A modular approach to constructing multi-site receptors for isophthalic acid

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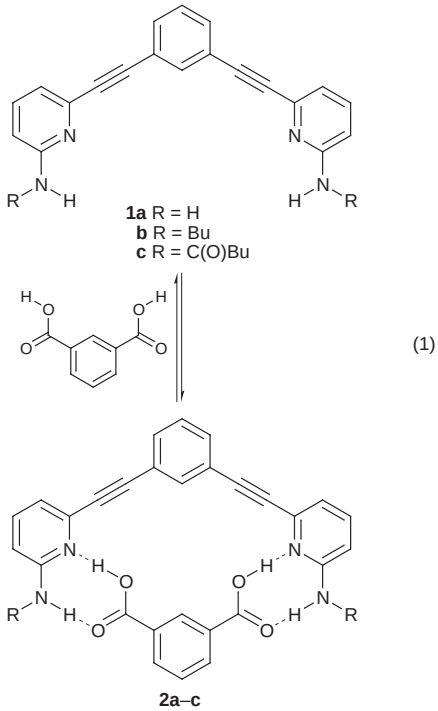
New multi-topic receptors which may serve as building blocks for constructing receptor arrays form highly stable complexes with isophthalic acid.

We are interested in developing simple, modular systems of receptor arrays and multi-topic ligands for the purpose of constructing stable, self-assembled nanostructures through multiple non-covalent interactions. This requires that the associating systems be easily synthesized, show strong supramolecular affinity, and be general for implementation in a variety of molecular designs. While molecular self-assembly is recognized as a method to prepare nanostructures,[1] there exists the need for simple building blocks that can be linked to form arrays of receptors and complementary ligands. Herein we report the design and synthesis of the primary receptor unit **1a**, its heterocomplexation with isophthalic acid, and demonstration of its use in modular construction of multi-site receptors.

The primary receptor unit was designed to be incorporated within oligo(phenyleneethynylene) backbones that have been extensively employed by our group to construct a variety of molecular architectures.[2] 2-Aminopyridines are well-known[3] to associate strongly with carboxylic acids, and a pair of these groups positioned on alternating sites of a 1,3-connected phenyleneethynylene backbone provides excellent shape complementarity to isophthalic acid, as shown in eqn. (1). Molecular



(1)

modeling‡ indicates that both **1a** and isophthalic acid can maintain favorable planar conformations with typical hydrogen bond distances, suggesting that tight binding should be realized. An important feature of this design is the torsional flexibility that exists between adjacent aromatic residues. The rotational barrier[4] about the sp–sp^2 bond is only *ca.* 600 cal mol^{-1}, which permits accessibility to favorable binding geometries. However, the most important aspect of **1a** is its ease of synthesis§ which was accomplished by coupling[5] 2 equiv. of the known[6] 2-amino-6-ethynylpyridine to 1,3-diiodobenzene in 78% yield.

Co-crystallization of **1a** and isophthalic acid from THF by slow evaporation resulted in single crystals suitable for X-ray structure determination.¶ The complex (Fig. 1) packs in 2D sheets with alternating hydrophobic and hydrophilic layers. All hydrogen bond donors and acceptors are fully saturated forming a set of six hydrogen bond interactions for each host and guest in the solid phase. The average dihedral angle between the heterocyclic residues and the phenyl ring is 12.5 ± 1.7°. Job's method[7] confirmed the stoichiometry of **1a** and isophthalic acid to be 1 : 1 in solution.

The binding characteristics of the receptor with 5-*tert*-butylisophthalic acid were determined in solvent systems with varying polarity at 20 °C using ^{1}H NMR titration and dilution methods.[8] As shown in Table 1, the association constant was found to be greater‖ than 10^6 M^{-1} in $CDCl_3$, reflecting a tight fit of the guest with the host. Due to increased solvation, the association constants in 1 : 9 and 1 : 4 [$^2H_6$]DMSO–$CDCl_3$ (v/v) solution were largely reduced to 320 and 80 M^{-1}, respectively.

