Supporting Text

Heat Capacity Change (ΔC_p)

It is well established that hydrophobic interactions upon complex formation lead to negative heat capacity change (ΔC_p) (24). Indeed, negative ΔC_p values have amply been reported for complexation of organic guests with cyclodextrins (CDs) (10) as well as for protein-ligand interactions (11). For instance, ΔC_p for avidin-biotin complexation is as large as –1000 J mol^{-1} K^{-1} (25). However, no ΔC_p data has been reported for CB complexation and hence we decided to determine the ΔC_p values for complexation of the ferrocenyl guests **1**, **2** and **3** with CB[7].

Direct ITC measurements were performed at 5, 15, 25, 35, and 45°C to determine the complexation enthalpies of CB[7]•**1**, CB[7]•**2**, and CB[7]•**3**. From the slope of the temperature dependence of the enthalpies obtained (Fig. 11), we can calculate the ΔC_p values as –250 ± 30, –140 ± 30, and –110 ± 30 J mol^{-1} K^{-1} for CB[7]•**1**, CB[7]•**2**, and CB[7]•**3**, respectively. The negative ΔC_p values are reasonable, as hydrophobic interactions are expected to play a crucial role upon inclusion of the ferrocene moiety of **1**, **2** and **3** into hydrophobic CB[7] cavity. The absolute ΔC_p values are much smaller than those reported for protein-ligand interactions (11) but comparable to those for CD complexes (10). Furthermore, CB and CD hosts share the same trend in heat capacity change that ΔC_p is always more negative for a neutral hydroxyl guest than for a cationic ammonium guest with the same hydrophobic moiety. This is simply due to the different size of effective hydration shell around the hydroxyl group (possessing a small and weak shell) and the ammonium group (possessing a large and strong shell) (12). In the latter case, larger part of the guest is covered with the hydration shell and hence the overall hydrophobic interactions with the host walls become less extensive to give a reduced ΔC_p.

Comparison of cucurbituril (CB) versus cyclodextrin (CD) complexes

Comparison of complexation thermodynamics of **2** toward comparably sized CB[7] versus β-CD is interesting. Previously, one of us reported the thermodynamic parameters for complexation of **2** with β-CD: $K = 2900\ M^{-1}$, $\Delta H° = -28.5\ kJ\ mol^{-1}$, and $T\Delta S°\ -8.9\ kJ\ mol^{-1}$ (26). Possessing a very rigid cavity that enables closer van der Waals contacts with the ferrocene guest, CB[7] affords an extremely favorable $\Delta H°$ of –90 kJ mol^{-1} (Table 1), and the differential enthalpic gain ($\Delta(\Delta H°)_{CB[7]-\beta CD}$) amounts to –61.5 kJ mol^{-1}, 85% of which survives from the entropic cancelling effect ($\Delta(T\Delta S°)_{CB[7]-\beta CD} = 9\ kJ\ mol^{-1}$) to give the trillion-fold affinity enhancement ($K_{CB[7]}/K_{\beta CD} = 1.4 \times 10^9$). This seems unusual from the viewpoint of the widespread enthalpy-entropy compensation phenomena but can be rationalized. Strong intra-cavity van der Waals interactions (enthalpy gain) lead inevitably to reduced freedoms of guest conformation (entropy losses), eventually showing the enthalpy-entropy compensation. This should be true not only for CDs but equally for CBs. However, the entropic contribution from host/guest desolvation is very different in the two cases. Upon CD complexation (12), positively charged group, such as ammonium cation, stays outside the CD cavity in bulk water and does not contribute by any means to the overall thermodynamics. In contrast, CB offers not only hydrophobic cavity to accommodate hydrophobic part of a guest but also strongly coordinates to the cationic group at the portal(s). Desolvation of both host and guest upon coordination of CB's carbonyl group to guest's cationic group is an extra source of positive entropy, which greatly stabilizes the CB complex with cationic guest. This is an unique host-guest system in which three closely-located parts of the host, i.e., one cavity and two portals, contribute independently to the overall thermodynamics and eventually the enthalpic gain from the intra-cavity host-guest interactions and the entropic gains from the desolvation of CB portal(s) and guest's cationic group(s) jointly contribute to the formation of extraordinarily stable complex without any mutual perturbing.

