Cucurbit[7]uril complexes of bis(isoquinolinium)alkane dicitcations in aqueous solution

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The 1:1 and 2:1 host–guest complexation of a series of 1,n-bis(isoquinolinium)alkane dications (Iq(CH2)nIq2^+, n = 2, 4, 5, 6, 8, 9, 10 and 12, and Iq(p-xylene)Iq2^+) by cucurbit[7]uril (CB[7]) in aqueous solution has been investigated by 1H NMR spectroscopy and ESI mass spectrometry. The site of binding of the first CB[7] is dependent on the nature of the central linker group, with encapsulation of the p-xylene group or the polymethylene chain when n = 6–10. With shorter (n = 2–5) or longer (n = 12) chains, the first CB[7] binds over an isoquinolinium group. With a second CB[7], the binding of the central group is abandoned in favour of the CB[7] hosts encapsulating the two cationic isoquinolinium termini. The 1:1 and 2:1 host–guest stability constants are related to modes of binding and the nature of the central linkers, and are compared with dicationic guests bearing different terminal groups.

Keywords: cucurbit[7]uril; isoquinolinium; host–guest; complexation; quaternary iminium cations

Introduction
The cucurbit[8–24]urils (CB[n], n = 5–8, 10, 14) are a family of macrocyclic host molecules comprised of n glycoluril units bridged by 2n methylene groups (1–5). The symmetrical CB[n] host molecules possess a hydrophobic cavity of very low polarisability (6) and two constrictive polar, ureido carbonyl-lined portals capable of ion–dipole and dipole interactions with guest molecules. The cavity and portal regions of the host employ hydrophobic interactions and electrostatic interactions, respectively, to provide for remarkably strong binding to a larger variety of organic and organometallic guests in aqueous solution (7). The release of high-energy water molecules from the cavity of CB[n] has also been shown to play a large role in the host–guest stability (8). As a result of ion–dipole interactions with the portal carbonyl groups, cationic guest molecules can form extremely stable host–guest complexes with cucurbiturils (7), particularly with CB[7] (Figure 1) which is the most soluble member of the non-substituted CB[n] family.

The interest in the encapsulation of drugs and other guests of biological and medicinal relevance by cucurbiturils has increased considerably in recent years (9–16) and promises further attention in light of recent studies indicating that the CB[n] hosts and their host–guest complexes are comparatively non-toxic in nature (17–19). Amongst the groups of drug molecules having received considerable study are the isoquinoline alkaloids (20), including berberine (21, 22), palmatine (23, 24), sanguinarine (25, 26) and coptisine (27). The hydrophobic aromatic rings, coupled with the positively charged nitrogen centre, provide for synchronous attractions of these regions to the cavity and portals, respectively, of the cucurbituril host molecules.

The simplest cationic derivative of isoquinoline, the N-methylisoquinolinium cation, has been frequently used as a guest species by the research groups of Dougherty (28–34) and Otto (35–38) to investigate the host–guest complexes of a variety of cyclophane host molecules in aqueous solution. It possesses both a cationic group and aromatic rings, such that it can interact with the host molecules using non-covalent ion–ion, ion–dipole, cation–π and π–π stacking interactions, in addition to the hydrophobic effect. Most recently, Otto’s group has incorporated the isoquinolinium group into a multivalent guest (38).

The antibacterial and antifungal activities of 1,n-bis(isoquinolinium)dications (Iq(CH2)nIq2^+, n = 10–20) were recognised nearly 60 years ago by Collier and co-workers (39–41). The antibacterial activity of Iq(CH2)nIq2^+ increases with the polymethylene chain length from n = 10 to n = 16, after which the activity plateaus (41, 42). A series of halide salts of polymethylene bridged 1,n-bis(isoquinolinium) dications (Iq(CH2)nIq2^+, n = 1–12) have recently been synthesised and investigated by Kuca and co-workers in terms of their anticholinesterase activity, particularly in the brain, which are associated with neurological diseases, such as Alzheimer’s (43) and myasthenia gravis (44). The inhibition potencies towards acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) were highest for n = 8 and 12, respectively, and were comparable to or exceeded the potencies of the standard anticholinesterase inhibitors BW284c51 (AChE) and...
ethopropazine (BChE). It has been demonstrated that the 1, n-bis(isoquinolinium)alkane dications have a strong affinity for the anionic binding area of the blood–brain barrier choline transporter, with $K_i$ values of 29, 10 and 22 μM for $n = 6, 10$ and 12, respectively (45). The in vitro studies of the brain anticholinesterase activity revealed that the activity of the dication increased with the polymethylene chain length, from $n = 1$ to $n = 11$, with the 1,12-bis(isoquinolinium)dodecane dication exhibiting activity between $n = 8$ and 9, likely as a result of its difficulty in fitting within the enzyme cavity. It was recently reported that while Iq(CH$_2$)$_8$Iq$^2^+$ is a potent AChE inhibitor, it has no effect as an antidote pre-treatment against soman poisoning in mice (46). A number of N-alkylated isoquinolinium cations have also been proven to be very useful ionic liquids (47).

