1 and S2). The second most populated form of CP is the 1,2-alternate conformer in DCM, and the partial cone in the other solvents (see Figure 4). Finally, the cone conformation

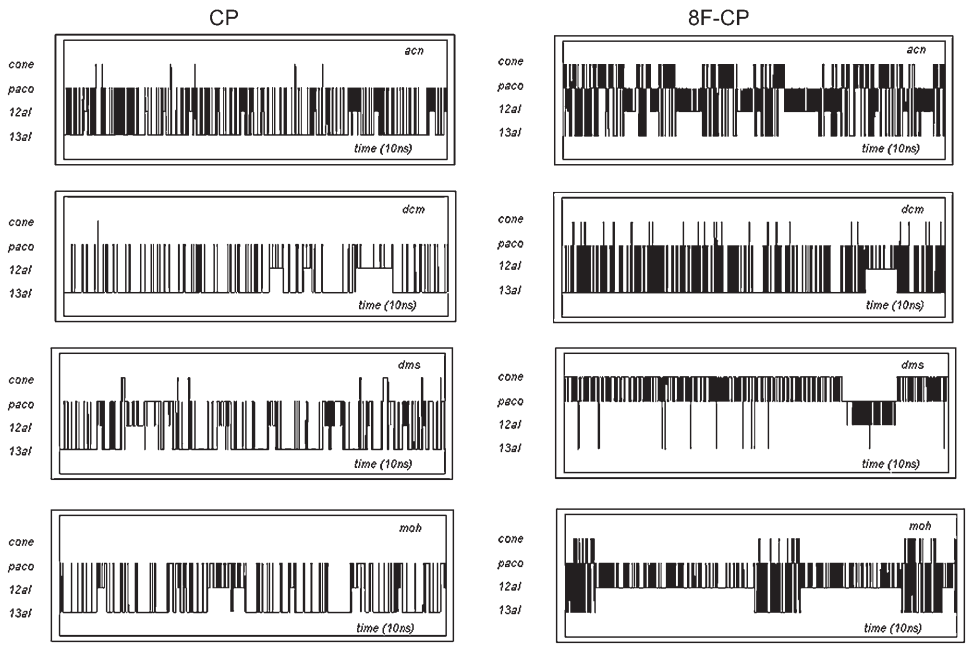


Figure 3. Transitions detected during 10-ns simulations carried out for CP and 8F-CP in different solvents. paco = partial cone, 12al = 1,2-alternate, 13al = 1,3-alternate.

is very rare (between 0.1 and 3%). [Note: These and other percentages given in parentheses are relative to the overall molecular population and since they are computed for the entire ensemble they do not have associated statistical errors.]

Quite surprisingly, the conformational scenario of 8F-CP differs notably with regard to that of the parent compound (see Figure 5). In DCM the 1,3-alternate form is the most stable conformer (67%), followed by the partial cone and the 1,2-alternate forms. However, the 1,2-alternate, partial cone, and cone conformers are almost equally populated in ACN. In MeOH, the 1,2-alternate form is the major conformation (around 60%), followed by the partial cone, while in DMSO the cone