Electrochemical Study

The reversible, one-electron oxidation of ferrocene derivatives affords an additional experimental method to examine the host-guest interactions with the CB[7] host and the roles of hydrophobicity in the tight binding. Cyclic voltammetric experiments were performed with the bromide salt of **3**. The reversible oxidation of this compound in aqueous solution (pH 7 phosphate buffer also containing 0.1 M NaCl) was observed at a half-wave potential ($E_{1/2}$) of + 0.65 V versus Ag/AgCl (Fig. 12). Addition of CB[7] leads to the appearance at more positive potentials of a new wave that grows with increasing concentration of the host at the expense of the original wave. When the concentration of added CB[7] equals the concentration of **3**, only the new wave (corresponding to the complex) was observed at a half-wave potential of 0.84 V. Further additions of the host fail to cause any other changes in the observed voltammetric behavior, which is fully consistent with the formation of a highly stable complex between CB[7] and **3**. The complexation-induced half-wave potential shift is very pronounced ($\Delta E_{1/2}$ = 0.19 V), revealing a loss in the stability of the inclusion complex ($\Delta\Delta G^{o}$ = 18 kJ mol^{-1}) upon oxidation of the ferrocene center. This free energy difference indicates destabilization of the CB[7]•**3** complex by a factor of 1400 in the *K* value.

We have previously reported the electrochemical behavior of the monocationic guest **2** in the presence of CB[7] (7). The results were similar, as we obtained $\Delta E_{1/2}$ of 0.11 V and $\Delta\Delta G^{o}$ of *ca.* 11 kJ mol^{-1} in the stability of the complex upon one-electron oxidation. The decreased stability of these complexes upon oxidation of the ferrocene center may stem from the increased hydrophilic character of the guest molecule and the resulting changes in the aqueous solvation of the ferrocene and ferrocenium species relative to their CB[*n*] complexes.

Computational Results

The detailed topology file for compound **3** is shown below. The floats of the atom block list, from left to right: mass, charge (au), Lennard-Jones ε (kcal/mol) and σ (Å) parameters, alternate ε and σ parameters for 1-4 interactions. The bond block lists the indices of the bonded atoms, the force constant (kcal/mol/Å^2), and the equilibrium bond-length (Å). The angle block lists the indices of the atoms forming each angle, the force constant (kcal/mol/radian^2), and the equilibrium value of the angle. The proper dihedral block lists the indices of the atoms defining the dihedral, the coefficient of the sinusoidal torsional energy term (kcal/mol), and the phase of the torsion (radians). The improper dihedral block lists the indices of the atoms defining the dihedral angle, the harmonic force constant (kcal/mol/radian^2), and the equilibrium value of the angle. The "NBFIX" block lists special Lennard-Jones ε (kcal/mol) and σ (Å) parameters, which override the standard combination rules for the specified atom-type pairs.

