Synthesis of new torands and new uses for old torands

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Abstract

Known torands 1 and 2 are preorganized host compounds having macrocyclic perimeters comprised of fully fused rings. Torand 1 was previously found to form strong 1:1 complexes with alkali metal ions. Spectroscopic studies now show that 1 also binds alkaline earth ions, transition metals, heavy metals, lanthanides and actinides. Triaryltri-*n*-butyl torands (4) have now been synthesized and are attractive precursors to novel materials. Torand 5, an "expanded porphyrin," has been synthesized by Piloty rearrangement of azines; macrocycle 6 binds Li^+ or Mg^{2+} with tautomerization to the bis(azine) form, producing dramatic UV-visible spectroscopic changes.

INTRODUCTION

The genesis of torands lies in the notion that planarization of crown ethers could produce exceptionally stable complexes of cations. Because planar host compounds do not encapsulate their guests, they can be rigidified without loss of rapid exchange kinetics. In torands the macrocyclic perimeter is completely formed of smaller rings, incorporating heterocycles bearing ligand atoms or hydrogen bond donors. Published examples include two pyridine-containing torands, tri-*n*-butyldodecahydro-hexaazakekulene (1, ref. 1-4) and expanded analogue 2 (ref. 5). The syntheses and complexation properties of these hosts are briefly reviewed and updated. Two new members of the torand family (4 and 5) are introduced and a novel bis(hydrazone) macrocycle (6) is also discussed.
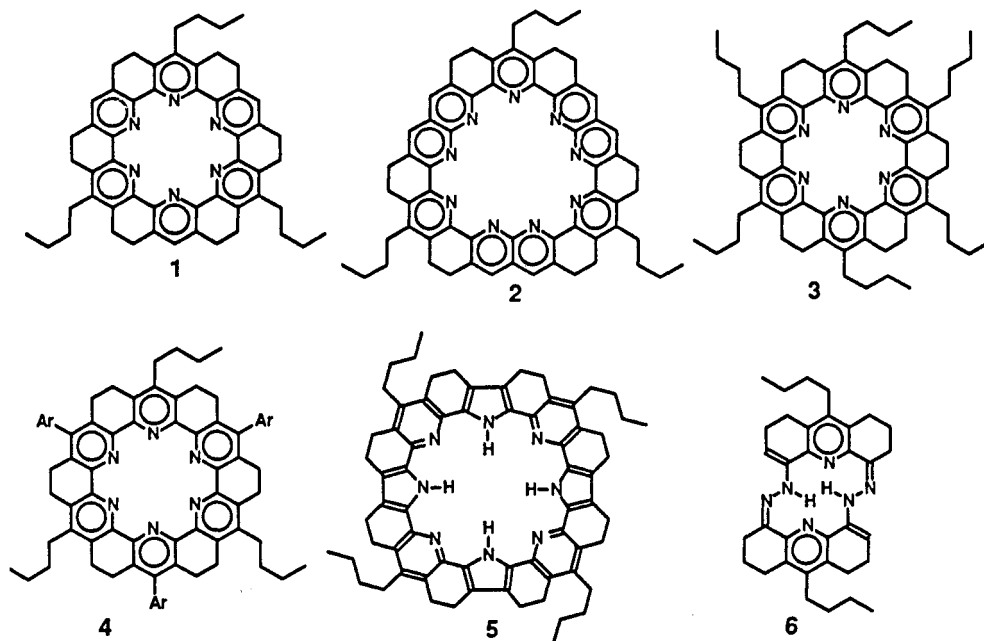
TRI-*n*-BUTYL TORAND 1

