Comparison of Computational Methods for Enthalpic and Entropic Contributions in the Enantiomeric Discrimination by Dimethyldiketopyridino-18-crown-6 Ether

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The enantiomeric recognition of dimethyldiketopyridino-18-crown-6 ether toward chiral amines was studied by molecular dynamics, free energy perturbation, and quantum mechanical calculations. The enthalpic and entropic contributions were evaluated. It was shown that the entropic contribution to the enantioselectivity decreased when the amine guest is large and has more π–π interaction with the host molecule.

Host-guest enantiomeric discrimination is important in a variety of chemical and biological processes including sensing, asymmetric catalysis reactions, and the resolution of enantiomers.[1–3] It is well known that the dimethyldiketopyridino-18-crown-6 ether (**1**) discriminates chiral protonated amines (**2–5**) (Figure 1) through host-guest interactions, mainly steric repulsion and π–π interaction. Characterization of the enantiomeric interaction of this system was conducted by various experimental methods. The kinetic and thermodynamic data such as the free energy, enthalpy, and entropy have also been reported.[4–6] It is generally believed that the change in enthalpy is partially compensated by a corresponding change in entropy. However, there are some reported exceptions.[7] So it is necessary to evaluate these contributions in order to attain an improved understanding of the enantiomeric recognition and achieve a better selector design. Moreover, the contributions are dependent upon the nature of the solvent, and the role of the solvent is not clear yet. Thus a gas phase study might be a useful starting point in a series of investigations on this subject.

In this letter, the investigation was focused on the comparison of enthalpic and entropic contributions to the enantioselectivity of **1** obtained by molecular dynamics (MD),[8] free energy perturbation (FEP),[9] and ab initio calculations with the experimental results.[4–6]

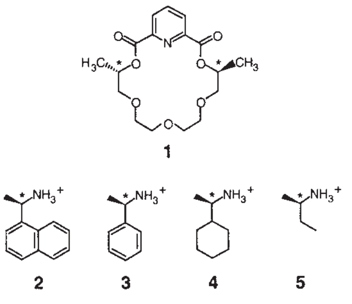

Figure 1. Structures of the chiral host (**1**) and protonated amine guests.

X-ray data and global minimum structures obtained by MD calculations were used as the starting geometry of all complexes.[4,10] In order to compute the difference in binding free energies between enantiomers of **2–5** with (S,S)-**1**, we used the standard FEP formula:

$$\Delta\Delta A = -k_{\mathrm{B}}T \sum_i \ln\langle \exp[-\Delta V_i / k_{\mathrm{B}}T]\rangle_i, \tag{1}$$

where $\Delta\Delta A$ is the free energy difference between diastereomeric complexes, $k_{\mathrm{B}}T$ is the Boltzmann constant times the absolute temperature, and ΔV_i is the difference in the potential energies of $\mathbf{1}\cdot(R)$-Guest and $\mathbf{1}\cdot(S)$-Guest complexes at the ith window in the mutation subdivided into several windows. It was shown that 40 windows are enough to ensure the efficiency of sampling for this system.[10] The symbol $\langle\rangle_i$ refers to an ensemble average over a reference state represented by potential energy V_i. A time step of 1 fs, an equilibration period of 100 ps, and a temperature range from 250 to 550 K with 50 K intervals were employed. 500 ps sampling time was applied to all calculations. The average enthalpy was also obtained by a 70 ns molecular dynamics simulation of each diastereomeric complex at 300 K. Since the configuration sampling was performed in a canonical ensemble, the calculated free energy corresponds to the Helmholtz free energy. Although the difference between the Helmholtz free energy and the Gibbs free energy, $P\Delta V$ $(= (\Delta n)RT$, where P is the pressure, V the volume, n the number of moles, and R the gas constant), is not negligible, the relative difference between them $(P\Delta\Delta V)$ is negligible, even in the gas phase. All simulations were done with the AMBER* force field implemented in the MacroModel 7.0 package.[11] In quantum mechanical calculation, the B3LYP/6-31G** basis set implemented in the Jaguar 4.1 package[12] was used. The relative free energy in the gas phase at $T = 300$ K and $p = 1$ atm was calculated with the rigid-rotor harmonic oscillator approximation[13] as

$$\Delta\Delta G = \Delta E(0) + \Delta\mathrm{ZPE} + \Delta\Delta H_{0\to300} - 300\Delta\Delta S, \tag{2}$$

where $\Delta E(0)$ is the quantum mechanical energy difference, ΔZPE the zero point energy difference, $\Delta\Delta H_{0\to300}$ the difference in enthalpy changes from $T = 0$ K to 300 K, and $\Delta\Delta S$ the entropy difference at 300 K. Since all the configurations of host **1** in this letter are (S,S)-**1**, hereafter the notation **1** will be used for (S,S)-**1** for clarity.