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    1 MFE    55.84700    0.18260   -0.02000    1.46500
    2 C5R    12.01100   -0.17905   -0.05000    2.04000   -0.10000    1.76000
    3 HA      1.00800    0.18400   -0.04200    1.33000
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   7 HA      1.00800    0.19005   -0.04200    1.33000
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  23 CT     12.01100   -0.45500   -0.09030    1.80000   -0.10000    1.75000
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   1    12   516.000   2.02000 MFE  C5R   1
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   1    16   516.000   2.02000 MFE  C5R   1
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   2     3   760.000   1.08000 C5R  HA    1
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   2    10   900.000   1.40000 C5R  C5R   1
   4     5   760.000   1.08000 C5R  HA    1
   4     6   900.000   1.40000 C5R  C5R   1
   6     7   760.000   1.08000 C5R  HA    1
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1	10	11	130.000	2.094395	MFE	C5R	HA
1	12	13	130.000	2.094395	MFE	C5R	HA
1	14	15	130.000	2.094395	MFE	C5R	HA
1	16	17	130.000	2.094395	MFE	C5R	CT
1	18	19	130.000	2.094395	MFE	C5R	HA
1	20	21	130.000	2.094395	MFE	C5R	HA
3	2	4	46.000	2.199115	HA	C5R	C5R
3	2	10	46.000	2.199115	HA	C5R	C5R
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2	4	5	46.000	2.199115	C5R	C5R	HA
2	4	6	140.000	1.884956	C5R	C5R	C5R
5	4	6	46.000	2.199115	HA	C5R	C5R
4	6	7	46.000	2.199115	C5R	C5R	HA
4	6	8	140.000	1.884956	C5R	C5R	C5R
7	6	8	46.000	2.199115	HA	C5R	C5R
6	8	9	140.000	2.199115	C5R	C5R	CT
6	8	10	140.000	1.884956	C5R	C5R	C5R
9	8	10	140.000	2.199115	CT	C5R	C5R
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8	9	24	80.000	1.910612	C5R	CT	HA
8	9	25	80.000	1.910612	C5R	CT	HA
22	9	24	110.000	1.881465	NT	CT	HA
22	9	25	110.000	1.881465	NT	CT	HA
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  14     1     2     3     0.100     2  0.000000 C5R  MFE  C5R  HA
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  14     1     2    10     0.100     2  2.094395 C5R  MFE  C5R  C5R
   2     1    14    12     0.100     2  2.094395 C5R  MFE  C5R  C5R
   2     1    14    15     0.100     2  0.000000 C5R  MFE  C5R  HA
   2     1    14    16     0.100     2  2.094395 C5R  MFE  C5R  C5R
  16     1     2     3     0.100     2  0.000000 C5R  MFE  C5R  HA
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   2     1    16    14     0.100     2  2.094395 C5R  MFE  C5R  C5R
   2     1    16    17     0.100     2  0.000000 C5R  MFE  C5R  CT
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2	1	18	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	2	3	0.100	2	0.000000	C5R	MFE	C5R	HA
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2	1	20	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
2	1	20	21	0.100	2	0.000000	C5R	MFE	C5R	HA
12	1	4	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
12	1	4	5	0.100	2	0.000000	C5R	MFE	C5R	HA
12	1	4	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	12	13	0.100	2	0.000000	C5R	MFE	C5R	HA
4	1	12	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	12	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	4	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	4	5	0.100	2	0.000000	C5R	MFE	C5R	HA
14	1	4	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	14	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	14	15	0.100	2	0.000000	C5R	MFE	C5R	HA
4	1	14	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	4	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	4	5	0.100	2	0.000000	C5R	MFE	C5R	HA
16	1	4	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	16	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	16	17	0.100	2	0.000000	C5R	MFE	C5R	CT
4	1	16	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	4	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	4	5	0.100	2	0.000000	C5R	MFE	C5R	HA
18	1	4	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	18	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	18	19	0.100	2	0.000000	C5R	MFE	C5R	HA
4	1	18	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	4	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	4	5	0.100	2	0.000000	C5R	MFE	C5R	HA
20	1	4	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	20	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	20	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
4	1	20	21	0.100	2	0.000000	C5R	MFE	C5R	HA
12	1	6	4	0.100	2	2.094395	C5R	MFE	C5R	C5R
12	1	6	7	0.100	2	0.000000	C5R	MFE	C5R	HA
12	1	6	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	12	13	0.100	2	0.000000	C5R	MFE	C5R	HA
6	1	12	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	12	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	6	4	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	6	7	0.100	2	0.000000	C5R	MFE	C5R	HA
14	1	6	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	14	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	14	15	0.100	2	0.000000	C5R	MFE	C5R	HA
6	1	14	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	6	4	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	6	7	0.100	2	0.000000	C5R	MFE	C5R	HA

