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Materials Science and Engineering C 18 (2001) 265–269

MATERIALS SCIENCE & ENGINEERING C

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Aromatic anion recognition by a self-assembled receptor in water

Hae-Jo Kim, Choon Woo Lim, Jong-In Hong *

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-747, South Korea

Abstract

Self-assembly of (1*R*,2*R*)-diaminocyclohexane derived bis(4-pyridyl)-substituted bidentate ligand L* by Pd(II) ion complexation leads to a water-soluble chiral receptor **1**. The new chiral receptor turns out to bind naphthalene derivatives bearing tethered carboxylate groups due to the entropically driven host–guest complexation process.

Keywords: Self-assembly; Bidentate; Chiral receptor; Entropically driven

1. Introduction

Water-soluble artificial receptors such as crown ether derivatives [1], cyclodextrins [2], and cyclophanes [3] with large hydrophobic cavities were used to mimic selective binding of the biological amino acids or their derivatives. The ability of a metal ion to assemble flexible ligands around its coordination sphere into highly organized structures has led to the development of hydrophobic binding site for the recognition of aromatic guests in aqueous solution [4]. Since the 1980s, water-soluble self-assembled structures have been extensively developed using metal–ligand interaction to investigate the binding properties toward neutral guests [4], anionic guests [5], cationic guests [6] and ligands [7].

We have recently described a series of self-assembled Pd(II) complexes [8]. The ability of the guests to induce organization of the self-assembled structures was attributed to hydrophobic interactions but the energetics of binding could not be studied since the hosts existed in different ratios of equilibrium mixtures depending on concentration or guest size. The focus of this study is to investigate the energetics and recognition mechanism between self-assembled receptor **1** and aromatic carboxylate derivatives in water.

2. Results and discussion

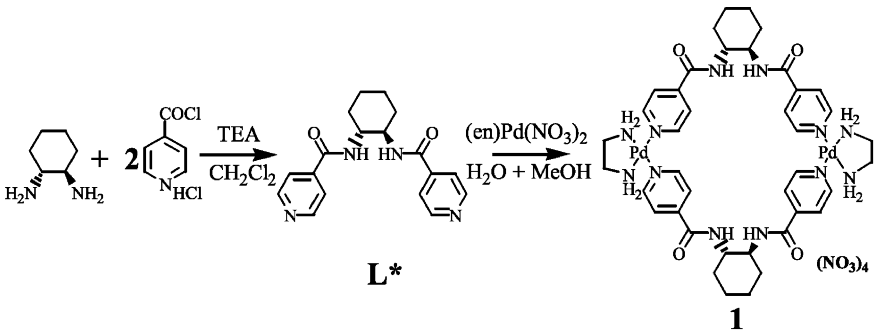
More rigid diaminocyclohexane derived self-assembled structure was designed to give rise to a set of structures which are independent of concentration from 0.2 to 200 mM, and independent of pH from 6.5 to 9.0. Ligand L* was synthesized by reaction of isonicotinoyl chloride hydrochloride with (1*R*,2*R*)-diaminocyclohexane in the presence of triethylamine. Treatment of L* with (en)Pd(NO_3)$_2$ in aqueous methanol led to a dimeric complex **1** (Scheme 1).

This structure turned out to be a dimer rather than a trimer, which was corroborated by typical ESI-MS fragmentation patterns corresponding to a dimeric structure. Quantification of the association constants of various aromatic guests was accomplished by ^{1}H NMR titrations. Job's plot indicated the formation of 1:1 host–guest complex with naphthalene carboxylates (Fig. 1).