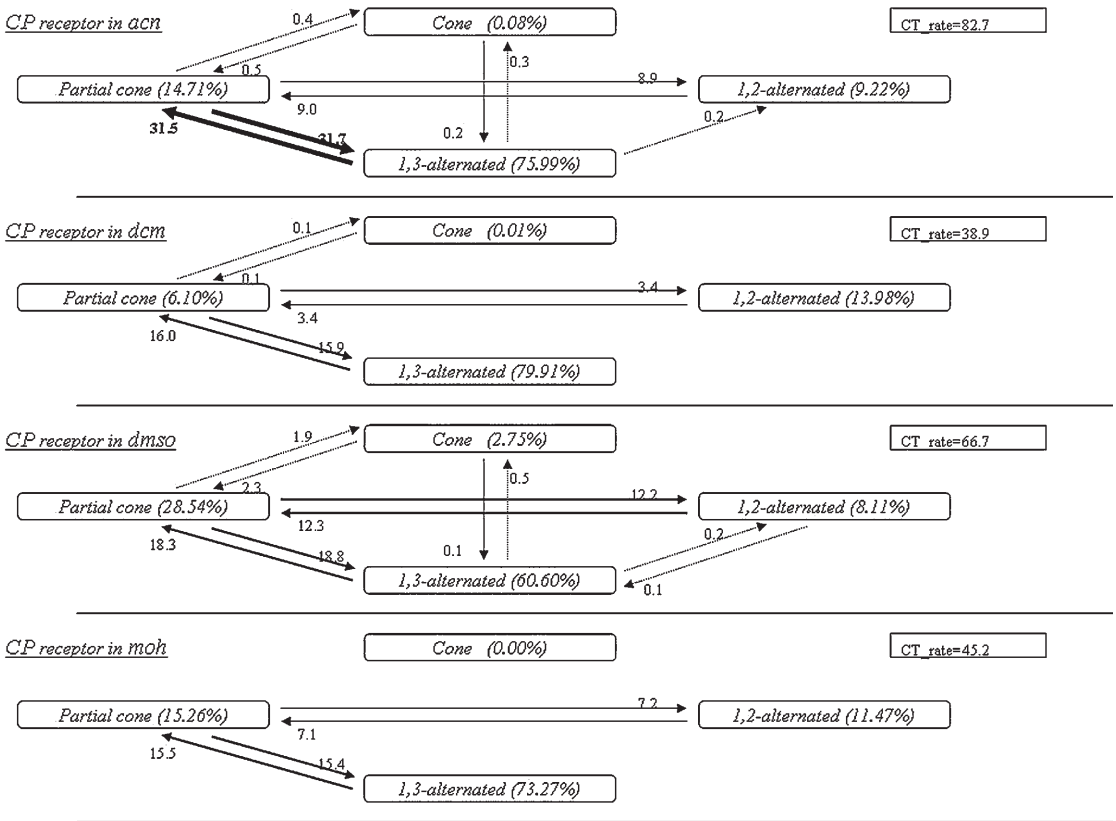


Figure 4. Transition rates (in changes per nanosecond) between specific conformations of CP as calculated in different solvents. The width of the arrow indicates the probability of a transition path. The population of each conformer (in percentage of the total population) and the total conformational transition rate, expressed quantitatively as the number of changes per nanosecond, are also shown.

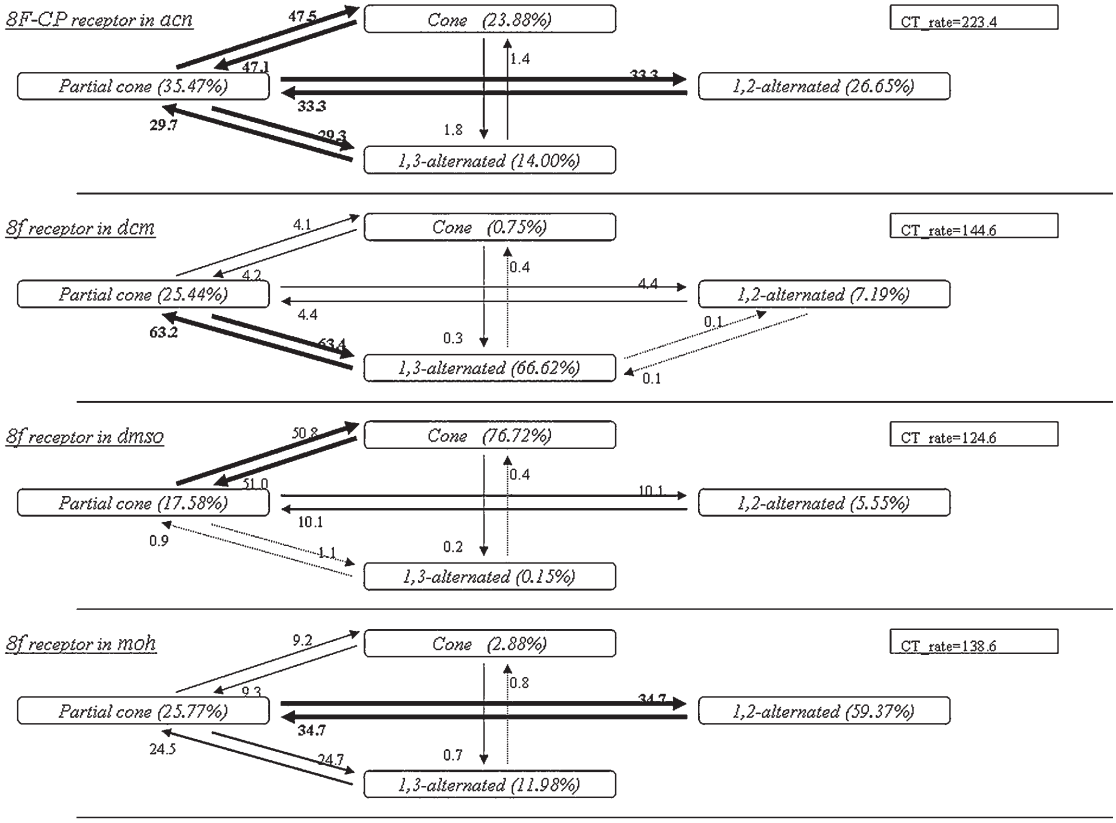


Figure 5. Transition rates (in changes per nanosecond) between specific conformations of 8F-CP in different solvents. The width of the arrow indicates the probability of a transition path. The population of each conformer and the total conformational transition rate, expressed quantitatively as the number of changes per nanosecond, are also shown.

conformation is the major form (77%), followed by the partial cone (18%). Clearly, the conformational preferences of CP derivatives can be strongly affected by chemical substitution at the pyrrole ring and by solvation. As such, the present results underscore the fact that CP derivatives should not be viewed as rigid structures that are fixed in the 1,3-alternate form in the absence of a bound anion.