With the CB[7] host, cationic moieties can be included in the host cavity provided they are of the correct size and are sufficiently hydrophobic. The tetraalkylammonium and tetraalkylphosphonium cations, for example, may be completely encapsulated within the cavity in the case of NMe$_4^+$ and PMe$_4^+$, while fewer of the aliphatic arms are bound as the size of the alkyl group increases (48). The CB[7] complexations of a variety of dicationic guests (49–55) of the type R(CH$_2$)$_n$R$^2^+$ (where the terminal R groups have included trialkylammonium, quinuclidinium, pyridinium and N-methylmorpholinium) and other related dications, including AChE inhibitors succinylcholine, decamethonium, and BW284c51, have previously been investigated in aqueous solution. With these and other extended dicationic guests (56–59), over which two or three CB[7] may reside, the locations of the host molecule (terminal moieties versus central linker) at the different host–guest complex stoichiometries have been found to be dependent on the size and hydrophobicity of the terminal groups and the nature and length of the central linker.

In this paper, we describe an investigation into the host–guest complexations of N-methylishoquinolinium cation (MeIq$^+$), the bis(isoquinolinium)alkane dications, Iq(CH$_2$)$_n$Iq$^2^+$, where $n = 2, 4, 5, 6, 8, 9, 10$ and 12, and Iq(p-xylene)Iq$^2^+$ (Figure 1) by cucurbit[7]uril in aqueous solution, using $^1$H NMR spectroscopy and electrospray ionisation mass spectrometry. The effects of the polymethylene or p-xylene linker groups on the CB[7] complexation behaviour will be discussed and compared with those of other extended dicationic guests.

**Experimental**

**Materials**

Cucurbit[7]uril was prepared and characterised by the methods of Day and co-workers (60). The starting materials and other chemicals were used as received from Sigma-Aldrich (Milwaukee, WI, USA). The N-methylisoquinolinium iodide was prepared by reacting isoquinoline with methyl iodide.

**N-methylisoquinolinium iodide**

Isoquinoline (1.29 g, 10 mmol) was added to a flask containing methyl iodide (1.3 ml, 40 mmol) in acetonitrile.
(15 ml) and refluxed for 24 h. The solution was allowed to cool to room temperature before adding diethyl ether to precipitate a bright yellow product. The product was then filtered and washed with diethyl ether. Yield: 56%. M.p. 162–165°C. Lit. 161–163°C (61). \(^1\)H NMR (D2O, 500 MHz) \(\delta\) 9.65 (s, 1H, H1), 8.40–8.44 (m, 3H, H3, H4, H8), 8.26 (d, 1H, \(J = 7.0\) Hz, H5), 8.22 (t, 1H, \(J = 7.0\) Hz, H7), 8.04 (t, 1H, \(J = 7.0\) Hz, H6) and 5.57 (s, 2H, H8) ppm.

The bromide or iodide salts of 1,2-bis(isoquinolinium)alkane dications (\(n = 2, 4, 5, 6, 8, 9, 10\) and 12) and \(\alpha,\alpha'\)-bis(isoquinolinium)-p-xylene dibromide were prepared using modifications of a method outlined by Kuca et al. (43, 44). A mixture of the appropriate 1,2-bis(isoquinolinium)alkane dibromide or diiodide (1.0 mmol) or \(\alpha,\alpha'\)-dibromo-p-xylene (1.0 mmol) and isoquinoline (9.0 mmol) in DMF was heated at 70°C for 1–4 days. The addition of diethyl ether to the cooled solution resulted in a light brown precipitate, which was filtered and washed with diethyl ether.

1,2-Bis(isoquinolinium)ethane dibromide

Yield 61.2%. M.p. 272–274°C. Lit. 269–271°C (43, 44). \(^1\)H NMR (D2O) \(\delta\) 9.66 (s, 2H, H1), 8.48 (s, 4H, H3 and H4), 8.26 (m, 6H, H5, H7 and H8), 8.04 (t, 2H, \(J = 7.5\) Hz, H6) and 5.57 (s, 2H, H8) ppm.

1,4-Bis(isoquinolinium)butane diiodide

Yield 59%. M.p. 247–250°C. Lit. 247–249°C (62). \(^1\)H NMR (D2O) \(\delta\) 9.66 (s, 2H, H1), 8.48 (s, 4H, H3 and H4), 8.26 (m, 6H, H5, H7 and H8), 8.04 (t, 2H, \(J = 7.5\) Hz, H6) and 5.57 (s, 2H, H8) ppm.

1,5-Bis(isoquinolinium)pentane dibromide

Yield 53%. M.p. 209–210°C (43, 44). \(^1\)H NMR (D2O) \(\delta\) 9.60 (s, 2H, H1), 8.42 (d, 2H, \(J = 6.5\) Hz, H3), 8.31 (d, 2H, \(J = 6.5\) Hz, H4), 8.29 (d, 2H, \(J = 7.5\) Hz, H5), 8.19 (m, 4H, H7 and H8), 8.00 (t, 2H, \(J = 7.5\) Hz, H6), 4.72 (t, 4H, \(J = 8.0\) Hz, H3), 2.16 (qn, 4H, \(J = 8.0\) Hz, H6) and 1.32 (qn, 2H, \(J = 8.0\) Hz, H4) ppm.

