Free Energy Perturbation Studies on Enantiomeric Discrimination of Pyridino-18-Crown-6 Ethers

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(Received May 24, 2000; CL-000505)

We performed FEP and MD simulations on enantiomeric complexes of seven 18-crown-6 ether compounds and a chiral protonated amine to obtain the free energy differences, and to elucidate the mechanism responsible for enantioselectivity. The FEP calculation reproduced the experimental enantioselectivity quite well. We partitioned the binding free energy in solution into the binding free energy in the gas phase and the solvation energy, and discussed the results. In the MD simulations, the detailed motion of host–guest complexes was monitored.

Various experimental techniques have shown that chirally substituted crown ethers differentiate amine enantiomers very successfully.[1,2] Nearly all of these studies have been carried out in condensed media, and thus the results are subject to influences exerted by solvents and counterions. In many cases, these complicating effects can obscure the fundamental components underlying and controlling the enantioselection.[3] In order to understand the host–guest interactions responsible for the enantioselectivity without interfering solvent effects, investigations on various host–guest pairs in the same solvent or in the gas phase are required. However, only a few systematic studies have been reported so far.[4] In this study, we employed free energy perturbation[5] (FEP) and molecular dynamics[6] (MD) simulations to explain the enantioselectivity of the chiral hosts (**1**–**7**) toward a chiral guest: phenylethyl amine (**PheEt**) (Figure 1). We compared the results with those from experiments with similar solvents, and analyzed the binding free energy in the solvent in terms of the binding free energy in the gas phase and the solvation energy.

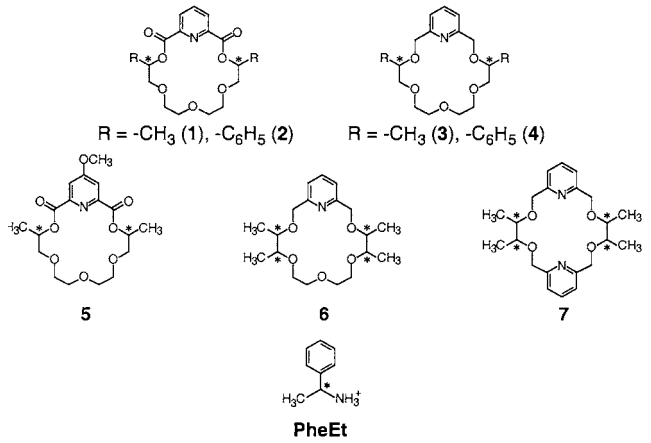
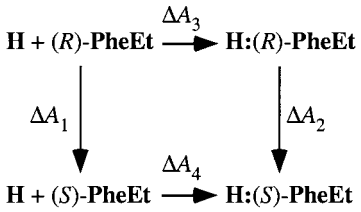


Figure 1. Structures of chiral hosts (**H**: **1**–**7**) and a chiral guest (**G**: **PheEt**).

In order to compute the differences in binding free energies between the host molecules **1**–**7** and the enantiomers of **PheEt**, the thermodynamic cycle in Scheme 1 was used.[5,7,8] In this cycle, **H:**(*R* or *S*)-**PheEt** denotes the complex structure of a host **H** and one of the enantiomeric guests. Since the Helmholtz free energy is a state function, $\Delta A_4 - \Delta A_3$ is the same as $\Delta A_2 - \Delta A_1$,

$$\Delta\Delta A \equiv \Delta A_4 - \Delta A_3 = \Delta A_2 - \Delta A_1. \quad (1)$$



Scheme 1.

i.e.,

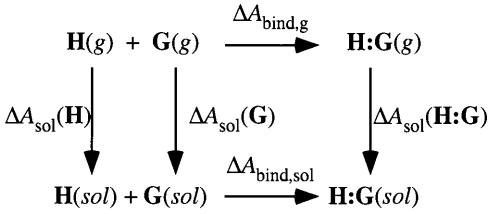
Since (*R*)-**PheEt** and (*S*)-**PheEt** have the same energy, ΔA_1 is zero. Thus only the ΔA_2 term is needed where the enantioselectivity is concerned.[9] For the calculation of ΔA_2, we used the finite difference thermodynamic integration algorithm.[10,11] The perturbation we used mutates (*R*)-**PheEt** into (*S*)-**PheEt** by interchanging guest molecule residues (i.e., $CH_3 \rightarrow NH_3^+$ and $NH_3^+ \rightarrow CH_3$) over 30 stages. A time step of 1 fs, an equilibration period of 50 ps, and a temperature of 300 K were used. A 250-ps sampling time was applied to all calculations. The length of the sampling time was chosen to obtain converged results. To prevent the host and guest from drifting apart during simulations, flat-bottomed harmonic restraints were applied between the center of the hosts and the chiral carbon of the guests.[9] Usually large statistical errors are associated with points near the middle windows (λ = 0.5) of the FEP simulations for enantioselectivity.[9] This is partly due to the existence of multiple low-energy conformers with high-energy barriers among them.[12] Instead of performing prohibitively long simulations to ensure the Boltzmann distribution of the conformers, we performed the free energy simulations five times, and averaged them with the Boltzmann weight.[13] The MD runs at the two end points (λ = 0 and λ = 1 in FEP) are useful for comparing the structures of the two states and to reveal the structural features responsible for the enantioselection. MD runs were performed at 300 K for 1000 ps with a 1-fs time step. Samples during the dynamics simulation were obtained every 4 ps. All the calculations above were performed in vacuo, using the CVFF force field 2.3 implemented in the *DISCOVER* package (version 2.98).[11]

The FEP simulation results are listed in Table 1. The simulation results are in good agreement with the experiments. Only in the case of host **6** does the uncertainty in the experi-