The energetic analyses of the different conformations provide valuable insights into the conformational behavior of CP and 8F-CP. The results of these studies, summarized in Tables 1 and 2, confirm that intramolecular terms favor the 1,3-alternate conformer (in the case of both CP and 8F-CP), while solvation always favors the cone conformation, which has the largest dipole moment and the strongest solute–solvent interactions (see also Figure 6). Furthermore, not all the conformations are energetically equivalent in different solvents. For example, the intramolecular energy of the 1,3-alternate conformer of CP in MeOH is about 4 kcal mol^{-1} less stable than the same conformer in DCM, that is, solvation (i.e., use of more polar solvents) not only modulates the energetics (i.e., inherent stability) of the individual conformers, but also affects the population distribution within the overall conformational family, which it biases towards more solvophilic conformations. Interestingly, the relative conformer energies are more sensitive to solvent in 8F-CP than CP (see Tables 1 and 2). In fact, the solvent-induced changes in intramolecular energies in 8F-CP are often in the range 2–6 kcal mol^{-1}, while such changes are always below

Table 1. Dipole moments μ [D], intramolecular energies, solvation free energies (values in normal and italic font were obtained by using the GB and LRT techniques, respectively) and total energies (solvation + intramolecular terms) for CP. All energy and free energy values are in kcal mol^{-1}. The very small cone population for CP in methanol precludes calculations.

Conformer	μ	E_{intra}	G_{solv}	E_{tot}
		dichloromethane		
1,3-alternate	0.2	16.3	−7.9 *(−3.7)*	10.5
1,2-alternate	0.4	21.8	−9.9 *(−5.4)*	14.2
partial cone	0.6	21.6	−9.9 *(−5.3)*	14.0
cone	1.0	25.2	−10.7 *(−5.5)*	17.2
		methanol		
1,3-alternate	0.2	20.2	−8.4 *(−5.1)*	13.5
1,2-alternate	0.3	26.1	−11.0 *(−10.6)*	15.4
partial cone	0.7	26.4	−11.7 *(−11.0)*	15.2
		acetonitrile		
1,3-alternate	0.2	17.2	−8.6 *(−3.2)*	11.3
1,2-alternate	0.5	23.4	−11.1 *(−6.1)*	14.8
partial cone	0.7	22.8	−11.2 *(−5.8)*	14.4
cone	1.1	25.4	−12.7 *(−7.7)*	15.2
		dimethyl sulfoxide		
1,3-alternate	0.2	17.5	−8.8 *(−4.4)*	10.9
1,2-alternate	0.5	22.6	−11.4 *(−7.7)*	13.1
partial cone	0.7	23.5	−11.9 *(−8.3)*	13.4
cone	1.3	30.4	−17.1 *(−13.4)*	15.2

Table 2. Dipole moments μ [D], intramolecular energies, solvation free energies (values in normal and italic font were obtained by using the GB and LRT techniques, respectively) and total energies (solvation + intramolecular terms) for 8F-CP. All energy and free energy values are in kcal mol^{-1}

Conformer	μ	E_{intra}	G_{solv}	E_{tot}
		dichloromethane		
1,3-alternate	0.6	122.6	−12.3 *(−5.1)*	114.0
1,2-alternate	0.7	127.1	−15.6 *(−7.3)*	115.7
partial cone	1.5	125.7	−15.5 *(−7.4)*	114.3
cone	2.5	130.8	−20.5 *(−11.1)*	115.0
		methanol		
1,3-alternate	0.8	127.8	−14.3 *(−9.2)*	116.1
1,2-alternate	0.8	131.1	−17.5 *(−13.5)*	115.6
partial cone	1.6	131.8	−18.2 *(−12.9)*	116.3
cone	2.6	134.9	−23.3 *(−16.5)*	115.0
		acetonitrile		
1,3-alternate	0.7	126.1	−14.2 *(−7.9)*	115.1
1,2-alternate	0.9	130.3	−17.7 *(−12.1)*	115.4
partial cone	1.7	130.6	−18.7 *(−12.3)*	115.2
cone	2.8	134.3	−24.1 *(−17.4)*	113.6
		dimethyl sulfoxide		
1,3-alternate	1.0	128.2	−18.4 *(−15.3)*	111.4
1,2-alternate	0.9	129.3	−18.1 *(−16.4)*	112.1
partial cone	1.9	131.2	−20.3 *(−18.0)*	112.0
cone	2.8	133.5	−24.7 *(−22.0)*	110.1