1,6-Bis(isoquinolinium)hexane diiodide

Yield 31%. M.p. 241–243°C. Lit. 233–234°C (62). \(^1\)H NMR (D2O) \(\delta\) 9.64 (s, 2H, H1), 8.45 (d, 2H, \(J = 7.5\) Hz, H3), 8.34 (m, 4H, H4 and H5), 8.20 (m, 4H, 8.45 (m, 2H, H7 and H8), 8.01 (t, 2H, \(J = 7.5\) Hz, H6) 4.70 (t, 4H, \(J = 7.0\) Hz, H3), 2.08 (qn, 4H, \(J = 7.0\) Hz, H6) and 1.40 (qn, 4H, \(J = 7.0\) Hz, H3).

**Methods**

The \(^1\)H NMR spectra were recorded on a Bruker Avance 500 MHz instrument (Bruker Biospin Ltd., Milton, ON, Canada). High-resolution electrospray ionisation mass spectra were recorded on a Waters 2Q Single Quadrupole MS spectrometer equipped with an ESI/APcI multiprobe. The samples prepared in distilled water and the spectra...
were acquired in the positive ion mode. The CB[7] host–guest stability constants were determined using $^{1}$H NMR competitive binding experiments in D$_2$O containing a buffer mixture (pD = 4.75) of 0.050 M deuterated sodium acetate and 0.025 M DCI, and analysed using the method of Isaacs and co-workers ($^{63}$). Benzyltrimethyl ammonium bromide $[K_{CB[7]} = (2.5 \pm 0.6) \times 10^8 \text{M}^{-1} \text{(48)}]$ and 1,6-diamino-hexane dihydrochloride $[K_{CB[7]} = (8.97 \pm 1.43) \times 10^7 \text{M}^{-1} \text{(63)}]$ were used as the competitor guests.

Results and discussion

The formation of 1:1 and 2:1 host–guest complexes between cucurbit[7]uril and the 1,$n$-bis(isoquinolinium)alkane dication (Iq(CH$_2$)$_n$Iq$^{2+}$) series of guests in aqueous solution was confirmed by electrospray ionisation mass spectrometry and $^1$H NMR spectroscopy. The electrospray ionisation mass spectra of the Iq(CH$_2$)$_n$Iq$^{2+}$ dications in the presence of a five-fold excess of CB[7] contain peaks for both the 1:1 {CB[7]·Iq(CH$_2$)$_n$Iq}$^{2+}$ and the 2:1 {CB[7]·Iq(CH$_2$)$_n$Iq·CB[7]}$^{2+}$ host–guest complexes (Table S1, Supplemental Material). The formations of host–guest complexes of cucurbiturils are conveniently monitored by $^1$H NMR spectroscopy as the proton resonances of the guest molecules exhibit significant chemical shift changes ($\Delta \delta_{\text{lim}} = \delta_{\text{bound}} - \delta_{\text{free}}$) upon complexation. The resonances of protons located within the hydrophobic cavity are shifted upfield ($\Delta \delta < 0$ ppm), while those located adjacent to the polar carbonyl-rimmed portals experience downfield shifts ($\Delta \delta > 0$ ppm). Representative titrations of the Iq(CH$_2$)$_n$Iq$^{2+}$ guests towards CB[7] are shown for $n = 4$ (Figure 2), $n = 8$ (Figure 3) and $n = 12$ (Figure 4) and the limiting chemical shift changes upon formations of the 1:1 {CB[7]·Iq(CH$_2$)$_n$Iq}$^{2+}$ and 2:1 {CB[7]·Iq(CH$_2$)$_n$Iq·CB[7]}$^{2+}$ host–guest complexes (along with the values for Iq(p-xyl)Iq$^{2+}$ and IqCH$_3$$^{+}$) are presented in Tables 1 and 2, respectively.

1:1 Host–guest complexes

The complexation behaviours of the Iq(CH$_2$)$_n$Iq$^{2+}$ guests towards CB[7] depend on the length of the polymethylene bridge between the two isoquinolinium groups. This aliphatic bridge would provide a potential site of binding for CB[7] by resulting in the placement of a positively charged iminium nitrogen adjacent to each of the two polar portals of the host. The polymethylene bridge would, however, be in competition as a binding site with the two terminal isoquinolinium groups, which offer both a positive charge for ion–dipole interactions with a CB[7] portal and a hydrophobic aromatic framework which is appropriately sized for the CB[7] cavity.

The encapsulation of the central polymethylene bridge by the first equivalent of CB[7] would be expected to result in upfield shifts in the polymethylene proton resonances and likely downfield shifts in resonances for the isoquinolinium protons H1 and H3. For the Iq(CH$_2$)$_n$Iq$^{2+}$ guests with $n = 6, 8, 9$ and $10$, pronounced upfield shifts in the polymethylene guest proton resonances upon addition of one equivalent of CB[7] are observed [Figure 3 ($n = 8$) and Table 1], while with the longest guest, Iq(CH$_2$)$_{12}$Iq$^{2+}$,
a pseudorotaxane, stabilised by the ion–dipole interactions at both portals (Figure 5). With the shorter chains, with \( n = 2, 4 \) and 5, however, the polymethylene proton resonances shift uniformly in a downfield direction (Figure 2 \((n = 4)\) and Table 1), with upfield shifts in most of the isoquinolinium proton resonances. With shorter chain lengths \((n = 2–5)\), the encapsulation of the polymethylene bridge would place the positive charges on the isoquinolinium groups within the CB[7] cavity, rather than adjacent to the polar carbonyl groups of the portals, and hence binding occurs over one of the isoquinolinium groups (Figure 5). With the longest guest, the length of the polymethylene chain prevents the two portals of the CB[7] from interacting with positive charges simultaneously. The \( \alpha,\alpha'-\text{bis(isoquinolinium)-}p\)-xylene dication \([\text{Iq}(p\text{-xyl})\text{Iq}^+\text{Iq}^+\text{Iq}^+\text{Iq}^+]\) binds to the first CB[7] over the \( p\)-xylene linker, with large upfield shifts in the H\( \alpha \) and phenyl proton resonances.