When we began our synthetic work in 1982, torand **1** was one of several potential targets having the hexaazakekulene skeleton. The 1,2,3,4,5,6,7,8-octahydroacridine ring system (**7**) proved sufficiently easy to functionalize and the 9-*n*-butyl derivatives display a good balance between crystallinity and solubility in organic solvents. Our current synthesis of tri-*n*-butyl torand **1** is shown in Fig. 1. By modifying methods reported for other octahydroacridine derivatives, we developed large scale syntheses of the initial intermediates (ref. 6). Several of the steps shown in Fig. 1 represent improvements over methods used in the original synthesis (ref. 1). Key modifications include use of the Albright-Goldman oxidation for synthesis of ketone intermediate **8** and pyridine synthesis by condensation of a Mannich salt with **8** and ammonium acetate in DMSO. The macrocyclization reaction promoted by trifluoromethanesulfonic (triflic) acid in acetic acid apparently gives a bis(pyrylium) macrocycle, which is converted to **1** *in situ* by reaction with ammonium acetate. Tri-*n*-butyltorand **1** is currently isolated as its salt with triflic acid rather than as its calcium triflate complex (ref. 1). The overall yield is 3 % for the 11 steps shown in Fig. 1. Despite the length of this synthesis, the individual steps are sufficiently simple that it is possible for one person to prepare one gram of this torand in one month.
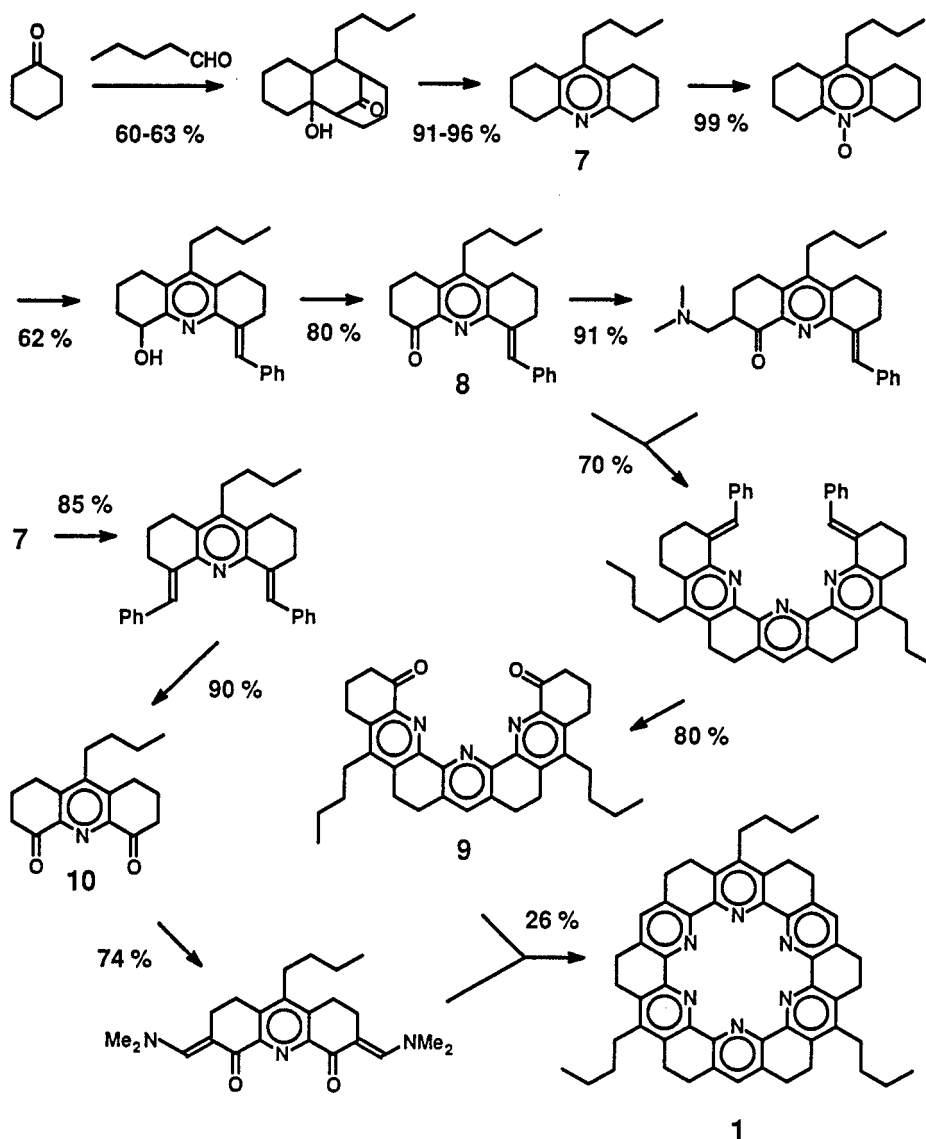

Fig. 1. Current synthesis of tri-*n*-butyltorand **1**.