While probing the potential of **1a** as a principle sub-unit in more complex systems, we anticipated encountering solubility problems. An obvious and synthetically simple solution was to transform the amine groups to more soluble derivatives. Therefore, a pair of analogues **1b** and **1c** were synthesized§ and studied. The association constants of receptors **1b** and **1c** with 5-*tert*-butylisophthalic acid were similar to that of receptor **1a**, all being greater‖ than 10^6 M^{-1} in $CDCl_3$. However, as shown in Table 1, the binding affinity in a 1 : 9 [$^2H_6$]DMSO–$CDCl_3$ (v/v)

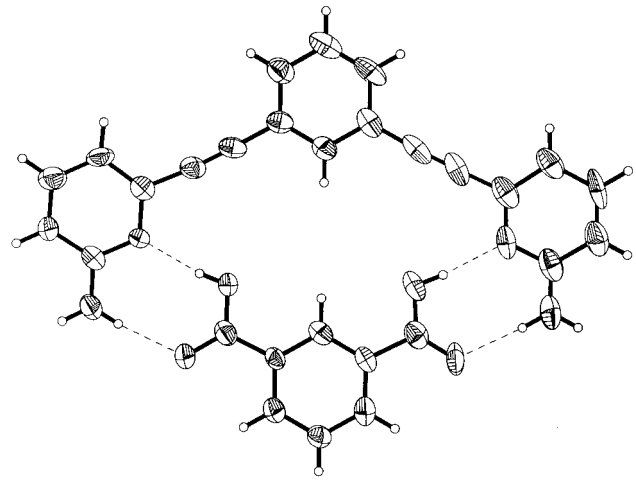
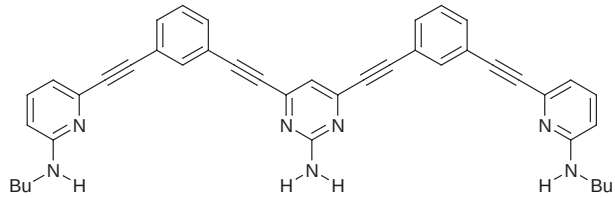


Fig. 1 ORTEP drawing at the 50% probability level of the complex formed between **1a** and isophthalic acid. Hydrogen bonding is indicated by thin dashed lines.

solution showed some noticeable differences. The association constants of **1b** and **1c** with 5-*tert*-butylisophthalic acid were 55 and 50 M^{-1} respectively. The reduction in affinity relative to receptor **1a** is believed to stem both from the increase in the extent of desolvation upon complexation and the greater entropic loss in rotational freedom about the aminopyridine bond. Our results showed that acylation or alkylation are synthetically simple ways to enhance the solubility of **1a** without significantly reducing the binding strength.



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To demonstrate the modularity of this building block set, receptor **3**, which can potentially bind two units of isophthalic acid, was synthesized§ in a manner similar to that of **1a**. After several attempts at obtaining a crystal structure of receptor **3** and various derivatives of isophthalic acid, only crystals from a dioxane solution of 5-hydroxyisophthalic and **3** were suitable for X-ray diffraction. Although the quality of the crystal¶ was poor, the data set obtained was sufficient to confirm the dual binding of 5-hydroxyisophthalic acid (Fig. 2) and reveal the packing pattern as being similar to complex **2**. In solution, the stoichiometry of the complex was determined to be 2 : 1 by Job's method.[7]

Table 1 Association constants of receptors **1a**–**c** with 5-*tert*-butylisophthalic acid at 20 °C in a variety of solvent systems[a]

	Association constant/M^{-1}		
Receptor	in $CDCl_3$[b]	in 1 : 9 [$^2H_6$]DMSO–$CDCl_3$ (v/v)	in 1 : 4 [$^2H_6$]DMSO–$CDCl_3$ (v/v)
1a	$> 10^6$	320	80
1b	$> 10^6$	55	[c]
1c	$> 10^6$	50	[c]

[a] Association constants were determined by non-linear least-squares fitting of the experimental binding isotherm. The error is ±15%. [b] Estimated lower limit (see footnote ‖). [c] No observable binding affinity.

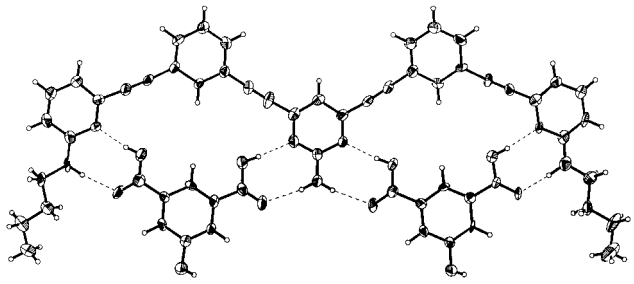

Fig. 2 ORTEP drawing at the 50% probability level of the complex formed between **3** and 5-hydroxyisophthalic acid. Hydrogen bondiong is indicated by thin dashed lines. The structure contains solvent molecules (dioxane) which have been removed for clarity.