In addition to the CB[7] complexation-induced chemical shift changes in the guest protons, the resonances for the protons on the CB[7] host molecule were also shifted by inclusions of the guest molecules. The CB[7] resonances are a singlet at 5.46 ppm for the methine glycoluril protons and two non-equivalent protons on the methylene bridges, doublets at 5.71 ppm (proton pointing towards the portals) and 4.16 ppm (proton pointing away from portals). The degree of the shift of the host protons depends on whether the CB[7] resides over the symmetric polymethylene chains or the asymmetric isoquinolinium rings. When located over the polymethylene linker, there are no significant shifts in the CB[7] resonances. The encapsulation of the isoquinolinium group leads to an upfield shift of about 0.10 ppm from the methine resonance at 5.46 ppm in free CB[7], and upfield shifts of about 0.10 and 0.06 ppm from the free CB[7] resonances at 5.71 and

The dodecamethylene proton resonances exhibit a modest downfield shift (Figure 4) throughout the titration with CB[7]. These observations indicate that with moderate chain lengths of \( n = 6–10\), the first equivalent of CB[7] prefers to reside over the central polymethylene group, generating a pseudorotaxane, stabilised by the ion–dipole

Figure 4. \(^1\text{H} \) NMR spectra of the 1,12-bis(isoquinolinium) dodecane dication (1.00 mM) in the presence of (a) 0.00, (b) 0.51, (c) 1.10, (d) 1.55, (e) 2.14 and (f) 2.45 equivalents of CB[7] in D\(_2\)O.

Table 1. The limiting \(^1\text{H} \) NMR chemical shift changes (\( \Delta\delta_{\text{lim}} \)) in the proton resonances of the \( N\)-methylisoquinolinium cation, and \( 1, n\)-bis(isoquinolinium)alkane and \( \alpha,\alpha'-\text{bis(isoquinolinium)-}p\)-xylene dication guests upon encapsulation by one CB[7] host molecule.

| Proton label | \( n = 2 \) | 4 | 5 | 6 | 8 | 9 | 10 | 12 | p-xyl | MeIq\(^+\) |
|-------------|----------|---|---|---|---|---|---|---|---|------|
| 1           | −0.03    | −0.29 | −0.27 | −0.10 | −0.17 | −0.21 | −0.19 | −0.30 | +0.04 | −0.79 |
| 3           | +0.16    | 0   | 0   | −0.01 | +0.14 | +0.17 | +0.17 | +0.06 | +0.19 | −0.17 |
| 4           | −0.13    | −0.34 | −0.30 | −0.02 | +0.22 | +0.15 | +0.05 | −0.41 | +0.24 | −0.96 |
| 5           | −0.85    | −0.28 | −0.43 | −0.07 | +0.02 | −0.01 | −0.08 | −0.43 | −0.20 | −1.04 |
| 6           | −0.59    | −0.20 | −0.19 | −0.06 | +0.01 | −0.02 | −0.04 | −0.2  | 0     | −0.47 |
| 7           | −0.70    | −0.19 | −0.17 | −0.12 | +0.01 | −0.02 | −0.03 | −0.21 | +0.02 | −0.46 |
| 8           | −1.00    | −0.34 | −0.37 | −0.09 | +0.02 | −0.03 | −0.02 | −0.40 | −0.07 | −1.07 |
| \( \alpha \) | +0.13    | +0.13 | −0.02 | −0.37 | −0.33 | −0.20 | −0.09 | +0.01 | −0.41 | +0.09 |
| \( \beta \) | +0.10    | +0.13 | −0.26 | −0.36 | −0.29 | −0.15 | +0.07 | −0.98\(^a\) |        |       |
| \( \gamma \) |         | +0.32 | −0.21 | −0.39 | −0.30 | −0.18 | +0.15 |       |        |       |
| \( \delta \) |         | −0.39 | −0.39 | −0.32 | −0.32 | +0.06 |       |        |        |       |
| \( \epsilon \) |        | −0.36 | −0.28 | +0.04 |       |        |        |        |        |       |
| \( \epsilon \) |        | +0.04 |       |        |        |        |        |        |        |       |

Note: Proton labels are given in Figure 1.

\(^a\) Phenyl protons of \( p\)-xylene bridge.
4.16 ppm, respectively, for the host methylene protons near the portal through which the isoquinolinium group is projecting.

