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The Effects of Alkali Metal Cations on Product Distributions in Cucurbit[*n*]uril Synthesis

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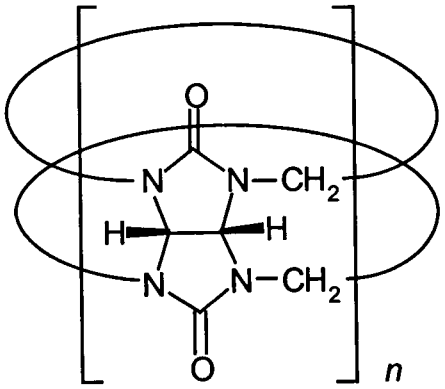
Abstract

Alkali metal cations act as templates in the synthesis of cucurbit[*n*]uril, Q[*n*], for $n = 5–8$, either from a preformed oligomer precursor, or directly from glycoluril and formaldehyde. Q[5] has been synthesised and isolated as an unusual, water-insoluble potassium salt complex. The formation of this new complex is a convenient method for isolating Q[5] as a salt from Q[*n*] mixtures. The complex is a convenient, high yielding source of Q[5].

Introduction

The cucurbit[*n*]uril, here abbreviated as Q[*n*] (**1**) [1], are a new and developing family of molecular hosts [2]. These rigid macrocycles have a unique cavity, with partially restricted portals that are rimmed by carbonyl oxygens. This study continues our investigation of the mechanism of formation of Q[*n*], formed from the acid catalysed condensation of glycoluril and formaldehyde, and of the selective control of the synthesis of any particular Q[*n*].



Stability constant studies and X-ray crystal structure determinations show that alkali metal cations bind to the electron-rich carbonyl oxygen portal openings of cucurbit[6]uril, Q[6] [3, 4]. The binding energies of alkali metal cations to Q[6] differ with the size of the cation, and are similar to alkali metal cation binding energies found for 18-crown-6 [4]. However, unlike crown ethers, the carbonyl "crowns" of Q[6] are quite rigid and cannot easily flex to accommodate different sized alkali metal cations. In the synthesis of crown ethers, the size of the crown can be influenced by the presence of different alkali metal cations acting as templates [5]. Here we have extended our previous work on the synthesis of Q[*n*] [1(c)], and investigated the possible templating action of alkali metal cations on product distributions in the synthesis of Q[*n*].

Our initial study [1(c)] of the acid catalysed synthesis of Q[*n*] concluded that a precursor oligomer is formed in which the glycoluril units are linked with their concave faces on the same or opposite sides of an oligomeric ribbon (mixed exo-endo conformation). The oligomer subsequently undergoes an acid catalysed disconnection and reconnection of the methylene linkers to form an oligomer ribbon, which adopts an all-endo conformation prior to condensation to a Q[*n*]. The ribbon carries an array of carbonyl oxygens and naturally curves into a loop (all-endo) (Figure 1). The oligomer ribbon could, in principle, bind alkali metal cations at the edges of the ribbon. A ribbon loop would have significantly greater flexibility than a closed Q[*n*], and could potentially accommodate any of the alkali metal cations. Individual alkali metal cations are likely to act as templates leading to particular sizes of Q[*n*]. We propose that the ionic radius of an alkali metal cation governs the size of the Q[*n*] formed, as is the case for the synthesis of crown ethers. Similarly, the addition of NH_4^+ could influence the ring size, by hydrogen bonding and electrostatic interactions with the carbonyl oxygens.

This paper describes the effects of alkali metal cations on the product distributions in Q[*n*] synthesis, under two sets of reaction conditions. *Method A* utilises the generation of the oligomer *in situ*, in the presence of cations, before the continued reaction to Q[*n*]. *Method B* involves the synthesis and isolation of the preformed oligomer [1(c)], followed by synthesis of Q[*n*] in the presence of metal cations. We also outline the optimisation of the synthesis of Q[5].

