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A monomolecularly imprinted dendrimer (MID) capable of selective binding with a tris(2-aminoethyl)amine guest through multiple functional group interactions†

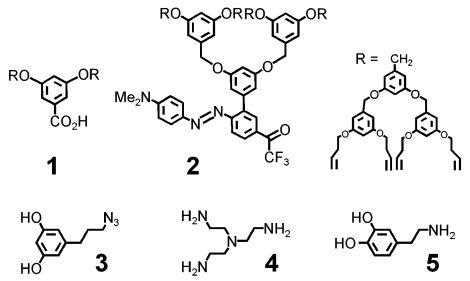
James B. Beil and Steven C. Zimmerman*

Department of Chemistry, 600 S. Mathews Street, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA. E-mail: sczimmer@uiuc.edu; Fax: +1 217 244 9919; Tel: +1 217 333 6655

Received (in Cambridge, UK) 12th December 2003, Accepted 20th January 2004
First published as an Advance Article on the web 29th January 2004

A molecularly imprinted dendrimer (MID) with a colorimetric reporter group exhibits three-point binding of tris(aminoethyl)-amine in THF with a K_{assoc} = 3.3 × 10^6 M^{-1}.

We recently reported that a porphyrin binding site could be imprinted into a single macromolecule, a cross-linked dendrimer.[1,2] Thus, **1** and tetrakis-meso(3,5-dihydroxyphenyl)porphyrin formed an octa-ester that could be extensively cross-linked using the ring closing metathesis (RCM) reaction,[3] and "cored"[4] to produce an MID that complexed porphyrins containing complementary functionality. Subsequently, a reporter dye for amines[5] was integrated into the focal point of the cross-linkable dendrimers (*i.e.*, **2**) for the synthesis of amine selective MID sensors.[6] An MID produced from the bis-imine of **2** and 1,4-butane diamine tightly and selectively bound alkane diamines by two-point (bis-carbinolamine) formation with a color change visible to the naked eye.[6a] However, control studies indicated that the observed selective binding did not arise from molecular imprinting but from a kinetic binding effect.[6b]

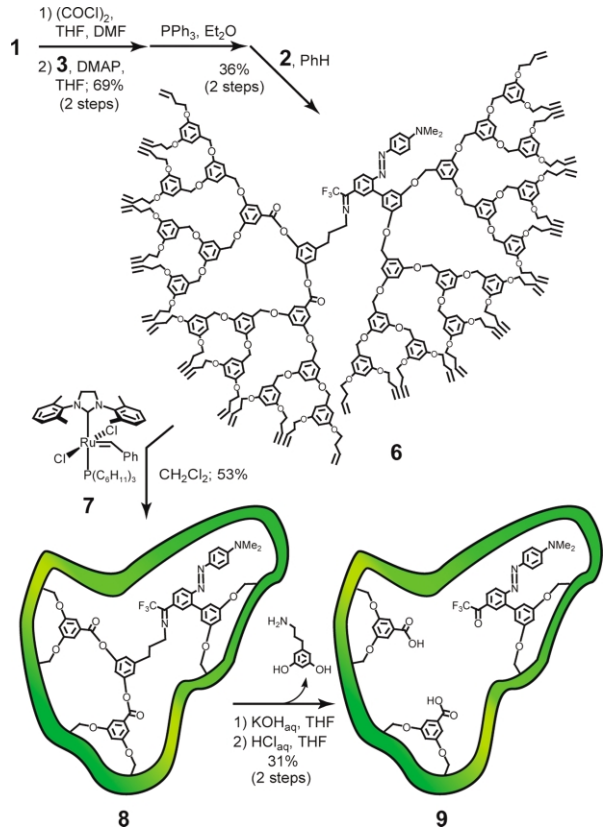


Whereas the porphyrin MID derived from **1** contained 30–32 cross-links, a polystyrene-based MW (MW_{PS}) of 8155, and the potential for guest complexation with >4 binding contacts, the butane diamine MID derived from **2** contained only 13–16 cross-links, a lower MW_{PS} = 3620, and featured two-point binding. The goals of the current study are two-fold: to begin to delineate the structural requirements for imprinting in the MID approach and to prepare MIDs that use more than one type of binding interaction. Thus, we describe herein the imprinting of template **3** into a dendrimer containing both subunits **1** and **2** with 32 alkenes that can produce a maximum of 16 cross-links. Based upon the earlier work, an MID derived from **1**, **2** and template **3** was expected to complex tetraamine **4** or dopamine **5**.

