

Alkali metal ion selectivities of podands that form pseudo-cyclic structures by intramolecular hydrogen bonding

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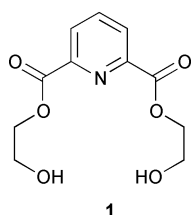
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New podands capable of intramolecular hydrogen bonding (1–3) have been synthesized. ¹³C NMR titration experiments and FAB mass spectra of the podands show that 1 and 2 form pseudo-cyclic structures under guest-free conditions. The X-ray crystal structure of the 2–NaSCN complex is also reported.

Introduction

Podands are open chain analogues of the crown compounds, and many kinds of podands have been prepared.¹ Podands are also important as biomimetic compounds for naturally occurring ionophores such as nigericin² and lasolocid.³ Several natural ionophore-mimic podands and semi-synthetic podands have been synthesized.⁴ They each have a carboxylic acid at one end and a hydroxy group at the other end of the molecule. In these systems, hydrogen bonding between the end-hydroxy and end-carboxy groups is an important factor in forming a cyclic structure when these podands bind cations.

Recently, we reported that podand 1 formed a pseudo-cyclic structure in the solid state and in solution.⁵ Those results prompted us to prepare new podands in order to investigate whether intramolecular pre-organization of the podands by weak hydrogen bonding influences complexing ability and cation selectivity. Here, we report the molecular design,⁶ preparation, crystal structure, and alkali metal cation selectivity of new podands that form pseudo-cyclic structures by weak hydrogen bonding in the gas phase.



Results and discussion

Two new podands 2 and 3 were designed and prepared (Scheme 1). We expected that podand 2 having *o*-hydroxyphenyl end groups would form a pseudo-cyclic structure because the two end OH groups would hydrogen bond with each other as shown in Fig. 1. Podand 3 with *o*-hydroxybenzoyl end groups would form a non-cyclic structure because the C=O and OH groups in each salicylic moiety would form hydrogen bonds as shown. To confirm our prediction, a conformer search using molecular mechanics (MMFF was used as a mechanic engine) and then optimization using semi-empirical AM1 calculations followed by *ab initio* 3-21G(*) calculations were carried out. As we expected, the global minima of 2 and 3 exhibited cyclic (Fig. 2a) and non-cyclic structures (Fig. 2b), respectively.

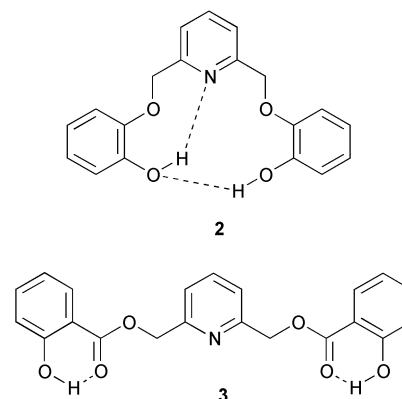


Fig. 1 Schematic drawings of podands 2 and 3.