16	1	6	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	16	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	16	17	0.100	2	0.000000	C5R	MFE	C5R	CT
6	1	16	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	6	4	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	6	7	0.100	2	0.000000	C5R	MFE	C5R	HA
18	1	6	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	18	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	18	19	0.100	2	0.000000	C5R	MFE	C5R	HA
6	1	18	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	6	4	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	6	7	0.100	2	0.000000	C5R	MFE	C5R	HA
20	1	6	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	20	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	20	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
6	1	20	21	0.100	2	0.000000	C5R	MFE	C5R	HA
12	1	8	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
12	1	8	9	0.100	2	0.000000	C5R	MFE	C5R	CT
12	1	8	10	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	12	13	0.100	2	0.000000	C5R	MFE	C5R	HA
8	1	12	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	12	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	8	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	8	9	0.100	2	0.000000	C5R	MFE	C5R	CT
14	1	8	10	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	14	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	14	15	0.100	2	0.000000	C5R	MFE	C5R	HA
8	1	14	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	8	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	8	9	0.100	2	0.000000	C5R	MFE	C5R	CT
16	1	8	10	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	16	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	16	17	0.100	2	0.000000	C5R	MFE	C5R	CT
8	1	16	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	8	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	8	9	0.100	2	0.000000	C5R	MFE	C5R	CT
18	1	8	10	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	18	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	18	19	0.100	2	0.000000	C5R	MFE	C5R	HA
8	1	18	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	8	6	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	8	9	0.100	2	0.000000	C5R	MFE	C5R	CT
20	1	8	10	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	20	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	20	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
8	1	20	21	0.100	2	0.000000	C5R	MFE	C5R	HA
12	1	10	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
12	1	10	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
12	1	10	11	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	12	13	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	12	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
10	1	12	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	10	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	10	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
14	1	10	11	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	14	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
10	1	14	15	0.100	2	0.000000	C5R	MFE	C5R	HA