Template **3** was prepared from 3,5-dimethoxyphenylpropyl bromide[7] by demethylation with boron tribromide (CH_2Cl_2, rt; 97%) and displacement with sodium azide (aqueous acetone; 78%). The dendron used in this study was the same as that used for porphyrin imprinting[1] and for the synthesis of "cored" dendrimers.[4] Dendron **1** was treated sequentially with oxalyl chloride and **3**, and the resulting diester converted to the iminophosphorane, which was directly reacted with **2** to produce imine dendrimer **6** (Scheme 1).‡ The cross-linking of **6** was performed at 1 × 10^{-5} M using Grubbs type 2 catalyst (**7**)[8] with **8** isolated in 53% yield. Core removal and extensive SEC purification afforded pure **9** in 31% yield. The MALDI-MS of both **8** and **9** showed nearly complete cross-linking (16 of 16 cross-links formed).

Two control dendrimers were prepared to test for imprinting and any binding contribution of the carboxylic acid groups. First, the two carboxylic acid groups in **9** were converted to ester groups by treatment with methyl iodide and K_2CO_3 in THF. The dimethylester of **9** (**9-CO_2Me**) was isolated in 48% yield. The second control dendrimer was prepared without template and only loose positioning of the two carboxylic acid groups. Thus, as outlined in Scheme 2, two units of **1** were linked by an ethylene unit and then treated with **2** and RCM catalyst **11** at a concentration that produced inter-dendrimer cross-linking. Extensive purification by SEC to remove other coupling products (*e.g.*, homodimers (**2**)$_2$, (**10**)$_2$ and oligomers) afforded pure **12** in low yield. The base hydrolysis of **12** led to loss of the dye color so it was protected as its phenylpropyl imine **13** and then cored affording cross-linked dendrimer (CLD) **14**. CLD **14** contains the same functional groups as MID **9** and exhibited similar spectroscopic and analytical SEC (*i.e.*, MW_{PS}) data.

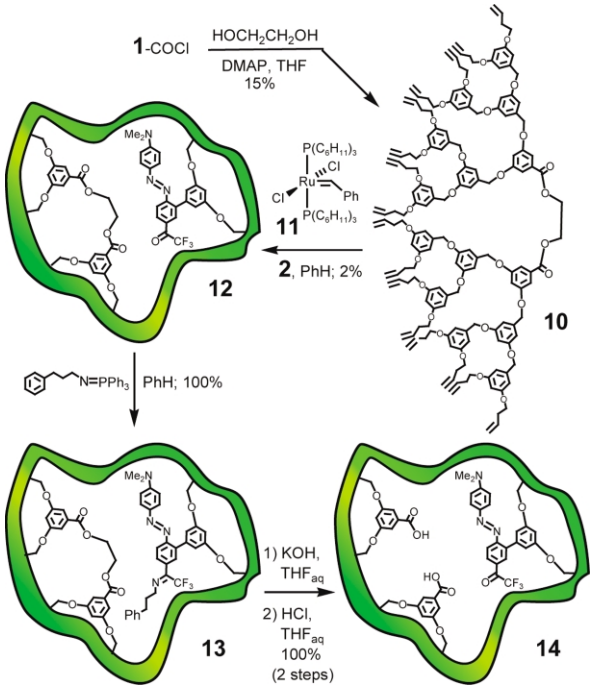
Instability and low solubility of **5** in common organic solvents prevented its binding with **9** from being studied. In contrast **4** was very soluble and rapidly changed the color of solutions of **9** in THF from red–orange to yellow. Indeed, titrations of the dye containing hosts, MID **9**, **9-CO_2Me**, and CLD **14**, with several simple amine



Scheme 1 Synthesis of MID **9** from template **3**.

† Electronic supplementary information (ESI) available: compound characterization data and representative UV-visible binding data with K_{assoc} plots. See http://www.rsc.org/suppdata/cc/b3/b316248f/

DOI: 10.1039/b316248f



Scheme 2 Synthesis of cross-linked dendrimer (CLD) **14**.