2:1 Host–guest complexes

For all of the dicationic guests in this study, the addition of further equivalents of CB[7] results in changes to the ¹H NMR spectra (Figures 2–4), which are consistent with the formation of 2:1 host–guest complexes in which the two host molecules are encapsulating the terminal isoquinolinium groups, rather than residing over the central polymethylene or p-xylene linkers (Figure 6). With the shorter (n = 2, 4 and 5) and longest (n = 12) chains, this is represented by increases in the chemical shift changes (Table 2) in the directions observed for the formation of the 1:1 complexes, as the first CB[7] host resided over one of the isoquinolinium group. In the case of Iq(CH₂)nIq²⁺, the resonances for the isoquinolinium H1, H3 and H4 protons, as well as the bridging ethylene protons, are considerably more downfield for the 2:1 host–guest complex than is observed with the more extended guests (Table 3). This indicates that these protons are experiencing the deshielding effects of carbonyl groups on a polar portal from both CB[7] host molecules and/or dipole–dipole repulsions between the two host molecules prevent as deep an inclusion of the isoquinolinium groups as would

Table 2. The limiting ¹H NMR chemical shift changes (Δδlim) in the proton resonances of the 1,n-bis(isoquinolinium)alkane and α,α’-bis(isoquinolinium)-p-xylene dication guests upon encapsulation by two CB[7] host molecules.

| Proton label | n = 2 | 4  | 5  | 6  | 8  | 9  | 10 | 12 | p-xyl |
|-------------|------|----|----|----|----|----|----|----|------|
| 1           | -0.16| -0.60| -0.59| -0.70| -0.75| -0.77| -0.80| -0.79| -0.57 |
| 3           | +0.51| +0.01| -0.06| -0.22| -0.20| -0.18| -0.18| -0.20| -0.25 |
| 4           | -0.13| -0.65| -0.80| -0.80| -0.90| -0.90| -0.90| -0.90| -0.68 |
| 5           | -0.84| -0.82| -0.98| -0.97| -1.02| -1.04| -1.00| -0.99| -0.99 |
| 6           | -0.59| -0.50| -0.51| -0.46| -0.50| -0.46| -0.45| -0.46| -0.50 |
| 7           | -0.71| -0.63| -0.47| -0.46| -0.53| -0.46| -0.43| -0.44| -0.50 |
| 8           | -0.13| -0.64| -0.92| -0.98| -1.03| -1.00| -1.04| -0.95| -0.96 |
| α           | +0.51| +0.57| +0.22| +0.20| +0.05| +0.09| +0.09| +0.07| +0.18 |
| β           | +0.44| +0.39| +0.36| +0.28| +0.25| +0.22| +0.20| +0.20| +0.25a |
| γ           | +0.65| +0.52| +0.43| +0.39| +0.38| +0.38| +0.34|     |     |
| δ           | +0.43| +0.33| +0.33| +0.33| +0.33| +0.29|     |     |     |
| ε           | +0.33| +0.32| +0.29|     |     |     |     |     |     |
| η           |     |     |     |     |     |     |     |     |     |

Note: Proton labels are given in Figure 1.

a Phenyl protons of p-xylene bridge.

Figure 5. Proposed structures of the 1:1 host–guest complexes: {CB[7]·Iq(CH₂)nIq}²⁺ and {CB[7]·Iq(p-xyl)Iq}²⁺.

Figure 6. Proposed structures of the 2:1 host–guest complexes: {CB[7]·Iq(CH₂)nIq·CB[7]}³⁻²⁺ and {CB[7]·Iq(p-xyl)Iq·CB[7]}³⁻²⁺.
Table 3. Stability constants $K_1$ and $K_2$ for the formation of host–guest complexes between cucurbit[7]uril and 1,1-n-bis(isoquinolinium) alkane dications from this study and other dicationic guests from previous reports.