10	1	14	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	10	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	10	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
16	1	10	11	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	16	14	0.100	2	2.094395	C5R	MFE	C5R	C5R
10	1	16	17	0.100	2	0.000000	C5R	MFE	C5R	CT
10	1	16	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	10	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	10	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
18	1	10	11	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	18	16	0.100	2	2.094395	C5R	MFE	C5R	C5R
10	1	18	19	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	18	20	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	10	2	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	10	8	0.100	2	2.094395	C5R	MFE	C5R	C5R
20	1	10	11	0.100	2	0.000000	C5R	MFE	C5R	HA
10	1	20	12	0.100	2	2.094395	C5R	MFE	C5R	C5R
10	1	20	18	0.100	2	2.094395	C5R	MFE	C5R	C5R
10	1	20	21	0.100	2	0.000000	C5R	MFE	C5R	HA
1	2	4	5	3.100	2	3.141593	X	C5R	C5R	X
1	2	4	6	3.100	2	3.141593	X	C5R	C5R	X
1	2	10	8	3.100	2	3.141593	X	C5R	C5R	X
1	2	10	11	3.100	2	3.141593	X	C5R	C5R	X
1	4	2	3	3.100	2	3.141593	X	C5R	C5R	X
1	4	2	10	3.100	2	3.141593	X	C5R	C5R	X
1	4	6	7	3.100	2	3.141593	X	C5R	C5R	X
1	4	6	8	3.100	2	3.141593	X	C5R	C5R	X
1	6	4	2	3.100	2	3.141593	X	C5R	C5R	X
1	6	4	5	3.100	2	3.141593	X	C5R	C5R	X
1	6	8	9	3.100	2	3.141593	X	C5R	C5R	X
1	6	8	10	3.100	2	3.141593	X	C5R	C5R	X
1	8	6	4	3.100	2	3.141593	X	C5R	C5R	X
1	8	6	7	3.100	2	3.141593	X	C5R	C5R	X
1	8	10	2	3.100	2	3.141593	X	C5R	C5R	X
1	8	10	11	3.100	2	3.141593	X	C5R	C5R	X
1	10	2	3	3.100	2	3.141593	X	C5R	C5R	X
1	10	2	4	3.100	2	3.141593	X	C5R	C5R	X
1	10	8	6	3.100	2	3.141593	X	C5R	C5R	X
1	10	8	9	3.100	2	3.141593	X	C5R	C5R	X
1	12	14	15	3.100	2	3.141593	X	C5R	C5R	X
1	12	14	16	3.100	2	3.141593	X	C5R	C5R	X
1	12	20	18	3.100	2	3.141593	X	C5R	C5R	X
1	12	20	21	3.100	2	3.141593	X	C5R	C5R	X
1	14	12	13	3.100	2	3.141593	X	C5R	C5R	X
1	14	12	20	3.100	2	3.141593	X	C5R	C5R	X
1	14	16	17	3.100	2	3.141593	X	C5R	C5R	X
1	14	16	18	3.100	2	3.141593	X	C5R	C5R	X
1	16	14	12	3.100	2	3.141593	X	C5R	C5R	X
1	16	14	15	3.100	2	3.141593	X	C5R	C5R	X
1	16	18	19	3.100	2	3.141593	X	C5R	C5R	X
1	16	18	20	3.100	2	3.141593	X	C5R	C5R	X
1	18	16	14	3.100	2	3.141593	X	C5R	C5R	X
1	18	16	17	3.100	2	3.141593	X	C5R	C5R	X
1	18	20	12	3.100	2	3.141593	X	C5R	C5R	X
1	18	20	21	3.100	2	3.141593	X	C5R	C5R	X
1	20	12	13	3.100	2	3.141593	X	C5R	C5R	X
1	20	12	14	3.100	2	3.141593	X	C5R	C5R	X