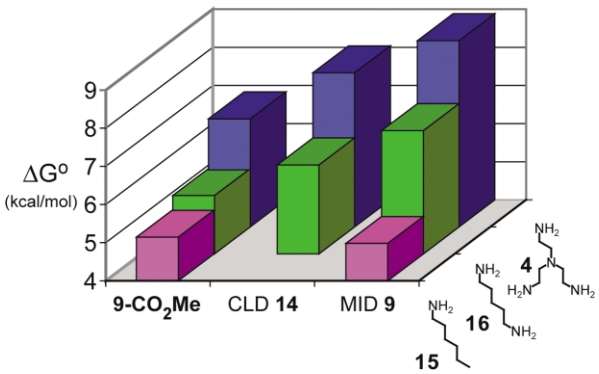
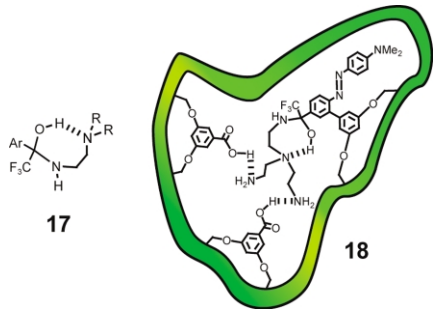


Fig. 1 $\Delta G°$ values for various complexes in THF at 298 K.

guests gave UV-visible plots with clean isosbestic points (see ESI). Plots of the change in absorption at $\lambda_{max} \approx 470$ nm *vs*. amine concentration were fit to 1 : 1 binding isotherms giving K_{assoc} values (see Table S1 in ESI). The free energies of complexation are compared graphically in Fig. 1.

In analyzing the data in Fig. 1, two main trends emerge. First, more amino groups in the guest result in tighter binding. This can be explained both by a statistical advantage (*e.g*., 3-fold for **4** *vs*. **15**) and a more subtle effect involving intramolecular hydrogen bonding to the carbinolamine. Thus, we recently described a significant thermodynamic stabilization in alkane diamine binding to the dye unit in **2**.[6b] In particular, the greatest stabilization was found for ethylene diamines due to the favorable 6.5-membered hydrogen-bonded ring formed in complexes such as **17**. However, these two effects cannot fully explain the strong binding of **16** and **4** by MID **9**. Indeed, the data suggest that two- and three-point binding are present in complexes of **9** with **16** and **4**, respectively. Whether the interactions between the amino and carboxylic acid groups involve ion-pairing is not known. One possible structure for the **4**·**9** complex is represented schematically by **18**.



The second trend emerging from the data in Table S1 (see ESI) is the small, but regular and experimentally significant increase in K_{assoc} values, MID **9** > CLD **14** > **9-CO$_2$Me**, found for complexes with both **16** and **4**. In **9-CO$_2$Me** the carboxylic acid groups are blocked, whereas in **14** their position has not been fully optimized by template-mediated imprinting. The latter result suggests that the high K_{assoc} values of the **4**·**9** complex result from imprinting. However, dendritic hosts **9** and **14** were prepared differently and it is not known whether solvent and catalyst effect the cross-linking process.

In summary, MID **9** synthesized from **3** exhibits very high affinity binding of **4**. The **4**·**9** complex features three point binding including both a covalent linkage to a reporter group that signals binding by a color change and two noncovalent amino–carboxylic acid contacts. Despite its comparatively small size ($MW_{PS} \approx 3000$) and a mere 16 cross-links, evidence obtained is consistent with template-mediated imprinting. Our current efforts are directed toward improving both the synthesis and binding properties of MIDs, applying the MID approach to new guests, as well as developing alternative macromolecular architectures for monomolecular imprinting.

Notes and references

‡ All new compounds, including dendrimers, were purified to homogeneity by chromatography on silica gel, preparative SEC, or both. Spectral data (^{1}H, ^{19}F NMR, MALDI or FD-MS, UV-vis) were in full accord with the assigned structures. The purity of **9** and **9-CO$_2$Me** was estimated to be at least 90% by analytical SEC (see ESI).

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