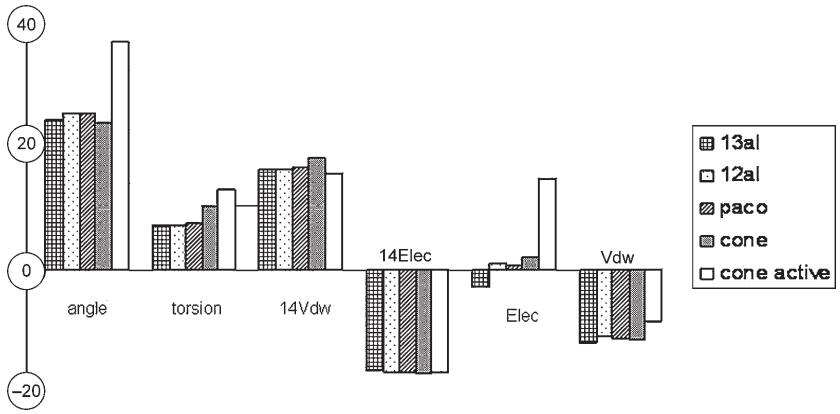


Figure 6. Contribution of each force-field term to the global internal energy of CP in the five studied conformations. The values are the average from 10 ns of MD simulation of the CP in dichloromethane in its unbound state and 1 ns of MD simulation in complex with fluoride anion in the same solvent. All energies are in kcal mol^{-1}. Standard errors (not shown) are always smaller than 0.1 kcal mol^{-1}.

2 kcal mol^{-1} for CP. This can be easily rationalized by the fact that the dipole moment changes by only 0.9–1.1 D between the 1,3-alternate and cone conformations for CP, but by more than 2 D for 8F-CP.

Interestingly, the internal energy of the 1,3-alternate conformation is on average about 10 kcal mol^{-1} lower than that of the cone form, which is notably smaller than the value obtained from previous DFT calculations (16 kcal mol^{-1}[65]). Furthermore, the difference in total energy (intramolecular energy + solvation) between the 1,3-alternate and cone conformations in DCM is about 4 kcal mol^{-1} (irrespective of the method used to compute the solvation term), while DFT-continuum[65] calculations on gas-phase geometries suggest a larger difference (ca. 11 kcal mol^{-1}), which would make the 1,3-alternate→cone transition very difficult in apolar solvents. This apparent discrepancy can be understood by noting that the "cone" conformation used in reference [65] was obtained by removing the anion from a CP–anion complex and is not identical to that spontaneously sampled by CP or 8F-CP. In fact, the total energy of the "active-cone" conformation taken from MD simulations of the CP–F$^-$ complex is 11.1 kcal mol^{-1} higher than that of the 1,3-alternate one and thus matches the DFT estimate (11 kcal mol^{-1}) and confirms the suitability of the force-field parameters used here to describe the conformational space of CP derivatives. This active-cone conformation is significantly distorted by the presence of the ion, which leads to important bending and electrostatic distortion in the receptor (see Figure 6). Our results suggest then that binding of ions to CP derivatives is a complex process that involves energetically important changes even when the ion binds directly to the cone conformation, which has to adopt the active-cone form to reinforce the pyrrole–anion electrostatic contacts but at the expense of unfavorable intramolecular interactions. Analysis of average force-field energies (see Figure 6) shows that the stress energy accumulated by the active-cone conformation is mostly due to unfavorable electrostatic interactions between the acidic pyrrole hydrogen atoms and bond-angle distortions.

The goodness of force-field calculations in describing not only minima but also distorted transient structures, and the high rate of conformational conversions in CP and 8F-CP, allowed us to analyze in some detail the mechanism(s) of conformational flipping, complementary to experimental kinetic measurements, which provide only a macroscopic view on the system. Figure 3 shows that the conformational transitions in CP and 8F-CP are very fast (picosecond timescale), and many of them are detected along the trajectory. Under these circumstances, a reasonable description of the preferred routes for the observed conformational changes can be inferred. The largest velocity for conformational changes for CP is found in ACN (the least viscous of the solvents considered), for which transitions occur every 12 ps, but even for other solvents transitions are very fast (transition time <25 ps). The 8F-CP derivative is 2–4 times more flexible than the parent compound CP, which corresponds on average to a conformational transition every 5–10 ps.

The pathway for conformational transitions is dominated by the presence of the partial cone, which generally serves as the connection hub (see Figures 4 and 5) between the

other three conformers. Direct transitions between 1,3-alternate and cone conformations are very rare (<2% in all the solvents). Indeed, the transition between the 1,3-alternate and cone conformations never involves the 1,2-alternate conformer, which can then be considered as an "abortive" form.

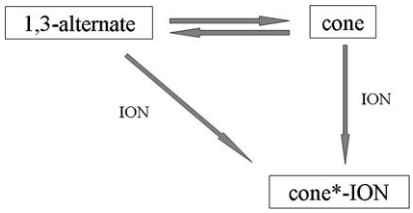


Figure 7. Alternative schemes for ion-induced organization of calix[4]pyrrole. According to the top pathway, the ion binds to the selected population of cone conformers, while the diagonal pathway implies binding to the 1,3-alternate conformer followed by an immediate flip to the active-cone conformation (cone*).