Torand 1 forms remarkably strong complexes with alkali metal salts and log K_s values of 1:1 complexes with all alkali metal picrates exceed 11 in water-saturated chloroform, according to the results of extraction experiments. We have refined the stability constants of the Na^+ and K^+ complexes (log K_s = 14.7 and 14.3, respectively) by ^1H NMR competition experiments. Previously we were unable to resolve the ^1H NMR signals of free [2.2.1]cryptand and [2.2.1]cryptand·Li^+ at 300 MHz. Recently we performed this competition at 600 MHz and found log K_s = 13.4 for 1·Li(picrate) in D_2O-saturated $CDCl_3$. Thus, 1 exhibits slight selectivity for Na^+ and K^+ over Li^+. Our discovery that torand complexes are more stable than those of cryptands refutes the idea that encapsulation is required for strong binding. Moreover, the poor selectivity of 1 contradicts the usual preference for the metal that best fits the cavity, since the hexacoordinate ionic radii of potassium, sodium and lithium are 1.38, 1.02 Å, and 0.76 Å, respectively, and we previously estimated the torand cavity radius as approximately 1.3 Å. Effective ionic radii vary with coordination number, so we then focused on crystallography of the alkali metal complexes of torand 1. We have determined the X-ray crystal structures of the lithium, potassium and rubidium picrate complexes (ref. 3,4). In the potassium and rubidium complexes the metal atoms are centered with respect to the cavity of 1, which adopts the staggered, pseudo D_{3d} conformation predicted by molecular modeling. Potassium is clearly the best fit, since it is only 0.23 Å from the best N plane with K-N distances ranging from 2.73-2.85 Å. Potassium has a 7th contact to picrate, so the cavity radius of 1 should be revised to almost 1.46 Å, the ionic radius of 7-coordinate potassium. The torand adopts the same conformation in 1·Rb^+; rubidium lies 1.06 Å from the best N plane and picrate is bidentate. In contrast to these 1:1 complexes, 1·Li(picrate) crystallizes as a 2:2 complex containing three water molecules. This structure is apparently unique for crystals containing lithium picrate, since no anion coordination is observed. The two torands are coaxially stacked and threaded by a hydrated dilithium chain (H_2O-Li^+-H_2O-Li^+-H_2O). Each lithium ion binds unsymmetrically to two of the six nitrogens of each torand and two water molecules complete the tetrahedral coordination sphere.

Comparison of the solid state structures of 1·Li^+ and 1·K^+ does not offer a clear explanation for the low size-selectivity of torand 1 and it remains to be determined whether this effect will be generally observed in planar crown compounds. It is possible that in rigidly planar systems entropy-enthalpy compensation exerts a leveling effect. Lithium in 1·Li^+ has a relatively low coordination number (4), suggesting that binding of small ions to 1 may release more solvent molecules than during binding to more flexible macrocycles. Despite the relatively large cavity size of 1, we have also found that complexes are formed with metal ions throughout the periodic table. Our spectroscopic studies have shown that 1 binds Ca^{2+}, Ba^{2+}, Sc^{2+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ag^+, Cd^{2+}, Eu^{3+}, Tb^{3+}, Tl^+, Pb^{2+} and UO_2^{2+} and 1:1 complexes of many of these metals have been characterized. Torand 1 and its metal complexes partition selectively into CH_2Cl_2 or $CHCl_3$ relative to water. Metals and other ions bind rapidly to the open-faced cavity of 1 and many can be re-extracted into water by protonation of the torand using aqueous acid.