| Guest                  | $K_1$ (M$^{-1}$) | $K_2$ (M$^{-1}$) | $K_1/K_2$ | Ref. |
|------------------------|------------------|------------------|-----------|------|
| MeIq$^+$                | (8.5 ± 1.6) × 10$^7$ | Not observed      |           | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (3.1 ± 0.8) × 10$^9$ | (3.3 ± 0.6) × 10$^8$ | 9.4       | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (1.6 ± 0.4) × 10$^7$ | (7.0 ± 1.3) × 10$^7$ | 23        | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (7.7 ± 2.0) × 10$^8$ | (9.2 ± 1.7) × 10$^7$ | 8.4       | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (1.2 ± 0.3) × 10$^9$ | (1.6 ± 0.3) × 10$^8$ | 7.5       | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (2.9 ± 0.8) × 10$^9$ | (7.3 ± 1.4) × 10$^8$ | 4         | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (1.9 ± 0.5) × 10$^9$ | (1.1 ± 0.2) × 10$^8$ | 17        | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (1.6 ± 0.2) × 10$^9$ | (1.6 ± 0.3) × 10$^8$ | 10        | a    |
| Iq(CH$_2$)$_3$Iq$^{2+}$ | (5.9 ± 1.5) × 10$^8$ | (2.5 ± 0.5) × 10$^7$ | 24        | a    |
| Iq(p-xyl)Iq$^{2+}$      | (5.9 ± 1.5) × 10$^9$ | (8.1 ± 1.5) × 10$^8$ | 7.3       | a    |
| Me$_3$N(CH$_2$)$_6$Me$_3$N$^+$ | (3.9 ± 0.9) × 10$^9$ | Not observed      |           | 50   |
| Me$_3$N(CH$_2$)$_6$Me$_3$N$^+$ | (2.8 ± 0.8) × 10$^{10}$ | Not observed      |           | 50   |
| Me$_3$N(CH$_2$)$_6$Me$_3$N$^+$ | (2.6 ± 1.3) × 10$^9$ | <10               |           | 50   |
| Me$_3$N(CH$_2$)$_6$Me$_3$N$^+$ | (1.7 ± 0.2) × 10$^7$ | (9 ± 1) × 10$^7$  | 2 × 10$^6$ | 55   |
| Me$_3$N(CH$_2$)$_6$Me$_3$N$^+$ | (2.9 ± 0.7) × 10$^7$ | (3.5 ± 0.5) × 10$^7$ | 8 × 10$^6$ | 55   |
| Me$_3$N(CH$_2$)$_6$Me$_3$N$^+$ | (7.9 ± 0.9) × 10$^7$ | (1.4 ± 0.1) × 10$^7$ | 56        | 55   |
| Et$_2$N(CH$_2$)$_6$Net$^+$ | (1.4 ± 0.3) × 10$^7$ | 250 ± 30          | 5.6 × 10$^6$ | 50   |
| Me$_3$Iq(CH$_2$)$_3$Me$_3$Iq$^+$ | (9.0 ± 1.5) × 10$^7$ | (6.5 ± 0.5) × 10$^7$ | 1.4 × 10$^7$ | 50   |
| Et$_2$Iq(CH$_2$)$_3$Et$_2$Iq$^+$ | (6.8 ± 1.0) × 10$^8$ | (1.1 ± 0.2) × 10$^7$ | 6.2 × 10$^6$ | 50   |
| quin(CH$_2$)$_3$quin$^+$ | (1.9 ± 0.6) × 10$^{10}$ | (5.6 ± 3.2) × 10$^8$ | 34        | 51   |
| MeMom(CH$_2$)$_3$MeMom$^{2+}$ | (2.5 ± 0.4) × 10$^9$ | (2.3 ± 0.6) × 10$^6$ | 1.1 × 10$^3$ | 52   |
| MePyrr(CH$_2$)$_3$MePyrr$^{2+}$ | (5.2 ± 0.8) × 10$^8$ | (7.2 ± 1.4) × 10$^8$ | 7.2 × 10$^7$ | 52   |
| MePip(CH$_2$)$_3$MePip$^{2+}$ | (9.2 ± 1.8) × 10$^8$ | (8.6 ± 1.6) × 10$^8$ | 1.1 × 10$^7$ | 52   |
| py(CH$_2$)$_3$py$^{2+}$ | (3.1 ± 0.6) × 10$^{10}$ | Not observed      |           | 51   |
| dmapy(CH$_2$)$_3$dmapy$^{2+}$ | (7.4 ± 1.3) × 10$^7$ | (6.8 ± 2.6) × 10$^7$ | 2.2 × 10$^7$ | 51   |
| tpy(CH$_2$)$_3$tpy$^{2+}$ | (1.0 ± 0.2) × 10$^{11}$ | (8.1 ± 2.3) × 10$^8$ | 12        | 51   |
| py(CH$_2$)$_3$py$^{2+}$ | (4.8 ± 1.1) × 10$^{10}$ | (8 ± 2) × 10$^7$   | 6 × 10$^6$ | 51   |
| tpy(CH$_2$)$_3$tpy$^{2+}$ | (5.2 ± 1.2) × 10$^{10}$ | (2.1 ± 0.4) × 10$^9$ | 25        | 51   |
| tpy(p-xyl)tpy$^{2+}$ | (1.2 ± 0.3) × 10$^{11}$ | (7.9 ± 0.4) × 10$^8$ | 15        | 51   |
| Mebpyp(CH$_2$)$_3$Mebpyp$^{2+}$ | (6 ± 2) × 10$^{12}$   | (6.8 ± 0.5) × 10$^3$ | 9         | 49   |

Note: quin, quinuclidinium; MeMom, N-methylmorpholinium; MePyrr, N-methylpyrrolylindium; MePip, N-methylpiperidinium; py, pyridinium; dmapy, 4-dimethylaminopyridinium; tpy, 4-tert-butylpyridinium; Mebpyp, N-methylbipyrindinium.

*aThis work.*

be possible with the longer bridging polymethylene linkers. With the intermediate length ($n = 6$ and 8–10) polymethylene chains and the $p$-xyylene group, downfield shifts were observed in the proton resonances of the linker groups, as the first CB[7] translocated from the linker group to a terminal isoquinolinium group upon the arrival of the second CB[7] host. The broadening of the guest resonances in the course of the formation of the 2:1 complex (Figure 3) is attributable to the barrier to the reversible slippage of the CB[7] from the polymethylene chain to the isoquinolinium terminus, on the positive charge on the guest. This process, which removes any dipole–dipole repulsions which would occur if one CB[7] remained over the linker while the second CB[7] was bound to a terminal isoquinolinium group, has been observed previously with a variety of other $R$(CH$_2$)$_n$R$^{2+}$ guests in which the terminal group exhibits significant binding to CB[7]. A recent report by Pessego et al. (55) demonstrates that for the Me$_2$N(CH$_2$)$_6$Me$_3$N$^+$ dications, a polymethylene chain length of $n = 14$ is required before two CB[7] can simultaneously bind to the aliphatic linker without the use of added alkali metal cations to buffer the dipole–dipole repulsions between adjacent portals of the two hosts.