It can be thought that anion binding takes place when CP (or 8F-CP) adopts the cone conformation and is driven to the active-cone form (Figure 7). However, since the preceding results suggest that CP is highly flexible and conformational transitions occur frequently, it can be hypothesized that an anion might bind initially to the 1,3-alternate form and thereby induce a transition to the active-cone state (Figure 7). CMIP calculations (see Figure 8) suggest that such a mechanism is possible, since even in the most apolar solvents the 1,3-alternate form maintains an ion pocket close to the pyrrole hydrogen atoms that can act as attractor for a negatively charged ion. To test the feasibility of this alternative mechanism, we performed MD simulations by placing a fluoride anion at binding distance to two pyrrole hydrogen atoms of CP and 8F-CP in the 1,3-alternate conformation. In most cases the receptor changes from this conformation to the active-cone form within the equilibration time window, and in two cases during the first picoseconds of the collection period (see Figure 9 and JAVA-powered video at http://mmb.pcb.ub.es/~jramon/CALIX/). Once the active-cone conformation is achieved, strong electrostatic interactions serve to "fix" it in this form for the rest of the 10 ns simulation period (data not shown). Therefore, preorganization of the receptor is not strictly necessary for the binding of anions to CP or 8F-CP.

Overall, our results underscore the fact that the conformational space for both CP and 8F-CP is quite complex in solution and that key conformational transitions occur very rapidly. The relative populations of the various conformers is not just an invariant feature of the CP skeleton but depends on the choice of solvent and on the nature of the substituents, if any, on the beta-pyrrolic positions. The cone conformation, although not the main conformer, is more populated than would be expected based solely on a gas-phase energetic analysis. The receptor can bind a targeted anionic ligand by two mechanisms, impossible to discriminate experimentally: 1) direct binding to the limited number of cone conformers present in the equilibrium population, or 2) by promoting a conformational transition after binding initially to the less ionophilic 1,3-alternate conformer. Both mechanisms are kinetically accessible, and their relative importance in defining the binding process is expected to reflect the relative population of the 1,3-alternate and cone conformers. Since, in the absence of an added anionic ligand this latter distribution is expected to be a function inter alia of the beta-pyrrolic substituents and the solvent, the possibility exists to fine-tune the anion-recognition properties of calixpyrroles in ways that might not be necessarily obvious.

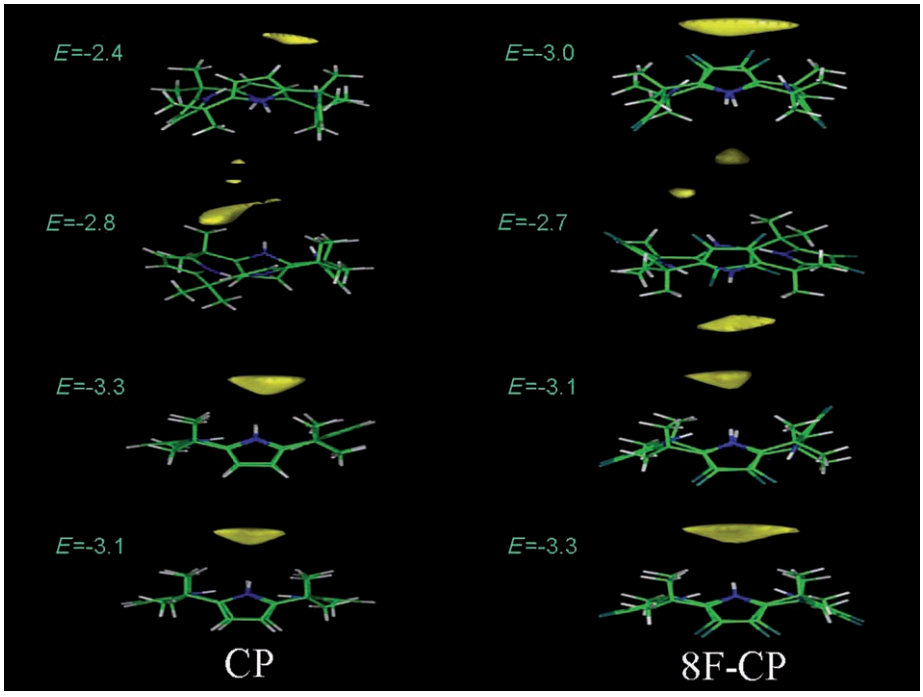


Figure 8. Classical molecular interaction potentials (CMIP; see Computational Methods) for the interaction of a negative probe (O^-) with different conformers of CP and 8F-CP. Calculations were performed by considering the limiting case of a very polar environment (water). The contour plotted corresponds to -2 kcal mol^{-1} and the value noted corresponds to the CMIP minimum.