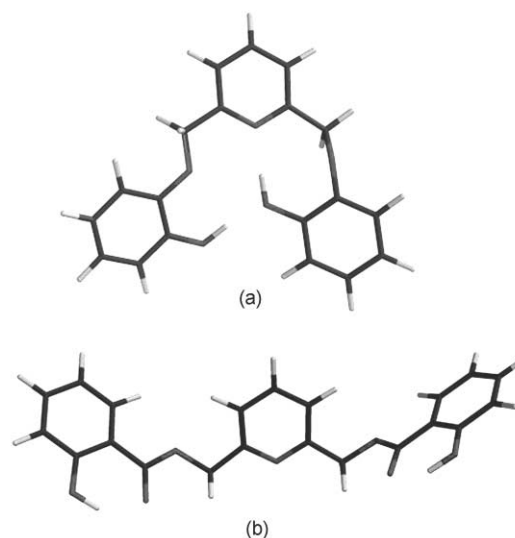
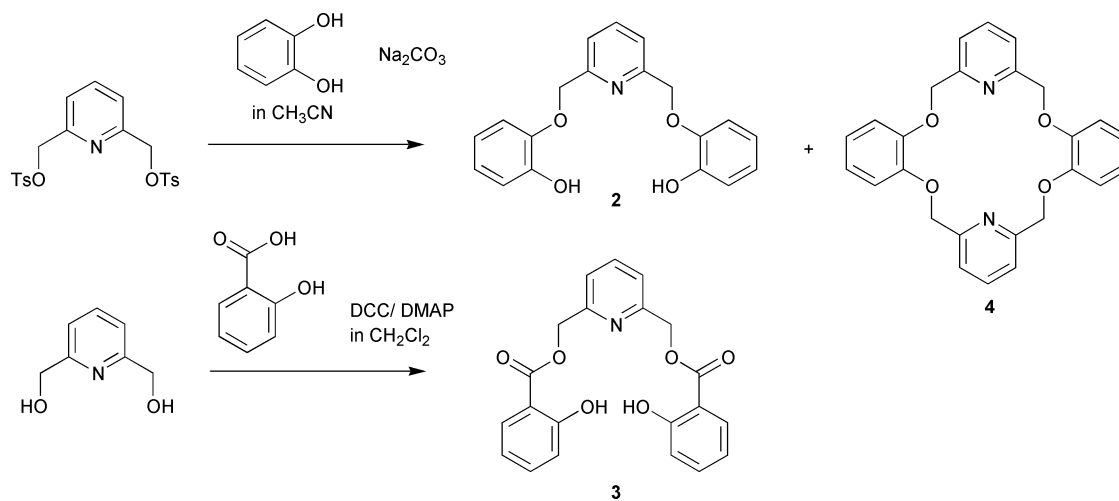


Fig. 2 Optimized structures of podands 2 and 3 by *ab initio* 3-21G(*) calculations.

Podand 2 was prepared by the reaction of 2,6-bis(tosyloxymethyl)pyridine with catechol in the presence of Na₂CO₃ in acetonitrile in 41% yield. Dimerization product 4⁷ was also isolated as a by-product in 3% yield. Podand 3 was prepared from pyridinedimethanol and salicylic acid in the presence of DCC–DMAP in CH₂Cl₂ in 41% yield. The structures of the



Scheme 1

new podands **2** and **3** were confirmed by ^1H and ^{13}C NMR, MS, FT-IR, elemental analyses, and X-ray crystallography. In the FT-IR spectra (Fig. 3), the O–H stretching vibrations of

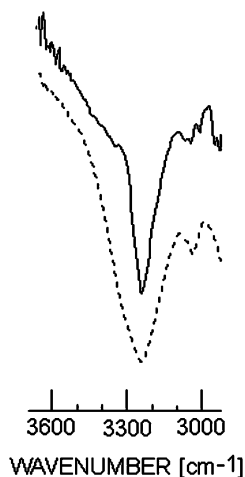


Fig. 3 FT-IR spectra of podands **2** (dotted line) and **3** (solid line) in the region for O–H stretching vibrations.

podands **2** (dotted line) and **3** (solid line) appear at 3249 and 3250 cm^{-1} , respectively. These IR data confirm that both podands form hydrogen bonds,⁸ as estimated by the *ab initio* 3–21G(*) calculations.

Figs. 4 and 5 show the ORTEP diagrams of podands **2** and **3**,

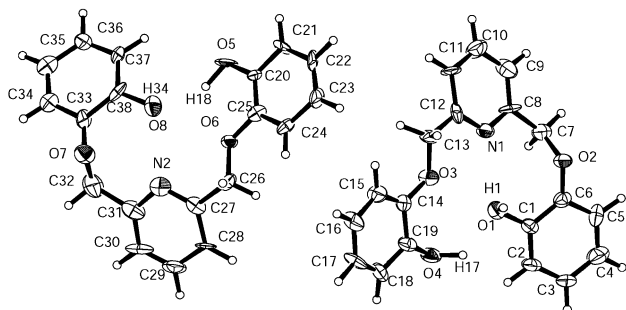


Fig. 4 ORTEP diagram of podand **2** (30% probability level).