1	20	18	16	3.100	2	3.141593	X	C5R	C5R	X
1	20	18	19	3.100	2	3.141593	X	C5R	C5R	X
3	2	4	5	2.500	2	3.141593	HA	C5R	C5R	HA
3	2	4	6	3.500	2	3.141593	HA	C5R	C5R	C5R
3	2	10	8	3.500	2	3.141593	HA	C5R	C5R	C5R
3	2	10	11	2.500	2	3.141593	HA	C5R	C5R	HA
10	2	4	5	3.500	2	3.141593	C5R	C5R	C5R	HA
10	2	4	6	3.100	2	3.141593	C5R	C5R	C5R	C5R
4	2	10	8	3.100	2	3.141593	C5R	C5R	C5R	C5R
4	2	10	11	3.500	2	3.141593	C5R	C5R	C5R	HA
2	4	6	7	3.500	2	3.141593	C5R	C5R	C5R	HA
2	4	6	8	3.100	2	3.141593	C5R	C5R	C5R	C5R
2	10	8	6	3.100	2	3.141593	C5R	C5R	C5R	C5R
2	10	8	9	3.100	2	3.141593	X	C5R	C5R	X
5	4	6	7	2.500	2	3.141593	HA	C5R	C5R	HA
5	4	6	8	3.500	2	3.141593	HA	C5R	C5R	C5R
4	6	8	9	3.100	2	3.141593	X	C5R	C5R	X
4	6	8	10	3.100	2	3.141593	C5R	C5R	C5R	C5R
7	6	8	9	3.100	2	3.141593	X	C5R	C5R	X
7	6	8	10	3.500	2	3.141593	HA	C5R	C5R	C5R
6	8	10	11	3.500	2	3.141593	C5R	C5R	C5R	HA
9	8	10	11	3.100	2	3.141593	X	C5R	C5R	X
13	12	14	15	2.500	2	3.141593	HA	C5R	C5R	HA
13	12	14	16	3.500	2	3.141593	HA	C5R	C5R	C5R
13	12	20	18	3.500	2	3.141593	HA	C5R	C5R	C5R
13	12	20	21	2.500	2	3.141593	HA	C5R	C5R	HA
20	12	14	15	3.500	2	3.141593	C5R	C5R	C5R	HA
20	12	14	16	3.100	2	3.141593	C5R	C5R	C5R	C5R
14	12	20	18	3.100	2	3.141593	C5R	C5R	C5R	C5R
14	12	20	21	3.500	2	3.141593	C5R	C5R	C5R	HA
12	14	16	17	3.100	2	3.141593	X	C5R	C5R	X
12	14	16	18	3.100	2	3.141593	C5R	C5R	C5R	C5R
12	20	18	16	3.100	2	3.141593	C5R	C5R	C5R	C5R
12	20	18	19	3.500	2	3.141593	C5R	C5R	C5R	HA
15	14	16	17	3.100	2	3.141593	X	C5R	C5R	X
15	14	16	18	3.500	2	3.141593	HA	C5R	C5R	C5R
14	16	18	19	3.500	2	3.141593	C5R	C5R	C5R	HA
14	16	18	20	3.100	2	3.141593	C5R	C5R	C5R	C5R
17	16	18	19	3.100	2	3.141593	X	C5R	C5R	X
17	16	18	20	3.100	2	3.141593	X	C5R	C5R	X
16	18	20	21	3.500	2	3.141593	C5R	C5R	C5R	HA
19	18	20	21	2.500	2	3.141593	HA	C5R	C5R	HA
1	8	9	22	0.010	6	0.000000	X	C5R	CT	X
1	8	9	24	0.010	6	0.000000	X	C5R	CT	X
1	8	9	25	0.010	6	0.000000	X	C5R	CT	X
6	8	9	22	0.010	6	0.000000	X	C5R	CT	X
6	8	9	24	0.010	6	0.000000	X	C5R	CT	X
6	8	9	25	0.010	6	0.000000	X	C5R	CT	X
10	8	9	22	0.010	6	0.000000	X	C5R	CT	X
10	8	9	24	0.010	6	0.000000	X	C5R	CT	X
10	8	9	25	0.010	6	0.000000	X	C5R	CT	X
8	9	22	23	0.160	3	0.000000	X	CT	NT	X
8	9	22	26	0.160	3	0.000000	X	CT	NT	X
8	9	22	27	0.160	3	0.000000	X	CT	NT	X
24	9	22	23	0.160	3	0.000000	X	CT	NT	X
24	9	22	26	0.160	3	0.000000	X	CT	NT	X
24	9	22	27	0.160	3	0.000000	X	CT	NT	X