In conclusion, we have shown that receptor **1a** possesses a high affinity towards isophthalic acid and can easily be modified to alleviate solubility difficulties. The synthesis of **3** demonstrates that **1a** can be implemented as a building block for the construction of arrays of multi-site receptors for isophthalic acid. By combining multi-topic ligands and multi-site receptors, it should be possible to form stable, self-assembled nanostructures. In addition, we are also working on linear (AB) and 2D (AB_2) supramolecular polymers based on host : guest complex **2**. Details of these studies will be reported in due course.

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Notes and References

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‡ Molecular modeling was performed on a Silicon Graphics Indigo workstation using Cerius² and MacroModel software packages.

§ All new compounds gave satisfactory analytical and spectral data.

¶ *Crystal data* for **1a**-isophthalic acid: $C_{28}H_{20}N_4O_4$, M_r = 476.48 g mol^{-1}, colorless, columnar crystal (0.26 × 0.06 × 0.06 mm), triclinic, space group $P\bar{1}$, a = 7.6156(10), b = 11.493(2), c = 14.462(2) Å, α = 108.586(3), β = 96.039(3), γ = 101.298(3)°, V = 1157.3(3) Å^3, Z = 2, ρ_{calc} = 1.367 g cm^{-3}, μ = 0.094 mm^{-1}. Of 5147 reflections measured, 3165 were independent, and 1524 were used for refinement; wR_2 = 0.1597 and R_1 = 0.1077 for 301 parameters. For **3**·[5-hydroxyisophthalic acid]$_2$·[dioxane]$_3$: $C_{70}H_{73}N_7O_{16}$, M_r = 1268.35 g mol^{-1}, pale yellow, tabular crystal (0.18 × 0.10 × 0.04 mm), triclinic, space group $P\bar{1}$, a = 13.0983(11), b = 14.6384(13), c = 18.0368(15) Å, α = 106.833(2), β = 93.572(2), γ = 93.343 (2)°, V = 3293.2(5) Å^3, Z = 2, ρ_{calc} = 1.279 g cm^{-3}, μ = 0.092 mm^{-1}. Of 14 147 reflections measured, 8808 were independent, and 4059 were used for refinement; wR_2 = 0.3410 and R_1 = 0.2181 for 823 parameters. Data for both structures were collected on a Siemans CCD/platform diffractometer using graphite-monochromated Mo-Ka radiation (λ = 0.71073 Å, 0.3° ω scans, $2\theta_{max}$ = 46.0°) at 198(2) K. No absorption corrections were applied. Using SHELXTL, each structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2 with anisotropic displacement parameters for the non-hydrogen atoms. Hydrogen atoms were included as fixed contributors in idealized positions. CCDC 182/866.

‖ Estimated by dilution to 50 μM.

1 S. C. Zimmerman, F. Zeng, D. E. C. Reichert and S. V. Kolotuchin, *Science*, 1996, **271**, 1095; J. S. Moore, *Curr. Opin. Solid State Mater. Sci.*, 1996, **1**, 777; G. M. Whitesides, J. P. Mathias and C. T. Seto, *Science*, 1991, **254**, 1312.

2 J. S. Moore, *Acc. Chem. Res.*, 1997, **30**, 402.

3 A. D. Hamilton, E. Fan, S. Van Arman, C. Vincent, F. Garcia-Tellado and S. J. Geib, *Supramol. Chem.*, 1993, **1**, 247; M. C. Etter and D. A. Adsmond, *J. Chem. Soc., Chem. Commun.*, 1990, 589; R. W. Gellert and I. N. Hsu, *Acta. Crystallogr., Sect. C*, 1988, **44**, 311.

4 K. Okuyama, T. Hasegawa, M. Ito and N. Mikami, *J. Phys. Chem.*, 1984, **88**, 1711.

5 K. Sonogashira, T. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4467.

6 M. Inouye, T. Miyake, M. Furusyo and H. Nakazumi, *J. Am. Chem. Soc.*, 1995, **117**, 12 416.

7 P. Job, *Ann. Chim.* (*Paris*), 1928, **9**, 113; K. C. Ingham, *Anal. Biochem.*, 1975, **68**, 660.

8 C. S. Wilcox, in *Frontiers in Supramolecular Chemistry and Photochemistry*, ed. H. J. Schneider and H. Durr, VCH, New York, 1991, p. 123.

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