**Host–guest stability constants**

The $N$-methylisoquinolinium cation (IqMe$^+$) provides a good model for binding over the terminal ends of the dications. The CB[7] host–guest stability constant for the $N$-methylisoquinolinium cation was determined to be $(8.5 ± 1.6) × 10^7$ M$^{-1}$ from a $^1$H NMR competition experiment (59) using benzyltrimethylammonium bromide [K$_{CB[7]}$ = (2.5 ± 0.6) × 10$^7$ M$^{-1}$ (48)] as the competing guest. The 1:1 and 2:1 stability constants for the host–guest complexes between the Iq(CH$_2$)$_3$Iq$^{2+}$ and Iq(p-xyl)Iq$^{2+}$ guests were also calculated by means of $^1$H NMR competitive binding studies. When determining the 1:1 host–guest binding constants, benzyltrimethylammonium bromide was used as the competitor guest, while the determination of the 2:1 binding constant employed 1,6-diaminohexane dihydrochloride [K$_{CB[7]}$ = (8.97 ± 1.43) × 10$^7$ M$^{-1}$ (63)] as the competitor. Table 3 presents the 1:1 and 2:1 host–guest binding constants determined for the
For the Iq(CH$_2$)$_n$Iq$^{2+}$ guests, a decrease in the 1:1 host–guest binding constants with an increasing value of $n$ is observed for $n = 2–5$, as the second positive charge becomes further removed from the CB[7] host encapsulating one of the terminal isoquinolinium groups. For $n = 6–10$, where the CB[7] is located over the polymethylene chain, an increase is observed from $n = 6–8$, followed by a decrease until $n = 10$. For the longest chain in Iq(CH$_2$)$_{12}$Iq$^{2+}$, the smallest value of $K_1$ for the series is observed. The second binding constant for the 2:1 host–guest complex in which both CB[7] hosts are located over the terminal isoquinolinium groups, a similar trend with the value of $n$ is observed.

The ratio of $K_1/K_2$ varies from about 4 to 24 over the Iq(CH$_2$)$_n$Iq$^{2+}$ guest series (Table 3). A purely statistical model of 1:1 and 2:1 binding, in which the binding of the first host has no steric or electronic effect on the binding of the second guest, would predict a ratio of $K_1/K_2 = 4$ (64). The relatively low observed values of $K_1/K_2$ for the Iq(CH$_2$)$_n$Iq$^{2+}$ series suggests that the first CB[7] has no net effect on the strength of the binding of the second host. For the most extended guest, Iq(CH$_2$)$_{12}$Iq$^{2+}$, the statistical model would also suggest that the value of $K_1$ for IqMe$^{2+}$ guest (modelling binding to the isoquinolinium end group) should be similar to $(K_1K_2)^{1/2}$ for well-separated and non-interacting terminal isoquinolinium groups, and these two quantities are in reasonably good agreement with one another. For the shortest dication, Iq(CH$_2$)$_2$Iq$^{2+}$, the increased ion–dipole attractions between the guest’s two positive charges and the hosts’ polar portals would balance the dipole–dipole repulsions between the two CB[7] hosts.

A plot of log $K (K_1$ and $K_2$) against polymethylene chain length for the 1,n-bis(isoquinolinium)alkane dications and Me$_2$N(CH$_2$)$_n$NMe$_3^+$ dications ($K_1$), illustrating the trend in the stability constants with the length of the polymethylene linkers, is given in Figure 7. With the (CH$_3$)$_2$N(CH$_2$)$_n$N(CH$_3$)$_2^+$ series of guests ($n = 6, 8, 10$), it has previously been observed by Wyman and Macartney (50) that the stability of the 1:1 host–guest complex with CB[7] reached a maximum at $n = 8$ ($K_1 = 2.8 \times 10^{10} M^{-1}$), the same as observed for the Iq(CH$_2$)$_2$Iq$^{2+}$ series. More recently, Pessego et al. (55) have observed that this trend continues with lower values of $K_1$ when $n = 12, 14, 18$ and $20$. With the R(CH$_3$)$_2$R$^{2+}$ guests, the 1:1 and 2:1 host–guest stability constants (Table 3) are very dependent on the nature of the terminal group(s) to which the CB[7] host molecule(s) is bound. The observed trend (Table 3) of pyridinium < 4-dimethylaminopyridinium < isoquinolinium < 4-tert-butylpyridinium for $K_1$ may be related to the increased hydrophobicity of the terminal group. For R(CH$_3$)$_2$R$^{2+}$, with the exception of R = 4-tert-butylpyridinium, the values of $K_1$ (Table 3) are reasonably similar to one another ($10^7$ – $10^8 M^{-1}$), with small differences likely a result of differences in the relative delocalisation of the positive charge on the quaternary nitrogens.