EXPANDED TORAND 2

Combining the 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine building block with the Friedlander condensation of o-aminoaldehydes, we have synthesized a series of new naphthyridine-containing macrocycles and clefts (ref. 5,7). "Expanded" torand 2 is prepared from ketone 8 and 4-amino-pyrimidine-5-carboxaldehyde (Fig. 2). Hydrolysis of the pyrimidine ring of the condensation product gives a new o-aminoaldehyde, which is ozonized to a ketoaminoaldehyde intermediate containing both moieties needed for Friedlander condensation. CsOH-templated trimerization gives expanded torand 2 in up to 50 % yield (ref. 5). Although 2 is a larger torand than 1, it can be prepared by this method *in higher overall yield and in fewer steps*. The cesium complex of 2 is much weaker than alkali metal complexes of 1 and the free ligand is obtained simply by boiling in water. Torand 2 also binds guanidinium, which fits the cavity almost exactly with formation of six hydrogen bonds.
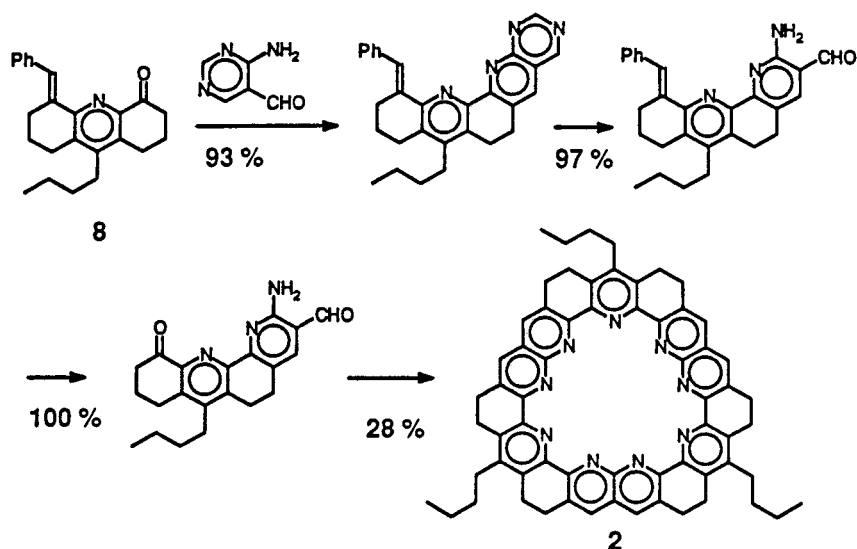
Fig. 2. Synthesis of "expanded" torand 2.

TRIARYLTRIALKYLTORANDS (4)

We are currently developing triaryltrialkyltorands (4) to modify solubility, produce optical sensors and induce molecular aggregation. So far, we have been unable to prepare hexaalkyltorands such as 3, which might align coaxially to form columnar discotic (tubular) mesophases. An alternate approach to liquid crystalline torands is to attach long alkyl chains to the para positions of each aryl group in triaryltrialkyltorands. Our synthesis (Fig. 3) again utilizes intermediate 8, which is condensed with aromatic aldehydes in the presence of LiI to produce β-arylenones (R = H, OCH$_3$, Cl or NO$_2$). Condensation of these β-arylenones with ketone 8 and ammonium acetate in DMSO gives various fused terpyridines in 30-60 % yield. Ozonolysis and condensation of the resulting diketone with various bis(β-arylenones) yields the triaryltributyltorands (4, R = H, NO$_2$, Cl) in 15-30 % macrocyclization yield. The overall efficiency of this torand synthesis is comparable to that of the
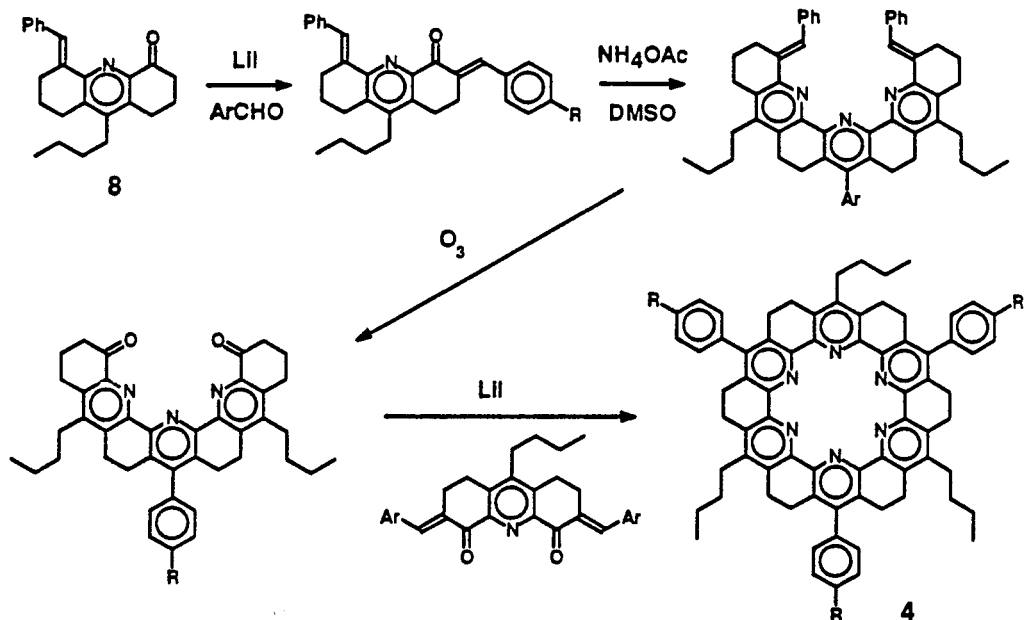
Fig. 3. Synthesis of tri-n-butyltriaryltorands (4).