respectively. As the molecular calculations indicated, podand **2** forms a pseudo-cyclic structure by hydrogen bonding between the OH groups. The hydrogens of the OH groups, H1, H17, H18, and H34, in podand **2** were located by difference Fourier maps, and were not refined. As shown in Fig. 4, the unit

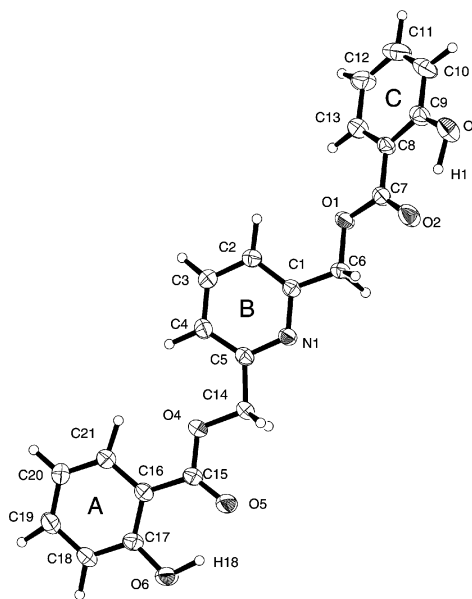


Fig. 5 ORTEP diagram of podand **3** (30% probability level).

structure contains two molecules of **2**. The O1–O4, O5–O6 and O5–O8, distances are 2.69 , 2.71 and 2.80 \AA , respectively (Table 1). These distances are typical of a cyclic structure in which the hydrogen atoms on O4 and O5 are hydrogen bonded to O1 and O8, respectively. There was a slight difference between the optimized structure and the crystal structure. Although the hydrogen bond between the ring N atom and the H atom of the HO group was predicted by the *ab initio* 3–21G(*) calculations, the hydrogen bond between them was not observed in the crystal structure, because the H1–N1 and H34–N2 atom distances are 2.75 and 2.82 \AA , respectively. The overall R_w factor of the podand **2** would be very large (12.5%), because it is very difficult to obtain good single crystals for X-ray crystallography. On the other hand, in podand **3** (Fig. 5), the two aromatic rings (ring A and ring B) approximately planar and the dihedral angle between ring B and ring C is about 38° . There are hydrogen bonds between O2 and O3 (2.63 \AA) and O5 and O6 (2.63 \AA) in the podand. Thus, we have prepared two podands, one of which has a pseudo-cyclic structure and the other a non-cyclic structure under guest-free conditions.

Association constants in CD_3CN between these podands and Na^+ were determined by ^{13}C NMR titration experiments⁹ in order to study their complexing abilities in solution, since molecular modeling also suggested that the cavity sizes of podands **1** and **2** are similar to the size of the Na^+ cation. The

Table 1 Intermolecular hydrogen bond parameters

D	H	A	D...A	D-H	H...A	D-H...A
Podand 2						
O(4)	H(17)	O(1)	2.69	1.10	2.11	110
O(5)	H(18)	O(6)	2.71	1.07	2.22	105
O(5)	H(18)	O(8)	2.80	1.07	1.85	144
Podand 3						
O(3)	H(1)	O(2)	2.63	1.15	1.65	139
O(6)	H(2)	O(5)	2.64	1.05	1.75	140