The enthalpic and entropic contributions to the enantiomeric recognition were estimated from the slope and the intercept of the $(\Delta\Delta G/T)$ vs $1/T$ plot

$$\frac{\Delta\Delta G}{T} = \frac{\Delta\Delta H}{T} - \Delta\Delta S. \tag{3}$$

In this equation, it is assumed that $\Delta\Delta H$ and $\Delta\Delta S$ are constant in the given temperature range.

$\Delta\Delta G$ of every host-guest complex was calculated at the temperature range from 250 to 550 K with 50 K intervals and $\Delta\Delta G/T$ as a function of $1/T$ is depicted in Figure 2 and the values of $\Delta\Delta H$ and $T\Delta\Delta S$ at 300 K are listed in Table 1. In this calculation, $\mathbf{1}\cdot(R)$-Guest was more stable than $\mathbf{1}\cdot(S)$-Guest in the enthalpic contribution for every diastereomeric complex,

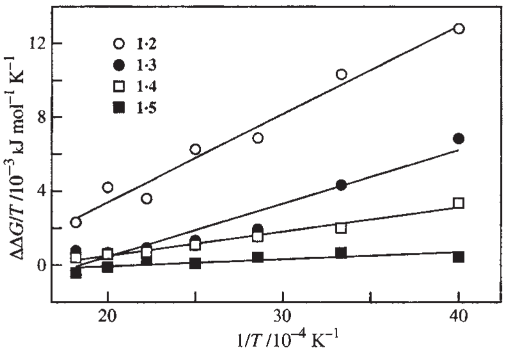

Figure 2. $\Delta\Delta G/T$ vs $1/T$ plot. The value of $\Delta\Delta G$ was obtained from FEP calculation at each temperature. The open circles are for **1**·**2**, closed circles for **1**·**3**, open squares for **1**·**4**, and closed squares for **1**·**5**.

Table 1. Enthalpic and entropic contributions to the enantioselectivity of **1** toward **2**–**5** at 300 K by FEP and MD. All Units are in kJ/mol

	FEP		MD
Guest	$\Delta\Delta H$	$T\Delta\Delta S$	$\Delta\Delta H$
2	4.78	1.86	3.7 ± 54.8
3	2.93	1.65	2.9 ± 51.4
4	1.31	0.63	1.9 ± 53.3
5	0.38	0.24	0.3 ± 49.4

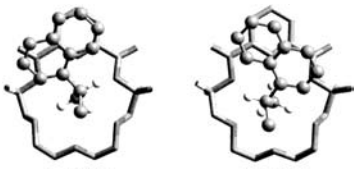
1·(R)-**2** **1**·(S)-**2**

Figure 3. Global minimum structures of **1**·(R)-**2** and **1**·(S)-**2** obtained by geometry optimization at the B3LYP/6-31G** level. Hydrogen atoms except for those attached to chiral carbon and heteroatoms are not shown for clarity.

Table 2. Components of the Gibbs free energy difference between diastereomeric complexes **1**·(R)-**2** and **1**·(S)-**2**. The B3LYP/6-31G** basis set was used for geometry optimization and frequency calculation. All units are in kJ/mol

$\Delta\Delta G^{a}$	$\Delta E(0)$	ΔZPE	$\Delta\Delta H_{0\rightarrow 300}$	$T\Delta\Delta S$
4.47	4.25	−0.14	−0.08	−0.44

[a] Experimental value = 3.5 ± 0.6 kJ/mol.[5]

whereas **1**·(S)-Guest was more stable than **1**·(R)-Guest in the entropic contribution. The enthalpic contribution was the largest in the **1**·**2** complex. The order of the enthalpic contribution was **1**·**2** > **1**·**3** ≅ **1**·**4** > **1**·**5**. Thus the enthalpic contribution was larger when the guest molecule was larger and had more π–π interaction with the host. As shown in Table 1, more than 50% of the enantioselectivity came from the enthalpic contribution.