Acknowledgements

We are indebted to Prof. J. L. Gelpí for assistance in CMIP calculations. This work was supported by the Spanish DGCYT (BIO2003-06848 and SAF2002-04282). We also thank the

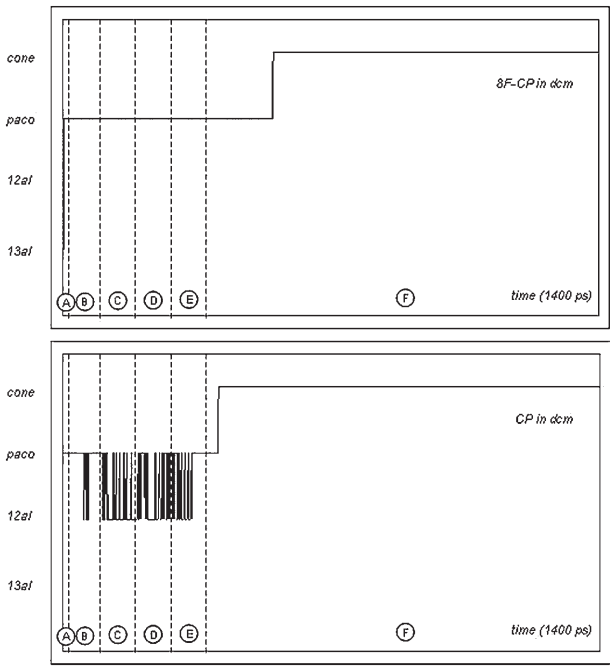


Figure 9. Transition between 1,3-alternate and cone conformers for CP and 8F-CP in dichloromethane. Note that transitions already occur during the thermalization/equilibration steps. The steps are: A = 10 ps at 10 K; B = 90 ps at 50 K; C = 100 ps at 100 K; D = 100 ps at 200 K: E = 100 ps at 300 K; F = 1000 ps at 300 K.

Barcelona Supercomputing Centre and the CESCA for computational resources. Studies of calixpyrroles in Austin are supported by the NIH (grant GM 58907 to J.L.S.).