Table 1. Calculated and experimentally determined enantioselectivity of **1–7** toward **PheEt** (all units are in kcal/mol)

Host	$\Delta\Delta A$(cal.)[a,b]	$\Delta\Delta G$(exp.)[a,c]	Solvent(exp.)[d]
(*S*,*S*)-**1**	0.2 ± 0.2	0.3 ± 0.1	M
(*S*,*S*)-**2**	0.7 ± 0.1	0.8 ± 0.1	1M/1C
(*S*,*S*)-**3**	0.2 ± 0.2	0.5 ± 0.1	1M/1C
(*R*,*R*)-**4**	–0.2 ± 0.2	–0.2 ± 0.1	M
(*S*,*S*)-**5**	0.3 ± 0.2	0.27 ± 0.08	M
(*R*,*R*,*R*,*R*)-**6**	–0.1 ± 0.1	0.4 ± 0.2	1M/9C
(*R*,*R*,*R*,*R*)-**7**	0.0 ± 0.2	0.2 ± 0.2	1M/9C

[a]The positive sign denotes that **H**:(*R*)-**PheEt** complex is more stable than **H**:(*S*)-**PheEt** complex. [b]The errors were estimated from the standard deviation of five independent simulations. [c]Reference 4. [d]M = methanol, 1M/1C = 50% methanol-50% Chloroform (v/v), and 1M/9C = 10% methanol-90% chloroform (v/v).



Scheme 2. Thermodynamic cycle for binding free energies of the host **H** and the guest **G**.

mental value lie outside the standard deviation of the computed results. As seen in Scheme 2, the binding free energy in solution ($\Delta A_{bind,sol}$) can be written as the sum of the binding energy

$$\Delta A_{bind,sol} = \Delta A_{bind,g} + \Delta A_{sol}(\mathbf{H{:}G}) - \Delta A_{sol}(\mathbf{H}) - \Delta A_{sol}(\mathbf{G}). \quad (2)$$

in the gas phase ($\Delta A_{bind,g}$) and the solvation energy:
Since the relative solvation energies of the host and the guest are zero ($\Delta\Delta A_{sol}(\mathbf{H}) = \Delta\Delta A_{sol}(\mathbf{G}) = 0$) in the case of enantiomeric recognition, the relative binding energy in solution is the sum of that in the gas phase and the relative solvation energy

$$\Delta\Delta A_{bind,sol} = \Delta\Delta A_{bind,g} + \Delta\Delta A_{sol}(\mathbf{H{:}G}). \quad (3)$$

between the two diastereomeric host:guest complexes:
Thus, comparing the results in solution with those in the gas phase gives the trends of the solvation energy. Good agreement for the hosts **1**, **4**, and **5** implies that the $\Delta\Delta A_{sol}(\mathbf{H{:}G})$ term is small for the methanol solvent. The results on 1M/1C solvent show that $\Delta\Delta A_{sol}(\mathbf{H{:}G})$ has the opposite trend to $\Delta\Delta A_{bind,g}$. The other source of difference between the solution and the gas phase results besides the solvation energy is the contribution from ion pair formation in solution. This contribution would be large for a nonpolar or aprotic solvent. The large discrepancy in the case of host **6** would be attributed to this term.

The structural features monitored in the MD simulations are depicted in Figure 2 and listed in Table 2. Small values of the standard deviations for the distances indicate that the guest molecule is tightly bound to the host through the interaction between the protonated amine group of the guest and the ring oxygen (and nitrogen) of the host, and the interaction between the two aromatic rings of host and guest. The data show that **1**:(*R*)-**PheEt** is more stable than **1**:(*S*)-**PheEt** through the combined effects of i) π–π interaction between the phenyl ring and pyridine ring, which was manifested by the smaller values of D2 and A1 of **1**:(*R*)-**PheEt** compared with those of **1**:(*S*)-**PheEt**, and ii) small steric hindrance between the guest and the host manifested by the larger value of D3.

Table 2. Structural features obtained from the analysis of the MD trajectories of **1**:**PheEt** complexes

	1:(*R*)-**PheEt**		**1**:(*S*)-**PheEt**	
D1 (Å)[a]	1.4	(0.2)	1.3	(0.2)
D2 (Å)[a]	4.0	(0.3)	4.1	(0.5)
A1 (degree)[a]	$12._2$	($6._4$)	$17._4$	($8._0$)
D3 (Å)[a]	3.5	(0.4)	3.4	(0.6)

[a]See Figure 2 for the details. The values in the parentheses are the standard deviations.

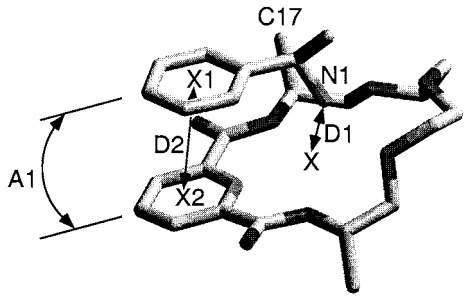


Figure 2. Structural features for the analysis of the MD trajectory. Hydrogen atoms are not depicted for clarity. N1 is the amine nitrogen, X the center of mass (CM) of 5 (or 4) oxygen atoms and 1 (or 2) nitrogen atom(s) of the host, X1 the CM of the phenyl ring of the guest, X2 the CM of the pyridine ring of the host, C17 the carbon atom of the substituent of the host. D3, not shown in Figure 2, represents the shortest distance from the hydrogen atoms of the guest to C17.

This work was supported by Creative Research Initiatives, the Ministry of Science and Technology, Korea. OSL thanks the Ministry of Education for the Brain Korea 21 fellowship.

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