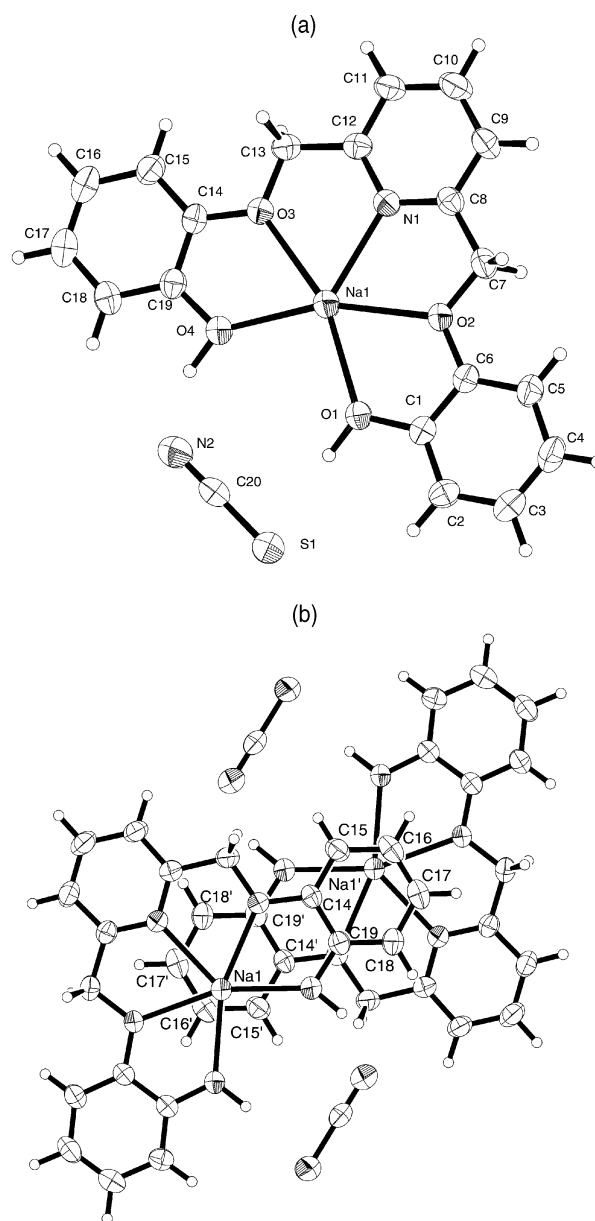
Table 2 Fragment ion peaks and relative intensities for $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, $[M + Rb]^+$ and $[M + Cs]^+$ in 1-alkali metals, 2-alkali metals and 3-alkali metals. The intensity of each peak was normalized on the basis of that of $[M + H]^+$ (in parentheses)

	1-Alkali metals	2-Alkali metals	3-Alkali metals
$[M + H]^+$	256 (100)	324 (100)	380 (100.0)
$[M + Li]^+$	262 (150)	329 (24)	386 (0.9)
$[M + Na]^+$	278 (1800)	346 (130)	402 (5.9)
$[M + K]^+$	294 (720)	362 (22)	418 (1.7)
$[M + Rb]^+$	340 (210)	408 (10)	464 (0.7)
$[M + Cs]^+$	388 (170)	456 (12)	512 (1.0)

$\log K$ values for 1- Na^+ , 2- Na^+ , and 3- Na^+ are 2.5, 2.3, and 1.3, respectively. These data clearly suggest that podands 1 and 2, which form a guest-free pseudo-cyclic structure, show higher complexing ability for Na^+ than 3, which forms a non-cyclic structure in solution.

In order to investigate the complexing properties of podands 1–3 with alkali metals in the gas phase, the FAB mass spectra of the podand-alkali metal systems were measured. Table 2 shows the relative intensities for $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, $[M + Rb]^+$ and $[M + Cs]^+$ in mixtures of 1-alkali metals, 2-alkali metals, and 3-alkali metals. In the mixture of 1-alkali metals, all the peak intensities of $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, $[M + Rb]^+$ and $[M + Cs]^+$ are greater than that of $[M + H]^+$ and the order is as follows; $[M + Na]^+ > [M + K]^+ > [M + Rb]^+ > [M + Cs]^+ > [M + Li]^+$. It is important to note that the intensities of $[M + Na]^+$ and $[M + K]^+$ are 18 and 7 times greater than that of $[M + H]^+$, respectively. These results suggest that podand 1 is selective for Na^+ . The results of the 2-alkali metal experiments also suggest Na^+ selectivity, but the relative intensities of the ion peaks arising from the 2-cation complexes, except that of 2- Na^+ , were weaker than that of $[M + H]^+$. In the case of the 3-alkali metal system, all the intensities of the ion peaks of [3-cations] $^+$ were very small, although 3 shows clear Na^+ selectivity. It is well known that FAB MS can be used to determine crown ether-alkali metal cation stability constants.¹⁰ Therefore, the FAB MS data suggest that the complexing abilities of podands 1–3 with alkali metal cations are as follows; podand 1 > podand 2 \gg podand 3. The data also suggested that podand 2, which forms a guest-free pseudo-cyclic structure, showed higher complexing ability than 3, which forms a non-cyclic structure. These results are consistent with the $\log K$ values determined in solution.