[1] R. Nishiyabu, P. Anzenbacher, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 8270–8271.
[2] J. M. Lehn, *Science* **1993**, *260*, 1762–1763.
[3] J. P. Desverne, A. W. Czarnik, *Chemosensors of Ions and Molecular Recognition*, Kluwer, Dordrecht, **1997**.
[4] A. P. de Silva, H. Q. Gunaratne, T. Gunnlaugsson, A. J. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515–1566.
[5] A. Bianchi, K. Bowman-James, E. García-España, *Supramolecular Chemistry of Anions*, Wiley, New York, **1997**.
[6] F. P. Schmidtchen, *Nachr. Chem. Tech. Lab.* **1988**, *36*, 10–17.
[7] F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646.
[8] W. L. Jorgensen, *Chemtracts: Org. Chem.* **1991**, *4*, 91–119.
[9] J. L. Sessler, M. Cyr, H. Furuta, V. Kral, T. Mody, T. Morishima, M. Shionoya, S. Weghorn, *Pure Appl. Chem.* **1993**, *65*, 393–398.
[10] P. D. Beer, *Chem. Commun.* **1996**, 689–696.
[11] J. J. Lavigne, E. V. Anslyn, *Angew. Chem.* **1999**, *111*, 3903–3906; *Angew. Chem. Int. Ed.* **1999**, *38*, 3666–3669.
[12] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 214–220.
[13] P. A. Gale, J. L. Sessler, V. Král, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.
[14] P. A. Gale, J. L. Sessler, W. E. Allen, N. A. Tvermoes, V. Lynch, *Chem. Commun.* **1997**, 665–666.
[15] P. A. Gale, J. L. Sessler, V. Král, *Chem. Commun.* **1998**, 1–8.
[16] J. L. Sessler, P. A. Gale, J. W. Genge, *Chem. Eur. J.* **1998**, *4*, 1095–1099.
[17] P. Anzenbacher, Jr., K. Jursikova, J. L. Sessler, *J. Am. Chem. Soc.* **2000**, *122*, 9350–9351.
[18] J. L. Sessler, P. Anzenbacher, Jr., H. Miyaji, K. Jursikova, E. R. Bleasdale, P. A. Gale, *Ind. Eng. Chem. Res.* **2000**, *39*, 3471–3478.
[19] P. Anzenbacher, Jr., A. C. Try, H. Miyaji, K. Jursikova, M. Marquez, J. L. Sessler, *J. Am. Chem. Soc.* **2000**, *122*, 10268–10272.
[20] H. Miyaji, W. Sato, J. L. Sessler, *Angew. Chem.* **2000**, *112*, 1847–1850; *Angew. Chem. Int. Ed.* **2000**, *39*, 1777–1780.
[21] H. Miyaji, P. Anzenbacher, Jr., J. L. Sessler, E. R. Bleasdale, P. A. Gale, *Chem. Commun.* **1999**, 1723–1724.
[22] B. Turner, A. Shterenberg, M. Kapon, K. Suwinska, Y. Eichen, *Chem. Commun.* **2001**, 13–14.
[23] P. Anzenbacher, Jr., K. Jursikova, V. Lynch, P. A. Gale, J. L. Sessler, *J. Am. Chem. Soc.* **1999**, *121*, 11020–11021.
[24] R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W. S. Cho, D. Gross, G. W. Bates, S. J. Brooks, M. E. Light, P. A. Gale, *Angew. Chem.* **2005**, *117*, 2593–2598; *Angew. Chem. Int. Ed.* **2005**, *44*, 2537–2542.
[25] J. L. Sessler, A. Gebauer, P. A. Gale, *Gazz. Chim. Ital.* **1997**, *127*, 723–728.
[26] R. Martinez-Manez, F. Sancenon, *Chem. Rev.* **2003**, *103*, 4419–4476.
[27] C. Suksai, T. Tuntulani, *Chem. Soc. Rev.* **2003**, *32*, 192–202.
[28] P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502–532; *Angew. Chem. Int. Ed.* **2001**, *40*, 486–516.
[29] H. Miyaji, W. Sato, J. L. Sessler, V. Lynch, *Tetrahedron Lett.* **2000**, *41*, 1369–1373.
[30] B. Turner, M. Botoshansky, Y. Eichen, *Angew. Chem.* **1998**, *110*, 2633–2637; *Angew. Chem. Int. Ed.* **1998**, *37*, 2475–2478.
[31] P. A. Gale, J. L. Sessler, V. Lynch, P. I. Sansom, *Tetrahedron Lett.* **1996**, *37*, 7881–7884.
[32] J. L. Sessler, P. Anzenbacher, Jr., J. A. Shriver, K. Jursikova, V. M. Lynch, M. Marquez, *J. Am. Chem. Soc.* **2000**, *122*, 12061–12062.
[33] G. Cafeo, F. H. Kohnke, G. L. L. La Torre, A. J. P. White, D. J. Williams, *Chem. Commun.* **2000**, 1207–1208.
[34] P. Piatek, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **2004**, *126*, 16073–16076.
[35] C. Bucher, R. S. Zimmerman, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **2001**, *123*, 9716–9717.
[36] A. F. Danil de Namor, M. Shehab, *J. Phys. Chem. B* **2005**, *109*, 17440–17444.
[37] J. L. Sessler, D. An, W. S. Cho, V. Lynch, *Angew. Chem.* **2003**, *115*, 2380–2383; *Angew. Chem. Int. Ed.* **2003**, *42*, 2278–2281.
[38] J. L. Sessler, D. An, W. S. Cho, V. Lynch, *J. Am. Chem. Soc.* **2003**, *125*, 13646–13647.
[39] J. L. Sessler, D. An, W. S. Cho, V. Lynch, M. Márquez, *Chem. Commun.* **2005**, 540–542.
[40] J. L. Sessler, D. An, W. S. Cho, V. Lynch, D. W. Yoon, S. J. Hong, C. H. Lee, *J. Org. Chem.* **2005**, *70*, 1511–1517.
[41] G. Cafeo, F. H. Kohnke, G. L. La Torre, M. F. Parisi, R. Pistone Nascone, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **2002**, *8*, 3148–3156.
[42] J. L. Sessler, D. An, W. S. Cho, V. Lynch, M. Marquez, *Chem. Eur. J.* **2005**, *11*, 2001–2011.
[43] V. Král, P. A. Gale, P. Anzenbacher, Jr., K. Jursikova, V. Lynch, J. L. Sessler, *Chem. Commun.* **1998**, 9–10.
[44] J. L. Sessler, W.-S. Cho, V. Lynch, V. Král, *Chem. Eur. J.* **2002**, *8*, 1134–1143.
[45] C. H. Lee, J. S. Lee, H. K. Na, D. W. Yoon, H. Miyaji, W. S. Cho, J. L. Sessler, *J. Org. Chem.* **2005**, *70*, 2067–2074.
[46] C. H. Lee, H. K. Na, D. W. Yoon, D. H. Won, W. S. Cho, V. Lynch, S. V. Shevchuk, J. L. Sessler, *J. Am. Chem. Soc.* **2003**, *125*, 7301–7306.
[47] P. K. Panda, C. H. Lee, *J. Org. Chem.* **2005**, *70*, 3148–3156.
[48] P. K. Panda, C. H. Lee, *Org. Lett.* **2004**, *6*, 671–674.
[49] D. W. Yoon, H. Hwang, C. H. Lee, *Angew. Chem.* **2002**, *114*, 1835–1837; *Angew. Chem. Int. Ed.* **2002**, *41*, 1757–1759.
[50] H. Miyaji, H. K. Kim, E. K. Sim, C. K. Lee, W. S. Cho, J. L. Sessler, C. H. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12510–12512.
[51] K. A. Nielsen, W. S. Cho, J. O. Jeppesen, V. Lynch, J. Becher, J. L. Sessler, *J. Am. Chem. Soc.* **2004**, *126*, 16296–16297.
[52] K. A. Nielsen, J. O. Jeppesen, E. Levillain, J. Becher, *Angew. Chem.* **2003**, *115*, 197–201; *Angew. Chem. Int. Ed.* **2003**, *42*, 187–191.