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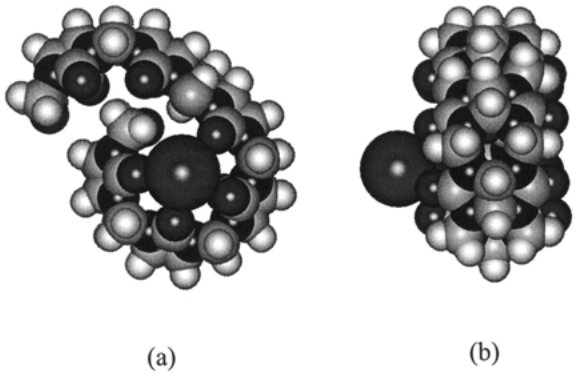

Figure 1. Molecular model of a hexameric oligomer ribbon associated with a metal cation. (a) Top view of developing carbony portal; (b) Side view.

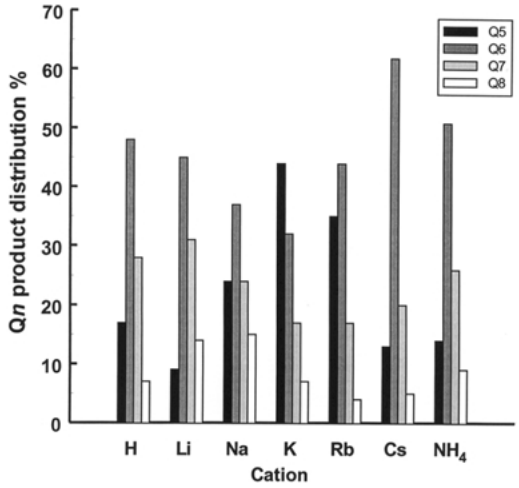

Figure 2. The acid catalysed synthesis of Q[*n*], from glycoluril and formaldehyde in the presence of alkali metal chlorides and NH_4Cl (*Method A*).

Experimental

All alkali metal chlorides and ammonium chloride were analytical grade commercial materials and used as supplied. Reactions were conducted on several scales, including that suitable for an NMR tube (80 mg), or up to 500 mg of glycoluril or preformed oligomer.

Typical reactions

Method A. Glycoluril (500 mg, 3.4 mmol) and the alkali metal chloride (1.7 mmol) were added to 32% HCl (2.8 mL). Shortly afterwards, paraformaldehyde (222 mg) was added to the solution. After 30 min, the clear gel that formed was heated to 90–100 °C for 3 h.

Method B. Preformed oligomer [1(c)] (500 mg) and the alkali metal chloride (1.7 mmol) were added to 32% HCl (2.8 mL) and heated to 90–100 °C for 3 h. The amount of alkali metal chloride was relative to the molecular weight of 166 for a monomeric unit of the preformed oligomer.

After 3 h, the solutions were homogeneous for both *Methods A* and *B*. Samples were taken and examined by ^{13}C NMR spectroscopy. The wt% of Q[*n*] (*n* = 5–8, 10) was determined by integrating the methine ^{13}C resonances [1(c)]. The total area attributable to known and clearly identifiable Q[*n*] signals was 95–97% of the total area for the reactions with the preformed oligomer, except for the examples, NaCl, RbCl, CsCl and NH_4Cl, which were 87–92%. In general, the reactions were 10% cleaner starting from the oligomer (*Method B*). All Q[*n*] described in this study have been previously discussed and characterised [1].

Synthesis of cucurbit[5]uril

Q[5] was synthesised using *Method B* from preformed oligomer (10 g) and potassium chloride (2.5 g) in 32% HCl (55 mL). After 3 h, the acid was removed *in vacuo*, H_2O (25 mL) was added to the residue and this mixture was neutralised with solid $KHCO_3$. After heating to boiling and cooling to 5 °C a white solid formed, which was collected by filtration, 4.0–4.6 g (mixture of Q[5] and Q[8]). This material was dissolved in hot conc HCl (10 mL) and a hot solution of 5% aqueous NH_4Cl (40 mL) was added. The mixture was boiled briefly, then cooled to 5 °C and filtered to remove Q[8] [1] 780 mg. The water and HCl were removed *in vacuo*, then additional water (20 mL) was added to the residue, followed by sufficient solid KOH to raise the pH to 7. Above pH 7 the further addition of KOH (2.2 g) gave a white precipitate. After cooling to 5 °C, a Q[5] potassium salt (purity > 99%) was collected by filtration and washed thoroughly with H_2O. Drying the product at 80 °C yielded 2.8–3.2 g, 28–32%. ^1H and ^{13}C NMR spectra (in 35% DCl/D_2O) of Q[5] [1] and this product were identical. Elemental analysis of the product showed it was a new complex, cucurbit[5]uril.1.5KOH.2KCl; *Calcd*: $C_{30}H_{30}N_{20}O_{10}$. 1.5KOH.2KCl: C 33.87, H 2.98, N 26.33, K 12.86, Cl 6.66. *Found*: C 34.24, H 3.68, N 26.85, K 13.64, Cl 6.67. Potassium-free Q[5] was obtained by repetitive recrystallisation from conc HCl.

