Template Effect of Intramolecular Hydrogen-bonding in the Synthesis of [1.1.1]Cryptates

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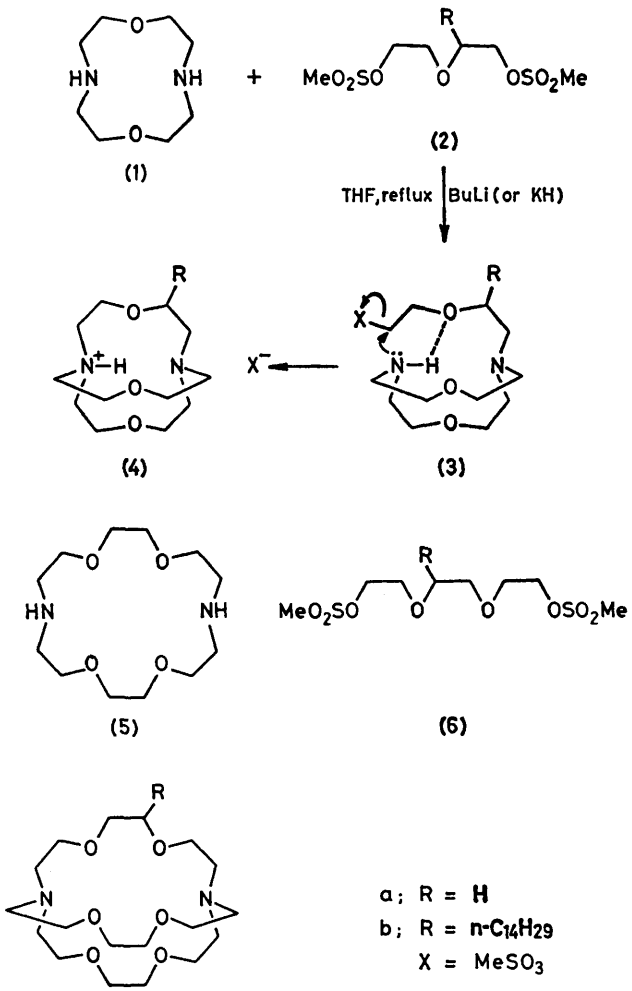
Summary Condensation of monometallated [1.1]diazacoronand with diethylene glycol bis(methanesulphonate), as well as with its alkyl substituted derivatives, gives the corresponding [1.1.1]azamacrobicyclic polyethers through a template effect due to NH intramolecular hydrogen-bonding.

AZAMACROPOLYCYCLIC polyethers (cryptands) are of great interest in organic chemistry.[1] However, their routine use is still severely limited by their long and expensive synthesis.[2] A striking case is that of [1.1.1]cryptand which is obtained in very low yield by Lehn's classical synthesis.† This cryptand is of exceptional interest because it is capable of selective and irreversible cryptation of protons.[3]

In an effort to overcome these drawbacks, the monolithium derivative of diazacoronand (**1**) was prepared from butyl-lithium (1 mol. equiv.) and (**1**) (1·44 g) in tetrahydrofuran (THF) (30 ml), and then condensed with diethylene glycol bis(methanesulphonate) (**2**; R = H) (2·19 g) in 30 ml of THF, first for 12 h at room temperature, and then under reflux for 4 days. In this way the macrobicyclic system was formed and directly precipitated from the boiling solution as the proton cryptate $[H^+ \subset (1.1.1)]MeSO_3^-$ (**4a**),- of satisfactory purity (40% yield, m.p. >250 °C).

† The main reaction product is a macrotricyclic tetra-amine in which two diazacoronand rings are connected by two diethyleneoxy bridges.



The ^{1}H n.m.r. spectrum of (**4**) displays absorptions at δ 3·52 (t, CH_2OCH_2), 3·1 (m, CH_2N), and 2·6 (s, $CH_3SO_3^-$). Furthermore, a broad singlet at δ 9·6 indicates the presence of an N^+–H hydrogen inside the bicyclic system. This hydrogen does not exchange with deuterium in D_2O solution, since intermolecular exchange is totally inhibited by the [1.1.1]bicyclic ligand.[3] These data, in addition to the ^{13}C n.m.r. spectrum, agree with those previously reported by Lehn *et al.*[3] for the same macrobicyclic cation.

Identical yields were obtained when the reaction was repeated with 1 mol. equiv. of KH instead of BuLi. When 2 mol. equiv. of base (BuLi or KH) were used, unresolvable mixtures were obtained.

Starting from the alkyl-substituted ether (**2b**; R = n-$C_{14}H_{29}$), the corresponding alkylated macrobicyclic system (**4b**) was obtained, again as the proton cryptate (N^+–H resonance at δ 9·6 in D_2O). It was isolated as [$H^+ \subset$ (1.1.1, C_{14})]I^-, in 43% yield by column chromatography (alumina, 1:1 MeCN–$CHCl_3$), m.p. 65—67 °C from cyclohexane.‡§

The experimental data exclude the possibility that a metal cation acts as a template in the formation of the [1.1.1]macrobicyclic ligands (**4a**) and (**4b**). However, they agree with the hypothesis that the NH hydrogen of the monosubstituted [1.1]diazacoronands (**3a**) and (**3b**) plays a template role by intramolecular hydrogen-bonding with the ethereal oxygen of the incoming chain and/or with the other nitrogen atom.

The synthetic approach to (**4a**) and (**4b**) described here rests therefore on two facts: (i) diversification of the two binding sites of the diazacoronand through monometallation; (ii) intramolecular binding of the incoming chain through the template effect of the NH hydrogen.

These criteria allow the formation of diazamacrobicyclic systems, avoiding the need for metal-ion template or high-dilution techniques.¶

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‡ In the ^{1}H and ^{13}C n.m.r. spectra of (**4b**), the hydrogen atoms and carbon atoms of the CH_2O and CH_2N groups each give rise to a series of distinct signals, as expected for a chiral molecule. Compound (**4b**) gave satisfactory C, H, N, and I analyses; *m/e* 441.

§ Under comparable dilution conditions and with BuLi as base, the macrobicyclic derivatives (**7a**) and (**7b**) were obtained in yields of 25 and 26%, respectively, from [2.2]diazacoronand (**5**) and the triethylene glycol bis(methanesulphonates) (**6a**; R = H) and (**6b**; R = n-$C_{14}H_{29}$). Compound (**7a**) was isolated as the [$K^+ \subset$ (2.2.2)]I^- cryptate; (**7b**) as the free cryptand[4] after decomplexation in acidic medium and addition of LiOH.

¶ The synthesis of N_4 macrocyclic imine ligands through the intervention of intramolecular hydrogen-bonding has recently been reported (ref. 5).

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