A single crystal of the Na^+ complex with podand 2 was obtained and the X-ray crystal structure was determined (Fig. 6a). The sodium ion is centered in the pseudo-cyclic structure of podand 2 and is five-coordinated by N1, O1, O2, O3 and O4. The sodium ion lies in the same plane as the other hetero atoms. Since the sodium ions (Na1 and Na1') of the unit structure are covered by benzene rings (C14'–C15'–C16'–C17'–C18'–C19' and C14–C15–C16–C17–C18–C19) (Fig. 6b), other donor atoms could not bind above or below the plane. The Na1–C14', Na1–C15', Na1–C16', Na1–C17', Na1–C18', and Na1–C19' distances are 3.61, 3.31, 3.23, 3.45, 3.74, and 3.82 Å, respectively. These distances are comparable to those of the Na^+ complex with the double-armed diaza-18-crown-6

**Fig. 6** (a) ORTEP diagram and (b) packing diagram of the 2- $NaSCN$ complex (30% probability level).

having indole side chains, which exhibit $Na^+ - \pi$ interactions between the incorporated cations and the aromatic moieties of the side chain.¹¹ Thus, the complex would be stabilized by $Na^+ - \pi$ interactions. The Na1–S1, Na1–C20, and Na1–N2 distances are 5.13, 4.47, and 4.31 Å, respectively. Therefore, atoms of the counter SCN^- ion do not participate in complex formation. The Na1–N1, Na1–O1, Na1–O2, Na1–O3, and Na1–O4 bond lengths are 2.41, 2.40, 2.41, 2.43, and 2.33 Å, respectively. These bond lengths are comparable to those of the Na^+ complex of monoaza-15-crown-5 derivatives¹² rather than those of the Na^+

Table 3 Crystal and selected experimental data for podands **2** and **3**, and the **2**-NaSCN complex

	2	3	2 -NaSCN
Formula	C ₃₈ H ₃₄ N ₂ O ₈	C ₂₁ H ₁₇ NO ₆	C ₂₀ H ₁₇ N ₂ O ₄ SNa
<i>M</i>	646.70	379.37	404.42
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>a</i>	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> /Å	8.117(6)	8.254(9)	9.744(5)
<i>b</i> /Å	19.978(7)	14.99(1)	16.192(8)
<i>c</i> /Å	19.981(8)	8.05(1)	12.099(6)
<i>a</i> /°		102.1(1)	
<i>β</i> /°	92.91(5)	111.99(9)	95.72(4)
<i>γ</i> /°		78.40(9)	
<i>U</i> /Å ³	3236(3)	894(2)	1899(1)
<i>Z</i>	4	2	4
<i>D</i> /g cm ⁻³	1.327	1.408	1.414
<i>F</i> (000)	1360.00	369.00	840.00
<i>μ</i> (Mo-Kα)/cm ⁻¹	0.94	1.04	2.23
Crystal dimensions/mm	0.25 × 0.10 × 0.60	0.50 × 0.25 × 0.50	0.75 × 0.50 × 0.75
No. of reflections for unit cell determination (2θ range)/°	20 (20.5–24.7)	25 (22.6–24.9)	
Scan width/°	1.47 + 0.30 tan θ	1.68 + 0.30 tan θ	1.52 + 30 tan θ
Limiting indices	−8 ≤ <i>h</i> ≤ 0, 0 ≤ <i>k</i> ≤ 19, −19 ≤ <i>l</i> ≤ 19	0 ≤ <i>h</i> ≤ 9, −17 ≤ <i>k</i> ≤ 17, −9 ≤ <i>l</i> ≤ 8	−12 ≤ <i>h</i> ≤ 12, 0 ≤ <i>k</i> ≤ 21, −15 ≤ <i>l</i> ≤ 0
No. of reflections measured	3879	3384	4733
Unique (<i>R</i> _{int})	3447 (0.219)	3147 (0.030)	4365 (0.037)
Used [all data], <i>N</i> _o	3438	3147	4361
<i>R</i>	0.321	0.117	0.088
<i>R</i> _w	0.329	0.152	0.139
<i>R</i> ₁ [<i>I</i> > 2.0σ(<i>I</i>)]	0.125	0.054	0.048
Goodness of fit	1.41	1.27	1.15
No. parameters, <i>N</i> _p	1020	1642	2088
Maximum shift/error in final cycle	0.004	0.001	0.001
Maximum, minimum peaks in final difference map/e Å ⁻³	0.78, −0.42	0.45, −0.41	0.24, −0.33
2θ _{max} /°	45	50	55