25	9	22	23	0.160	3	0.000000	X	CT	NT	X
25	9	22	26	0.160	3	0.000000	X	CT	NT	X
25	9	22	27	0.160	3	0.000000	X	CT	NT	X
9	22	23	28	0.160	3	0.000000	X	NT	CT	X
9	22	23	29	0.160	3	0.000000	X	NT	CT	X
9	22	23	30	0.160	3	0.000000	X	NT	CT	X
26	22	23	28	0.160	3	0.000000	X	NT	CT	X
26	22	23	29	0.160	3	0.000000	X	NT	CT	X
26	22	23	30	0.160	3	0.000000	X	NT	CT	X
27	22	23	28	0.160	3	0.000000	X	NT	CT	X
27	22	23	29	0.160	3	0.000000	X	NT	CT	X
27	22	23	30	0.160	3	0.000000	X	NT	CT	X
9	22	26	31	0.160	3	0.000000	X	NT	CT	X
9	22	26	32	0.160	3	0.000000	X	NT	CT	X
9	22	26	33	0.160	3	0.000000	X	NT	CT	X
23	22	26	31	0.160	3	0.000000	X	NT	CT	X
23	22	26	32	0.160	3	0.000000	X	NT	CT	X
23	22	26	33	0.160	3	0.000000	X	NT	CT	X
27	22	26	31	0.160	3	0.000000	X	NT	CT	X
27	22	26	32	0.160	3	0.000000	X	NT	CT	X
27	22	26	33	0.160	3	0.000000	X	NT	CT	X
9	22	27	34	0.160	3	0.000000	X	NT	CT	X
9	22	27	35	0.160	3	0.000000	X	NT	CT	X
9	22	27	36	0.160	3	0.000000	X	NT	CT	X
23	22	27	34	0.160	3	0.000000	X	NT	CT	X
23	22	27	35	0.160	3	0.000000	X	NT	CT	X
23	22	27	36	0.160	3	0.000000	X	NT	CT	X
26	22	27	34	0.160	3	0.000000	X	NT	CT	X
26	22	27	35	0.160	3	0.000000	X	NT	CT	X
26	22	27	36	0.160	3	0.000000	X	NT	CT	X
1	16	17	37	0.010	6	0.000000	X	C5R	CT	X
1	16	17	39	0.010	6	0.000000	X	C5R	CT	X
1	16	17	40	0.010	6	0.000000	X	C5R	CT	X
14	16	17	37	0.010	6	0.000000	X	C5R	CT	X
14	16	17	39	0.010	6	0.000000	X	C5R	CT	X
14	16	17	40	0.010	6	0.000000	X	C5R	CT	X
18	16	17	37	0.010	6	0.000000	X	C5R	CT	X
18	16	17	39	0.010	6	0.000000	X	C5R	CT	X
18	16	17	40	0.010	6	0.000000	X	C5R	CT	X
16	17	37	38	0.160	3	0.000000	X	CT	NT	X
16	17	37	41	0.160	3	0.000000	X	CT	NT	X
16	17	37	42	0.160	3	0.000000	X	CT	NT	X
39	17	37	38	0.160	3	0.000000	X	CT	NT	X
39	17	37	41	0.160	3	0.000000	X	CT	NT	X
39	17	37	42	0.160	3	0.000000	X	CT	NT	X
40	17	37	38	0.160	3	0.000000	X	CT	NT	X
40	17	37	41	0.160	3	0.000000	X	CT	NT	X
40	17	37	42	0.160	3	0.000000	X	CT	NT	X
17	37	38	43	0.160	3	0.000000	X	NT	CT	X
17	37	38	44	0.160	3	0.000000	X	NT	CT	X
17	37	38	45	0.160	3	0.000000	X	NT	CT	X
41	37	38	43	0.160	3	0.000000	X	NT	CT	X
41	37	38	44	0.160	3	0.000000	X	NT	CT	X
41	37	38	45	0.160	3	0.000000	X	NT	CT	X
42	37	38	43	0.160	3	0.000000	X	NT	CT	X
42	37	38	44	0.160	3	0.000000	X	NT	CT	X
42	37	38	45	0.160	3	0.000000	X	NT	CT	X

```
  17    37    41    46     0.160     3  0.000000 X    NT   CT   X
  17    37    41    47     0.160     3  0.000000 X    NT   CT   X
  17    37    41    48     0.160     3  0.000000 X    NT   CT   X
  38    37    41    46     0.160     3  0.000000 X    NT   CT   X
  38    37    41    47     0.160     3  0.000000 X    NT   CT   X
  38    37    41    48     0.160     3  0.000000 X    NT   CT   X
  42    37    41    46     0.160     3  0.000000 X    NT   CT   X
  42    37    41    47     0.160     3  0.000000 X    NT   CT   X
  42    37    41    48     0.160     3  0.000000 X    NT   CT   X
  17    37    42    49     0.160     3  0.000000 X    NT   CT   X