Binding constants for various aromatic guests are summarized in Table 1. While K_a's of N–Ac aromatic amino acid or N–Ac–Leu sodium salts were less than several tens, naphthalene derivatives bearing two tethered carboxylate groups were shown to bind up to several hundreds stronger in neutral water (**G1** except **G1c** vs. **G2**). The same trends were observed in basic aqueous medium at pD = 8.5 (**G1g** vs. **G2**). Neutral guest **G1c** was more weakly bound than its monocarboxylate counterpart **G1b**. This indicates the participation of the electrostatic interaction in the binding process. These lower binding affinities of host **1** to all the guests, compared to Fujita's macrocyclic dinuclear complexes [9], seem to result from the deficient hydrophobic capacity of host **1** because an aromatic spacer is replaced by a cyclohexyl group. However, when using dicarboxylate derivatives with appropriately positioned carboxylate groups as guests to compensate for the lower hydrophobicity of host **1**, binding constants increased owing to the electrostatic interaction between Pd(II) and carboxylate groups [10]. Larger K_a values were

* Corresponding author. Tel.: +82-2-874-5902; fax: +82-2-889-1568.
E-mail address: jihong@plaza.snu.ac.kr (J.-I. Hong).

0928-4931/01/$ - see front matter
PII: S0928-4931(01)00392-7



Scheme 1.

obtained when additional hydrophobic groups were introduced to the naphthalene dicarboxylate guests (**G2a** vs. **G2b–d**).

The effect of basic buffer on the binding was not large. K_a's decreased less than half of those in neutral water.

In order to elucidate the thermodynamic parameters controlling the complexation process, temperature-dependent ^{1}H NMR titrations were performed to give a van't Hoff plot between **1** and **G2b** (Fig. 2), and it was shown that the complexation process for dianionic guest is entropically driven. The origin of the entropically driven binding seems to be the desolvation of the ionic groups of both binding partners upon salt bridge formation. CPK models suggest that if the naphthalene unit of **G2b** positions itself symmetrically in the middle of a symmetric host cavity with one carboxylate pointing toward Pd^{2+}, a second carboxylate could interact more favorably with the second Pd because of the probable lesser entropy to be frozen out by the second binding event.

What is the effect of chirality in the hydrophobic cavity of the host on the chiral recognition? To address this question, D and L amino acid derivatives were tested. It turns out that the degree of chiral recognition is less than $\Delta\Delta G = 0.1$ kcal/mol. This is because the hydrophobic cavity is too rigid and is not able to differentiate subtle difference in the chiral shape of the guest.

The fact that both H_α and H_β of pyridine unit in host **1**, and aromatic protons of **G2b** experienced upfield shifts upon complexation indicates that the naphthyl group of the guest reside in the shielding region of the pyridine cavity of the host due to the hydrophobic interaction between host and guest (Fig. 3).

From the ^{1}H NMR titration experiments, a binding mode of **1** for naphthalene derivatives bearing tethered two carboxylate groups can be proposed as shown in Fig. 4.

To summarize, binding of dianionic aromatic guests by a positively charged macrocyclic dinuclear Pd(II) complex was driven by entropically favorable desolvation. The degree of chiral recognition turned out to be less than $\Delta\Delta G = 0.1$ kcal/mol in water.

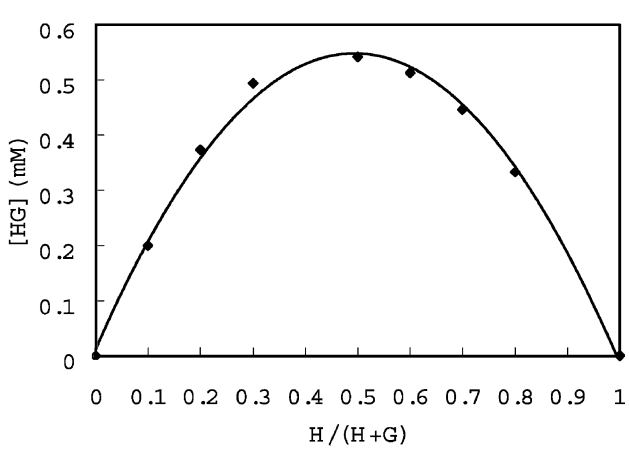


Fig. 1. Job's plot between host **1** and *rac*-**G2d** at 292 K, pD = 8.5. $[H]_o = [G]_o = 2$mM, each in 500 μl. Changes of chemical shifts of pyridine H_α in host **1** were monitored during the continuous variation plot.