[53] J. L. Sessler, V. Král, T. V. Shishkanova, P. A. Gale, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4848–4853.
[54] W. Chen, Z. R. Li, D. Wu, Y. Li, C. C. Sun, F. L. Gu, *J. Am. Chem. Soc.* **2005**, *127*, 10977–10981.
[55] J. Radecki, A. Radecka, T. Piotrowski, S. Depraetere, W. Dehaen, J. Plavec, *Electroanalysis* **2004**, *15*, 2073–2081.
[56] V. Král, J. L. Sessler, T. V. Shishkanova, P. A. Gale, R. Volf, *J. Am. Chem. Soc.* **1999**, *121*, 8771–8775.
[57] J. R. Blas, M. Marquez, J. L. Sessler, F. J. Luque, M. Orozco, *J. Am. Chem. Soc.* **2002**, *124*, 12796–12805.
[58] J. L. Sessler, W. S. Cho, D. E. Gross, J. A. Shriver, V. M. Lynch, M. Marquez, *J. Org. Chem.* **2005**, *70*, 5982–5986.
[59] A. F. Danil de Namor, M. Shehab, *J. Phys. Chem. B* **2003**, *107*, 646–6468.
[60] A. F. Danil de Namor, M. Shehab, *J. Phys. Chem. A* **2004**, *108*, 7324–7330.
[61] F. P. Schmidtchen, *Org. Lett.* **2002**, *4*, 431–434.
[62] T. G. Levitskaia, M. Marquez, J. L. Sessler, J. A. Shriver, T. Vercouter, B. A. Moyer, *Chem. Commun.* **2003**, 2248–2249.
[63] D. F. Wang, Y. D. Wu, *J. Theor. Comput. Chem.* **2004**, *3*, 51–68.
[64] H. D. Banks, A. Dondoni, M. Kleban, A. Marra, *Chirality* **2002**, *14*, 173–179.
[65] Y. D. Wu, D. F. Wang, J. L. Sessler, *J. Org. Chem.* **2001**, *66*, 3739–3746.
[66] W. E. Allen, P. A. Gale, C. T. Brown, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472.
[67] D. Jacoby, C. Floriani, A. Chiesivilla, C. Rizzoli, *J. Chem. Soc. Chem. Commun.* **1991**, 790–792.
[68] T. D. Lash, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4506–4509.
[69] J. He, T. A. Kaprak, M. A. Jones, T. D. Lash, *J. Porphyrins Phthalocyanines* **2005**, *9*, 170–185.
[70] C. I. Bayly, P. Cieplak, W. Cornell, P. A. Kollman, *J. Phys. Chem.* **1993**, *97*, 10269–10280.
[71] W. L. Jorgensen, J. Tirado-Rives, *J. Am. Chem. Soc.* **1988**, *110*, 1657–1666.
[72] E. Guàrdia, R. Pinzón, J. Casulleras, M. Orozco, F. J. Luque, *Molecular Simulations* **2001**, *26*, 287–306.
[73] J. P. Ryckaert, G. Ciccotti, H. J. C. Berendsen, *J. Comput. Phys.* **1977**, *23*, 327–341.
[74] A plane was defined between three of the four interpyrrolic methylene atoms. The unit normal vector to this plane is taken as V1. For each pyrrole ring, a vector pointing to the N atom and starting at the middle point of the opposite bond is defined. This vector taken as unitary is called V2. Applying basic geometry, if the difference between V1 and V2 is greater than the square root of 2, this ring is pointing down; if it is smaller, this ring is pointing up.
[75] J. L. Gelpi, S. G. Kalko, X. Barril, J. Cirera, X. de La Cruz, F. J. Luque, M. Orozco, *Proteins* **2001**, *45*, 428–437.
[76] V. Tsui, D. A. Case, *J. Am. Chem. Soc.* **2000**, *122*, 2489–2498.
[77] D. A. Case, D. A. Pearlman, J. W. Caldwell, T. E. Cheatham, III, W. S. Ross, C. L. Simmerling, T. L. Darden, K. M. Marz, R. V. Stanton, A. L. Cheng, J. J. Vincent, M. Crowley, V. Tsui, R. J. Radmer, Y. Duan, J. Pitera, I. Massova, G. L. Seibel, U. C. Singh, P. K. Weiner, P. A. Kollman, AMBER6, University of California, San Francisco, **1999**.
[78] C. J. F. Böttcher, *Theory of electrostatic polarisation*, Elsevier, Amsterdam, **1952**.
[79] W. L. Jorgensen, BOSS, Yale University, New Haven, **2000**.
[80] Gaussian 98, M. J. T. G. W. Frisch, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, Montgomery Jr., J. AR. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, Gill, P. M. W. B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian Inc., Pittsburgh, **1998**.

Received: May 30, 2006
Revised: August 18, 2006
Published online: November 6, 2006