tri-*n*-butyltorand synthesis shown in Fig. 1. The tris(*p*-nitrophenyl)tri-*n*-butyl torand is particularly attractive as a synthetic intermediate, since the nitro groups can be reduced to amino groups, allowing further derivatization or attachment of torands to solid supports.

EXPANDED PORPHYRIN 5

The synthetic approach to the first torands of a new class, expanded porphyrins, is shown in Fig. 4. Again, the synthesis begins with benzylideneketone 8, which is converted to the monoketal of 10 in two steps. The key steps in the synthesis involve thermal Piloty rearrangement of azines. This reaction, in combination with deketalization, constitutes an effective homologation method to produce curved molecular bands consisting of alternating pyrrole and pyridine rings which are mutually fused to 6-membered carbon rings. The key macrocyclization step is performed by bis(semicarbazone) pyrolysis, forming expanded porphyrin 5 in up to 69 % yield. Partial dehydrogenation of the ethano bridges occurs during these thermal pyrrole-forming reactions. Torand 5 can also be completely dehydrogenated to a fully aromatic expanded porphyrin by reaction with DDQ. These are the largest expanded porphyrins known; their anionic forms are of interest for complexation of polymetallic species and polyprotonated forms may bind large anionic guests.
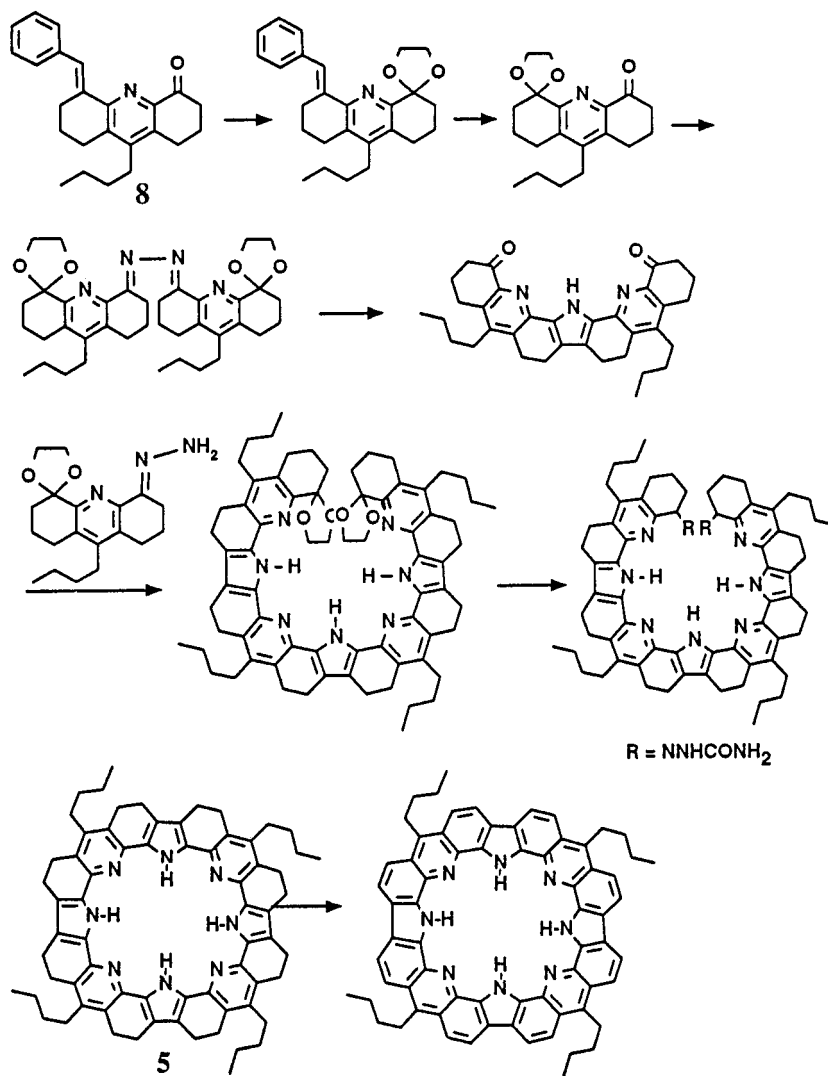