Details in common: ω-2θ scan; $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w F_o^2]^{1/2}$, $R_1 = \sum ||F_o| - |F_c|| / \sum F_o$, goodness of fit $[\sum w(|F_o| - |F_c|)^2 / (N_o - N_p)]^{1/2}$.

complex of pyridinodibenzo-18-crown-6.¹³ This is the first instance of a planar five-coordinated complex of Na⁺ with podands and crown ether compounds.¹⁴

In conclusion, we have demonstrated that a podand that forms a pseudo-cyclic structure by hydrogen bonding shows higher affinity for metal ions than a podand that forms a non-cyclic structure.

Experimental

Melting points were obtained with a Mel-Temp capillary apparatus and are not corrected. EI and FAB mass spectra were recorded using a JEOL 600 H spectrometer. ¹H NMR and ¹³C NMR spectra were measured in CDCl₃ and CD₃CN, respectively, on a JEOL ECP400 (400 MHz for ¹H) spectrometer. Ligand **1** was prepared as reported.⁵ Other starting materials were used as purchased.

Preparation of 2,6-bis[(2'-hydroxyphenyl)oxymethyl]pyridine (**2**)

A mixture of catechol (0.25 g, 2.3 mmol), 2,6-bis(tosyloxymethyl)pyridine (0.50 g, 1.1 mmol), and K₂CO₃ (1.5 g, 11 mmol) in acetonitrile (50 mL) was refluxed for 24 h under N₂. The reaction mixture was cooled and filtered. The precipitate was washed with CHCl₃ (30 mL × 4). The CHCl₃ layers were combined, dried over Na₂SO₄ and evaporated. The residual solid was extracted with ether (10 mL × 3), and the ether layer was concentrated to give pure dimer **4** (*s*-dipyridino-18-crown-6) in 3% yield. The precipitate was suspended in water, and neutralized by a 1 mol L⁻¹ HCl solution. The aqueous phase was extracted with CHCl₃ (20 mL × 3). The CHCl₃ solutions were combined, dried over Na₂SO₄ and evaporated. Crystallization was induced by addition of ether (5 mL). The crystals were recrystallized from MeOH to give **2** as white needles in 41% yields.

s-Dipyridino-18-crown-6 (**4**). Mp 178.5–179.5 °C (lit.,⁷ 183–185.5 °C). ¹H NMR (400 MHz, CDCl₃) 5.17 (8H, s), 6.99–7.12 (8H, m), 7.31 (2H, d, *J* 7.7 Hz), and 7.58 (1H, t, *J* 7.7). FAB-MS (*m*-NBA as a matrix) *m/z* 427 ([M + 1]⁺, 100%).