As shown in Figure 2, the enantioselectivity increased as the temperature decreased in all complexes. The (R)-Guests formed more stable complexes with **1** than the (S)-Guests, except for **1**·**5** at higher temperatures. In **1**·**5**, the free energy difference was small between the two diastereomeric complexes and **1** could not distinguish the enantiomers of **5** at higher temperatures.

The average enthalpies obtained by 70 ns MD simulations are also listed in Table 1. Since the total time used to obtain the values of $\Delta\Delta H$ and $T\Delta\Delta S$ by FEP was 140 ns, 70 ns MD was applied to the **1**·(R)-Guest and **1**·(S)-Guest, which are corresponding to the initial and the final points in the FEP simulation, for comparison. The errors in the average enthalpy were too large to obtain meaningful values of the enthalpic contribution. This is because $\Delta\Delta H$ was determined from two large ΔH values. It is well known that the inherent errors in $\Delta\Delta H$ obtained from MD are at least one order of magnitude larger than those for $\Delta\Delta G$ obtained by FEP.[9]

The enantiomeric recognition in **1**·**2** complexation was also assessed quantum mechanically. The diastereomeric complexes of **1**·(R)-**2** and **1**·(S)-**2** were optimized with the B3LYP/6-31G** basis set. The optimized structures of **1**·**2** are depicted in Figure 3. Then, a frequency calculation for the optimized structures with the same basis set was performed. The resulting values for the terms in Eq. (2) are listed in Table 2. In the quantum mechanical calculation, **1**·(R)-**2** was more stable than **1**·(S)-**2** in terms of both the enthalpy and entropy. Additionally, the absolute value of the enthalpic contribution was larger than that of entropy. Although the gas phase values of enthalpy and entropy were not reported, it was observed that **1**·(R)-**2** was more stable than **1**·(S)-**2** in both of the enthalpic and entropic terms when the dielectric constant was less than 14.8, and that the enthalpic contribution was dominant.[14] The Gibbs free energy obtained by this quantum mechanical calculation, 4.5 kJ/mol was slightly larger than that obtained by a gas-phase experiment, 3.5 ± 0.6 kJ/mol.[5]

In conclusion, the quantum mechanical calculation gave a result that is in accordance with the experimental trend for the enthalpic and entropic contributions. The FEP calculation yielded the best estimation for the Gibbs free energy difference, in spite of the entropy contribution inconsistent with the experimental result. The MD calculation did not properly reproduce the enantiomeric recognition as a result of the large uncertainty. However, the CPU time for the geometry optimization and frequency calculation using the quantum mechanical method was much longer than those for FEP and MD calculations. Thus FEP is suitable for calculating the Gibbs free energy difference, whereas quantum mechanical calculation is better in separately obtaining enthalpic and entropic contributions.

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References

1 R. Janoschek, in "Chirality: From Bosons to the α-helix," Springer-Verlag, Berlin (1991).
2 W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.*, **89**, 347 (1989).
3 O.-S. Lee, Y. H. Jang, Y. K. Cho, M. H. Hyun, H.-J. Kim, and D. S. Chung, *Chem. Lett.*, **2001**, 232.
4 R. B. Davidson, N. K. Dalley, R. M. Izatt, J. S. Bradshaw, and C. F. Campana, *Isr. J. Chem.*, **25**, 33 (1985).
5 D. V. Dearden, C. Dejsupa, Y. J. Liang, J. S. Bradshaw, and R. M. Izatt, *J. Am. Chem. Soc.*, **119**, 353 (1997).
6 X. X. Zhang, R. M. Izatt, C. Y. Zhu, and J. S. Bradshaw, *Supramol. Chem.*, **6**, 267 (1996).
7 E. Gallicchio, M. Kubo, and R. M. Levy, *J. Am. Chem. Soc.*, **120**, 4526 (1998).
8 M. P. Allen and D. J. Tildesley, in "Computer Simulation of Liquids," Clarendon Press, Oxford (1987).
9 P. Kollman, *Chem. Rev.*, **93**, 2395 (1993).
10 O.-S. Lee, S. Hwang, and D. S. Chung, *Supramol. Chem.*, **12**, 255 (2001).
11 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, and W. C. Still, *J. Comput. Chem.*, **11**, 440 (1990).
12 "Jaguar 4.1," Schrodinger, Inc., Portland (2000).
13 D. A. McQuarrie, in "Statistical Mechanics," Harper Collins Publisher, New York (1973).
14 J. K. Hathaway, R. M. Izatt, C. Y. Zhu, P. Huszthy, and J. S. Bradshaw, *Supramol. Chem.*, **5**, 9 (1995).