  17    37    42    50     0.160     3  0.000000 X    NT   CT   X
  17    37    42    51     0.160     3  0.000000 X    NT   CT   X
  38    37    42    49     0.160     3  0.000000 X    NT   CT   X
  38    37    42    50     0.160     3  0.000000 X    NT   CT   X
  38    37    42    51     0.160     3  0.000000 X    NT   CT   X
  41    37    42    49     0.160     3  0.000000 X    NT   CT   X
  41    37    42    50     0.160     3  0.000000 X    NT   CT   X
  41    37    42    51     0.160     3  0.000000 X    NT   CT   X
!NIMPHI: 20
  10     2     4     6   260.000  0.000000 C5R  X    X    C5R
   4     2    10     8   260.000  0.000000 C5R  X    X    C5R
   2     4     6     8   260.000  0.000000 C5R  X    X    C5R
   4     6     8    10   260.000  0.000000 C5R  X    X    C5R
   6     8    10     2   260.000  0.000000 C5R  X    X    C5R
  20    12    14    16   260.000  0.000000 C5R  X    X    C5R
  14    12    20    18   260.000  0.000000 C5R  X    X    C5R
  12    14    16    18   260.000  0.000000 C5R  X    X    C5R
  14    16    18    20   260.000  0.000000 C5R  X    X    C5R
  16    18    20    12   260.000  0.000000 C5R  X    X    C5R
   2     4    10     3   150.000  0.000000 C5R  X    X    HA
   4     2     6     5   150.000  0.000000 C5R  X    X    HA
   6     4     8     7   150.000  0.000000 C5R  X    X    HA
   8     6    10     9   260.000  0.000000 C5R  X    X    CT
  10     2     8    11   150.000  0.000000 C5R  X    X    HA
  12    14    20    13   150.000  0.000000 C5R  X    X    HA
  14    12    16    15   150.000  0.000000 C5R  X    X    HA
  16    14    18    17   260.000  0.000000 C5R  X    X    CT
  18    16    20    19   150.000  0.000000 C5R  X    X    HA
  20    12    18    21   150.000  0.000000 C5R  X    X    HA
!NBFIX: 14
 CT   HO     -0.15       3.00
 HA   HO     -0.05       3.10
 HT   HT     -0.04598    0.4490
 HT   OW     -0.08363    1.9927
 O2M  MAL    -0.1855     2.81
 O2M  MSI    -0.1855     2.61
 O2M  O2M    -0.5596     3.59
 OSH  MAL     0.0        0.000001
 OSH  MSI     0.0        0.000001
 OSH  O2M     0.0        0.000001
 OSH  OSH     0.0        0.000001
 OW   OW     -0.152073   3.5365
 MFE  N5R    -0.05       2.70
 MFE  OM     -0.05       1.58
!NFINAL: 6
        51          60        100         320         20 9999
!NDON: 0
```

References

7. Jeon WS, Moon K, Park SH, Chun H, Ko YH, Lee JY, Lee ES, Samal S, Selvapalam N, Rekharsky MV, Sindelar V, Sobransingh D, Inoue Y, Kaifer AE, Kim K (2005) *J. Am. Chem. Soc*. 127:12984-12989.
10. Rekharsky MV, Inoue Y (1998) *Chem. Rev*. 98:1875-1918.
11. Sturtevant JM (1977) *Proc. Natl. Acad. Sci. U.S.A*. 74:2236-2240.
12. Rekharsky MV, Inoue Y (2000) *J. Am. Chem. Soc*. 122:4418-4435.
24. Tanford C (1973) The Hydrophobic Effect, Wiley-Interscience, New York.
25. Suurkuusk J, Wädso I (1972) *Eur. J. Biochem*. 28:438-441.
26. Godinez LA, Schwartz L, Criss CM, Kaifer AE (1997) *J. Phys. Chem. B* 101:3376-3380.