Compound **2**. Mp 100–101 °C (Found: C, 70.8; H, 5.4; N, 4.3. Calc. for C₁₉H₁₇NO₄: C, 70.6; H, 5.3; N, 4.3%). ¹H NMR (400 MHz, CDCl₃) 5.62 (4H, s), 7.44 (2H, d, *J* 7.7), 7.78 (1H, t, *J* 7.9), and 9.66 (2H, s). The aromatic moiety of the 2-hydroxybenzene fragment showed an ABCD pattern: δH_A 6.83 (2H, triple doublet), δH_B 7.05 (2H, dd), δH_C 7.05 (2H, dd), δH_D 6.99 (2H, triple doublet), for H_A–H_D, *J*_{AB}(*ortho*) = *J*_{BC} = *J*_{CD} = 7.7 Hz, *J*_{AC}(*meta*) = *J*_{BD} = 1.5 Hz. ¹³C NMR (CD₃CN) 157.50, 148.92, 148.07, 139.72, 124.53, 122.44, 120.97, 117.95, 117.40, and 73.69. EI-MS *m/z* 323 (M⁺, 60%).

Preparation of pyridin-2,6-diyl dimethyl disalicylate (**3**)

A mixture of pyridine-2,6-dimethanol (0.21 g, 1.4 mmol), salicylic acid (0.42 g, 3.0 mol), *N,N*-dimethylaminopyridine (0.35 g, 2.7 mmol), and dicyclohexylcarbodiimide (0.58 g, 2.8 mmol) in CH₂Cl₂ (10 mL) was stirred for 24 h under N₂. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residual oil was chromatographed on silica gel (ethyl acetate–hexane = 3 : 2 as eluent) to give **3** as a white powder in 46% yield.

Mp 99.5–100 °C (Found: C, 66.3; H, 4.6; N, 3.6. Calc. for C₂₁H₁₇NO₆: C, 66.5; H, 4.5; N, 3.7%). ¹H NMR (400 MHz; CD₃Cl) 5.52 (4H, s), 7.48 (2H, d, *J* 7.7), 7.87 (1H, t, *J* 7.7), and 10.55 (2H, s). The aromatic moiety of the salicylate showed an ABCD pattern: δH_A 7.00 (2H, dd), δH_B 6.90 (2H, triple doublet), δH_C 7.48 (2H, triple doublet), δH_D 7.92 (2H, dd), for H_A–H_D, *J*_{AB}(*ortho*) = *J*_{BC} = *J*_{CD} = 7.9 Hz, *J*_{AC}(*meta*) = 1.8 Hz, *J*_{BD}(*meta*) = 1.1 Hz. ¹³C NMR (CD₃CN) 170.56, 162.42, 156.28, 139.12, 137.16, 131.13, 122.16, 120.56, 118.37, 113.49, and 68.06. EI-MS *m/z* 379 (M⁺, 67%).

Na⁺ complex with **2**

Podand **2** (0.01 mmol) in acetonitrile (1 mL) was reacted with NaSCN (0.01 mmol) in methanol (1 mL). After the solvent had been evaporated, the crystals were recrystallized from acetonitrile. The crystals were dried with an Abderhalden's dryer (50 °C, 0.5 Torr). **2**-NaSCN complex: found: C, 58.5; H, 4.2; N, 7.0. Calcd. for C₂₀H₁₇N₂O₄SNa + ½H₂O: C, 58.1; H, 4.4; N, 6.8%.

Computer-modeling calculations

The *ab initio* 3-21G(*) calculations using the MMFF geometry from the conformer search were performed on a Power Book G4 (500 MHz processor and 500 MB memory). Mac Spartan Pro™ was used as the computer molecular modeling software.

¹³C NMR titration experiments

Titration experiments were carried out by addition of 0.5, 1.0, 1.5, 2.0 and 5.0 equiv. of NaSCN in CD₃CN (0.002 mmol μL⁻¹) to podands **1**–**3** in CD₃CN (0.02 mmol in 0.65 mL) at 25 °C.

Crystallography †

Crystal and selected experimental data for podands **2** and **3**, and the **2**-NaSCN complex are summarized in Table 3.

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† CCDC reference numbers 175380–175382. See <http://www.rsc.org/suppdata/p1/b2/b201525k/> for crystallographic files in .cif or other electronic format.

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