3. Experimental

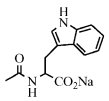
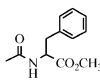
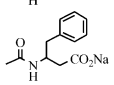
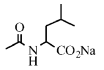
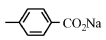
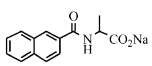
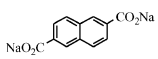
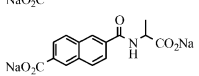
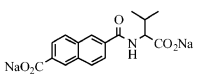
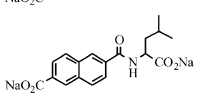
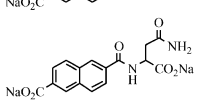
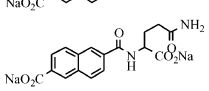
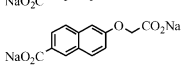
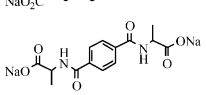
3.1. Chiral ligand (L^*)

To a solution of 60 mg (0.525 mmol) of (1*R*, 2*R*)-diaminocyclohexane and 0.50 ml of TEA in 10 ml of dry THF was added 1.203 mmol of isonicotinoyl chloride at portions at 0 °C under N_2. The resulting white suspension was further stirred at r.t. for 8 h. Evaporation of solvent, followed by extraction with EtOAc (1×50 ml) from 0.1 M aqueous $NaHCO_3$ solution (10 ml), drying over Na_2SO_4, evaporation under reduced pressure, and recrystallization in nitromethane gave the desired bipyridine ligand (L^*) as a white needle solid in 80% yield.

300 MHz ^{1}H-NMR in MeOD-d_4: 8.6 (dd, $J = 4.5$, 1.6 Hz, 4 H of pyH_α), 7.6 (dd, $J = 4.5$, 1.6 Hz, 4 H of pyH_β), 4.1 (dd, $J = 5.7$, 3.7 Hz, 2 H of C^*H), 2.1 (m, 2 H of C^*CH_{ax}), 1.9 (m, 2 H of C^*CH_2CH), 1.6 (m, 2 H of C^*CH_{eq}), 1.5 (m, 2 H of C^*CH_2CH).

75 MHz ^{13}C-NMR in MeOD-d_4: 166.8 (carbonyl C), 149.9, 143.1, 121.9 (3 C of pyC), 54.1, 31.7, 25.0 (3 C of c-Hex C).

Table 1
Binding constants between various aromatic carboxylates and **1**[a]

Guest structure	Name(symbol)	$K_a(D_2O)$	K_a(pD=8.5)[b]
	N-Ac-TrpCO_2Na**(G1a)**	L 7 D 6	
	N-Ac-PheCO_2Na **(G1b)**	L 16 D ND[c]	
	N-Ac-PheCO_2CH_3**(G1c)**	L 0.2	
	N-Ac-b-PheCO_2Na**(G1d)**	*rac* 35	
	N-Ac-LeuCO_2Na**(G1e)**	*rac* 9	
	p-ToluicCO_2Na**(G1f)**	6	
	Naph-Ala-monoCO_2Na**(G1g)**		L 5 D 8
	Naph-CO_2Na**(G2a)**	30	
	Naph-AlaCO_2Na**(G2b)**	*rac* 160 L 280	*rac* 100 L 146 D 134
	Naph-ValCO_2Na**(G2c)**	*rac* 280 L 260	L 120 D 155
	Naph-LeuCO_2Na**(G2d)**	*rac* 450 L 430	L 210 D 125
	Naph-AsnCO_2Na**(G2e)**		L 174
	Naph-GlnCO_2Na**(G2f)**		L 152
	Naph-O-CO_2Na**(G2g)**		132
	Tere-AlaCO_2Na**(G2h)**		L 45

[a] ^{1}H NMR titration of 2 mM of **1** in D_2O at 292 K. L, D and *rac* stand for L, D and racemic forms of amino acids derivatives, respectively.
[b] 20 mM sodium borate buffer.
[c] Titration curve was not well fitted to 1:1 binding mode.