Results and discussion

The effect of cations on the synthesis of Q[*n*] was tested in two ways: firstly, by adding ammonium and alkali metal chloride salts to conc HCl solutions of glycoluril and formaldehyde (*Method A*), and secondly, by adding the salts to solutions containing preformed oligomer (*Method B*). We have previously established that HCl is a very effective medium in which to synthesise Q[*n*] as mixtures. In conc HCl (90–100 °C), without an alkali metal salt present and where the concentration of glycoluril was 0.19 g mL^{-1} of acid solution, the product distribution [1(c)] for Q[5], Q[6], Q[7] and Q[8] was found to be 17, 48, 28 and 7% respectively. When the reactions were carried out at the same concentrations as above, with the addition of 0.5 mol equivalents (relative to glycoluril) of the alkali metal chloride, the distribution of Q[5–8] changes significantly. These results are summarised in Figure 2.

The proportion of Q[5–8] varies by 35, 30, 14 and 11 wt%, respectively, in the presence of the individual cations, H^+, Li^+, Na^+, K^+, Rb^+, Cs^+, or NH_4^+, as shown in Figure 2. Li^+ (ionic radius 0.76 Å) [6] unexpectedly favours

the higher homologues Q[6–8], and K^+ (ionic radius 1.38 Å) [7] favours Q[5]. The chlorides were used throughout these studies to avoid possible differences due to anionic effects.

The results shown in Figure 2 initially appear inconsistent with our alkali metal cation templating model, in which we assume that cation size directly determines the size of the oligomeric loop, and hence the size of the Q[*n*]. This model predicts that Li^+ would favour the formation of a relatively small Q[*n*], and similarly, Cs^+ would favour a larger Q[*n*]. Our results show no obvious correlation between the Q[*n*] product distribution and the ionic radii of the metal cations and their coordination spheres [8]. The presence of cations does affect this distribution, but the relationship is more complex than our proposed model. The metal salts are likely to affect the formation of the oligomer, either by dictating the length of the oligomer, or by influencing the proportion of exo to endo combinations, or both. The predominance of Q[5] in the presence of K^+ might be explained on the basis that K^+ favours endo oligomer growth, and at a length of five glycoluril units, the formed loop immediately closes to Q[5].

The addition of Li^+ to the reaction mixture leads to an increase in the proportion of Q[7] and Q[8]. This outcome might be due to the formation of short oligomers, such as endo-trimers and tetramers, which then condense with each other and cyclise to increase the proportion of these larger Q[*n*]. Our model suggests that Li^+, with its small ionic radius, should favour coordination with four oxygens, as in the templated crown ether synthesis [5]. The model suggests that the formation of Q[4] should be favoured for reactions carried out in the presence of Li^+. The proportion of alkali metal cation added, (0.5 mol equivalents relative to glycoluril), was sufficient to coordinate to both carbonyl-crowns of a 4-unit all-endo oligomer, and should allow the formation of Q[4]. However, no NMR resonances were observed that could be attributed to Q[4]. The absence of Q[4] is supported by theoretical calculations [9].

Where the solubility of the alkali metal salts is not a limiting factor, we observed that an increase in the proportion of salt relative to glycoluril has little or no effect on the proportional distribution of Q[*n*]. This suggests that the 0.5 mol equivalents of salts left no free coordination sites.

When monitoring the effects of K^+ on the synthesis of Q[*n*], from glycoluril and formaldehyde, we noted that the Q[5]@Q[10] complex [10] formed as a significant proportion (5%) of the Q[*n*] mixture. The addition of K^+ produced a high proportion of Q[5]. The extent of formation of Q[5]@Q[10] most likely reflects the high proportion of Q[5], combined with the stabilisation of Q[10] by encapsulated Q[5]. Alternatively, K^+ might stabilise an all-endo loop of 10 glycoluril units. This oligomer ribbon could adopt a figure-of-eight geometry of two loops of 5 units (apparently the optimum size for K^+) before cyclisation to Q[10]. Since the mixture was homogeneous throughout the reaction, precipitation was not a driving force to yield the high proportions of Q[5].