Fig. 4. Synthesis of Expanded Porphyrin Torands

BIS(HYDRAZONE) MACROCYCLE 6

Experimenting with the Piloty pyrrole synthesis just discussed, we discovered that diketone **10** and its bis(hydrazone) undergo condensation in high yield to form macrocycle **6** as a yellow-orange solid (Fig. 5). Yellow solutions of this compound in CH_2Cl_2 or $CDCl_3$ are decolorized when solid LiCl, $LiNO_3$, $MgCl_2$ or $CaCl_2$ are added. Spectroscopic studies of the $MgNO_3$ complex formed in acetonitrile showed that decolorization is caused by tautomerization of the bis(hydrazone) form to the bis(azine) form upon complexation (ref. 8). This ion-selective optical response in a preorganized macrocycle might be used to construct reversible optical probes for analytical applications.
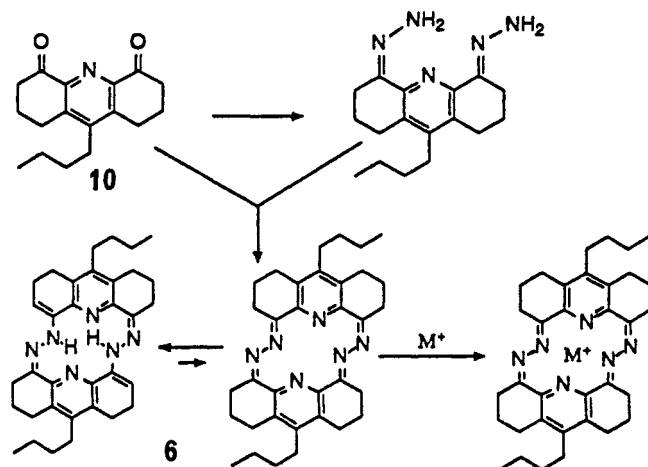

Fig. 5. Synthesis and complexation-induced tautomerism of bis(hydrazone) macrocycle **6**.

Acknowledgement

REFERENCES

1. T.W. Bell and A. Firestone, *J. Am. Chem. Soc.* **108**, 8109-8111 (1986).
2. T.W. Bell, A. Firestone and R. Ludwig, *J. Chem. Soc., Chem. Commun.* 1902-1904 (1989).
3. T.W. Bell, P.J. Cragg, M.G B. Drew, A. Firestone and D.-I. Kwok, *Angew. Chem., Int. Ed. Eng.* **31**, 345-347 (1992).
4. T.W. Bell, P.J. Cragg, M.G B. Drew, A. Firestone and D.-I. Kwok, *Angew. Chem., Int. Ed. Eng.* **31**, 348-350 (1992).
5. T.W. Bell and J. Liu, *Angew. Chem., Int. Ed. Eng.* **29**, 923-925 (1990).
6. T.W. Bell, Y.-M. Cho, A. Firestone, K. Healy, J. Liu, R. Ludwig and S.D. Rothenberger, *Organic Syntheses* **69**, 226-237 (1990).
7. T.W. Bell and J. Liu, *J. Am. Chem. Soc.* **110**, 3673-3674 (1988).
8. T.W. Bell and A.T. Papoulis, *Angew. Chem.* 792-794 (1992).