HRMS (FAB$^+$, m-NBA): 325.1674 (observed M + H), 325.1665 (calculated).

$[\alpha]_D^{26} = -81.76°$ ($c = 0.085$, MeOH).

mp: 270–272 °C.

3.2. *[(enPd)$_2$L$_2^*$](NO$_3$)$_4$(1)*

A solution of 32.4 mg (0.100 mmol) of ligand (L*) in 1.0 ml of MeOH was added dropwise, until a solution of 29.0 mg of (en)Pd(NO_3)$_2$ in 1.0 ml of H_2O, which was sonicated for 3 min and evaporated to give [(enPd)$_2$L$_2^*$](NO_3)$_4$ as a brownish solid in quantitative yield.

300 MHz ^{1}H-NMR in D_2O: 8.69 (d, $J = 6.6$ Hz, 8 H of pyHα), 7.58 (d, $J = 6.6$ Hz, 8 H of pyHβ), 3.89 (d, $J = 9.3$ Hz, 4 H of C*H), 1.89 (m, 2 H of C*CH_{ax}), 1.73 (m, 2 H of C*CH_2*CH*), 1.46 (m, 2 H of C*CH_{eq}), 1.30 (m, 2 H of C*CH_2*CH*).

75 MHz ^{13}C-NMR in D_2O: 166.4 (carbonyl C), 152.4, 145.2, 124.6 (3 C of py C), 54.5, 47.1, 32.0, 24.5 (4 C of aliphatic C).

Mass (ESI, 5% MeOH in H_2O): m/z = 1166.5 (found), 1166 (calculated major isotope peak for [(enPd)$_2$L$_2^*$](NO_3)$_4$–NO_3}$^+$); 552.3 (found), 552 (calculated major

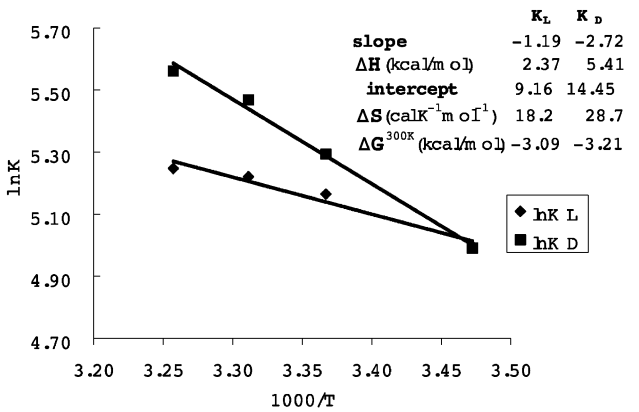


Fig. 2. van't Hoff plot for both L and D forms of **G2b** in D_2O at pD = 8.5.

isotope peak for $\{[(enPd)_2L_2^*](NO_3)_4-2NO_3\}^{2+}$); 347.4 (found), 347.3 (calculated major isotope peak for $\{[(enPd)_2L_2^*](NO_3)_4-3NO_3\}^{3+}$); 244.1 (found), 245 (calculated major isotope peak for $\{[(enPd)_2L_2^*](NO_3)_4-4NO_3\}^{4+}$).

$[\alpha]_D^{28} = -86.2°$ ($c = 0.125$, H_2O); UV: $\lambda_{max} = 260$ nm, $\varepsilon_{260\ nm} = 2.33 \times 10^4\ m^{-1}\ cm^{-1}$.

Supporting information available. Selected spectral data (^1H, ^{13}C and H–H COSY) for compounds L^* and **1**, concentration and pH-dependent ^1H-NMR of **1**, and ^1H NMR titration curve at pD = 8.5. This material is available free of charge via the Internet.