To eliminate any possible effects of the cations upon oligomer formation, we carried out the same series of alkali metal cation reactions, but instead starting with the preformed oligomer (*Method B*). The oligomer was prepared as previously described in conc HCl [1(c)]. By contrast with the results shown in Figure 2 (*Method A*), *Method B* shows a correlation between the radii of the cations and the preferential formation of Q[5] or Q[6] (Figure 3). Li^+, Na^+, K^+ and Rb^+ show enhanced selectivity for Q[5], with >20% increase compared with the product distribution in the absence of a metal cation. The maximum selectivity for Q[5] again occurs with the addition of K^+. The optimal selectivity for Q[6] occurs in the presence of the comparatively large Cs^+ ion. The effect of the ammonium ion falls between those of Rb^+ and Cs^+. While Li^+, the smallest of the alkali metal ions, favours the production of Q[5], the selectivity is less than optimal compared with K^+. The direct interaction between the preformed oligomer and Li^+ in Method B contrasts with the more involved reaction pathways possible in Method A. The absence of Q[4] as an optional product in the cucurbituril family [1, 9] suggests that Li^+ influences the formation of Q[5] from preformed oligomer through less than ideal coordination to give predominantly the smallest possible Q[*n*].

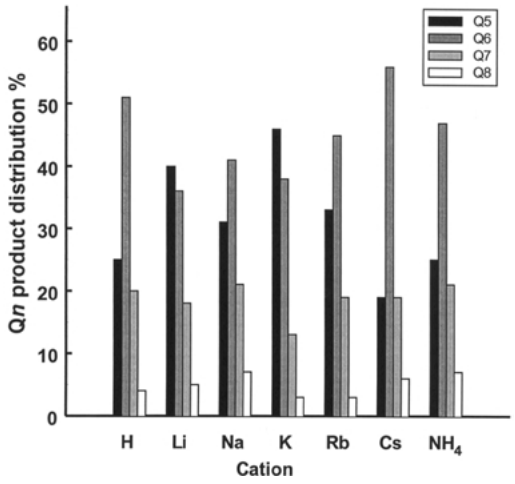

Figure 3. The acid catalysed synthesis of Q[*n*], from the preformed oligomer precursor in the presence of alkali metal chlorides or NH_4Cl (*Method B*.

The preformed oligomer, which is a mixture of exo-endo conformers, must form an all-endo-loop to cyclise to Q[*n*]. The results indicate that the metal cations are acting as templates for the formation of particular Q[*n*], under these conditions (*Method B*), and in accordance with our proposed model. The alkali metal cations are likely to influence the formation of different Q[*n*] through a process of coordination of the cations to the carbonyls, and stabilisation of endo-loops. We expect that the selectivity in the synthesis of Q[*n*] is influenced by the size of the coordination sphere surrounding each metal cation. Furthermore, the K^+ preferred formation of Q[5], at the expense of Q[6] and Q[7], supports a proposed oligomeric ribbon [1(c)] cyclising at an intermediate point along the preformed oligomer. The presence, absence, or choice of cation shows no obvious pattern, or influence, on the product distribution of Q[7] or Q[8]. The insensitivity of the product distribution of Q[7–8] to

metal cations, supports the proposal that the metal cations predominantly stabilise the 5 and 6 units of the endo oligomer, which subsequently closes to form Q[5] and Q[6]. We have achieved an improved synthesis of Q[5] using this templating method (KCl). We have also developed an effective method for the purification of Q[5] by taking advantage of the insolubility of a potassium salt of Q[5], in neutral or basic aqueous solutions. Additional improvements are under investigation in order to establish an efficient method for removing potassium from the Q[5] complex. During our studies of the synthesis of Q[n], we have observed evidence for anion binding in Q[5] [1(c), 10]. NO_3^- has been reported in the cavity of Me_{10}Q[5] [11]. The presence of an electropositive cavity in Q[5] [1(c)], which would be very similar to those in the endo- loops of oligomers, suggests that anions might also play a templating role in the selective synthesis of Q[n].

Chloride was used as the sole anion in this work, but the effect of other anions in the synthesis of Q[n] is currently under investigation.

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