Acknowledgements

Financial support from CMDS (KOSEF) and KRF (Grant No. 99-042-D00073) is gratefully acknowledged. HJK and CWL thank the Ministry of Education for the BK 21 fellowship.

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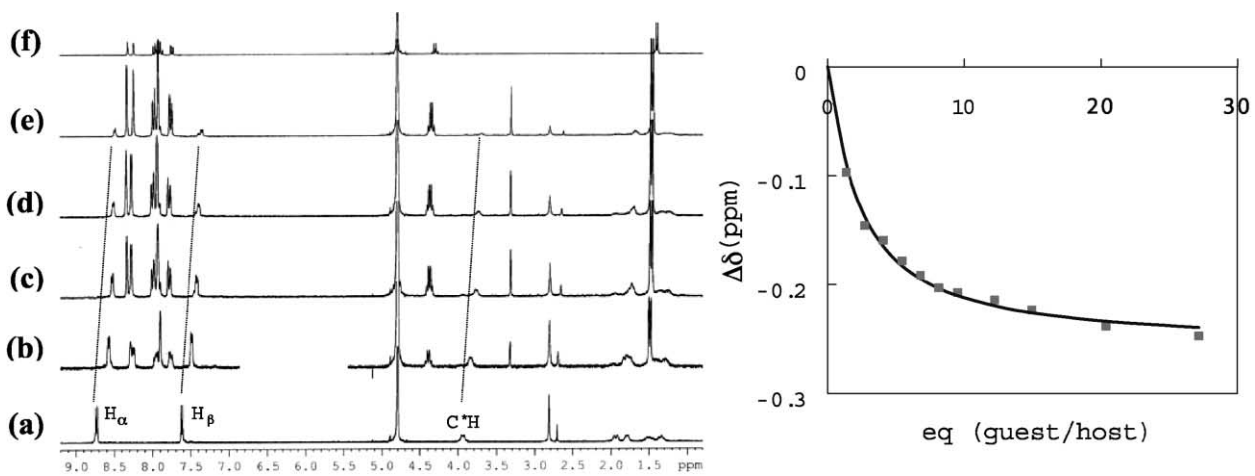

Fig. 3. (Left) ^1H NMR titration spectra between **1** and **G2b** in D_2O at 292 K. H_α, H_β and C^*H represent α, β protons of a pyridine unit and chiral protons of a *c*-hexyl unit in host **1**, respectively. (a) Only host, $[H]_o = 2.0$ mM (b) 4 equiv of guest added (c) 10 equiv of guest (d) 15 equiv of guest (e) 27 equiv of guest (f) only guest. Saturation binding curve for the complex between **1** and **G2b** (right). H_α of a pyridine unit in host **1** was used for plotting the binding curve.

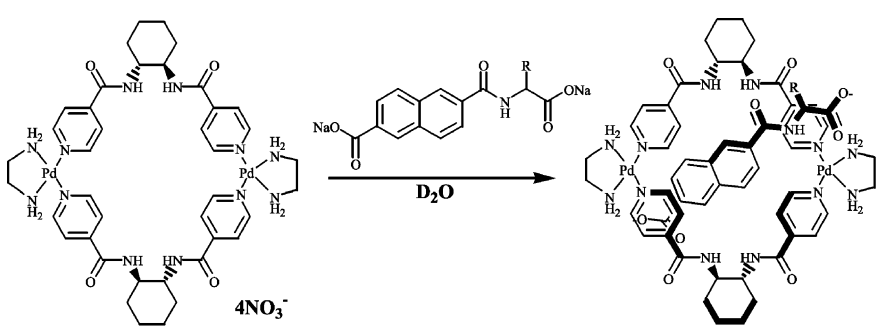

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Fig. 4. Proposed binding mode between host **1** and guest **G2**. Some bonds are marked in bold to represent a projection in front of the paper.

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