Tao and co-workers have recently reported a similar change in the 1:1 and 2:1 binding modes for the sym-bis (benzimidazole)-2,2’-ethylene and sym-bis(benzimidazole)-2,2’-hexylene to that observed for Iq(CH$_2$)$_2$Iq$^{2+}$

Figure 7. Plots of the host–guest stability constants against the polymethylene bridge length in dicaticon guests with CB[7]: (○) $K_1$ for the 1,n-bis(isoquinolinium)alkane dications, (□) $K_2$ for the 1,n-bis(isoquinolinium)alkane dications, (■) $K_1$ for the [Me$_2$N(CH$_2$)$_n$NMe$_3$]$^{2+}$ dications and (▲) $K_1$ for the N-methylisoquinolinium cation. The lines are drawn for illustrative purposes.
and Iq(CH$_2$)$_n$Iq$^{2+}$, supported by $^1$H NMR chemical shift changes and a crystal structure for the 1:1 complex of CB [7] with sym-bis(benzimidazole)-2,2'hexylene (34). The results of this study and previous investigations on R (CH$_2$)$_n$R$^{2+}$ guests indicate that, provided the R termini can form stable complexes with CB[7] and allow passage of the host over the R group onto the polymethylene linker, the modes of binding of the CB[7] in the 1:1 and 2:1 host–guest complexes can be predicted from the length of the polymethylene chain.

Conclusions

Cucurbit[7]uril forms very stable 1:1 and 2:1 host–guest complexes with Iq(CH$_2$)$_n$Iq$^{2+}$ and Iq-p-xyl$Iq^{2+}$ cations in aqueous solution. With polymethylene central linkers where $n = 6$–10 or with p-xylene, the 1:1 complex involves encapsulation of the central binding site, while with shorter ($n = 2, 4$ and $5$) or longer ($n = 12$) chains, the CB[7] prefers to bind to the terminal isooquinolinium group. In the former case, the formation of the 2:1 host–guest complex involves the translocation of the original CB[7] to a terminal site, such that in all cases, the two host molecules in the 2:1 complexes encapsulate the terminal isooquinolinium groups.

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References

(1) Lagona, J.; Mukhopadlyay, P.; Chakrabarti, L.; Isaacs, L. Angew. Chem. Int. Ed. 2005, 44, 4922–4949.
(2) Kim, K.; Selvapalam, N.; Ko, Y.H.; Park, K.M.; Kim, D.; Kim, J. Chem. Soc. Rev. 2007, 36, 267–279.
(3) Isaacs, L. Chem. Commun. 2009, 619–629.
(4) Masson, E.; Ling, X.; Joseph, R.; Kyremeh-Mensah, L.; Lu, X. RSC Adv. 2012, 2, 1213–1247.
(5) Cheng, X.-J.; Liang, L.-L.; Chen, K.; Ji, N.-N.; Xiao, X.; Zhang, Y.-Q.; Xue, S.-F.; Zhu, Q.-J.; Ni, X.-L.; Tao, Z. Angew. Chem. Int. Ed. 2013, 52, 7252–7255.
(6) Nau, W.M.; Florea, M.; Assaf, K.I. Isr. J. Chem. 2011, 51, 559–577.
(7) Ko, Y.H.; Hwang, I.; Lee, D.W.; Kim, K. Isr. J. Chem. 2011, 51, 506–514.
(8) Biedermann, F.; Uzunova, V.D.; Scherman, O.A.; Nau, W.M.; De Simone, A. J. Am. Chem. Soc. 2013, 134, 15318–15323.
(9) Macartney, D.H. Isr. J. Chem. 2011, 51, 600–615.
(10) Walker, S.; Oun, R.; McInnes, F.J.; Wheate, N.J. Isr. J. Chem. 2011, 51, 616–624.
(11) Ghosh, I.; Nau, W.M. Adv. Drug Deliv. Rev. 2012, 64, 764–783.
(12) Day, A.I.; Collins, J.G. Supramol. Chem. Mol. Nanomater. 2012, 3, 983–1000.
(13) Jeon, Y.J.; Kim, S.Y.; Ko, Y.H.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Org. Biomol. Chem. 2005, 3, 2122–2125.
(14) Bush, M.E.; Bouley, N.D.; Urbach, A.R. J. Am. Chem. Soc. 2005, 127, 14511–14517.
(15) Heitmann, L.M.; Taylor, A.B.; Hart, P.J.; Urbach, A.R. J. Am. Chem. Soc. 2006, 128, 12574–12581.
(16) Logsdon, L.A.; Urbach, A.R. J. Am. Chem. Soc. 2013, 135, 11144–11146.
(17) Wheate, N.J.; Buck, D.P.; Day, A.I.; Collins, J.G. Dalton Trans. 2006, 451–458.
(18) Uzunova, V.D.; Cullinan, C.; Brix, K.; Nau, W.M.; Day, A.I. Org. Biomol. Chem. 2010, 8, 2037–2042.
(19) Hettiarachchi, G.; Nguyen, D.; Wu, J.; Lucas, D.; Ma, D.; Isaacs, L.; Brien, V. PLoS One 2010, 5, e10514.
(20) Biczok, L.; Wintgens, V.; Miskolczy, Z.; Megyesi, M. Isr. J. Chem. 2011, 51, 625–633.
(21) Megyesi, M.; Biczok, L.; Jablonkai, I. J. Phys. Chem. C 2008, 112, 3410–3416.
(22) Li, Y.P.; Wu, H.; Du, L.M. Chin. Chem. Lett. 2009, 20, 322–325.
(23) Li, C.; Li, J.; Jia, X. Org. Biomol. Chem. 2009, 7, 2699–2703.
(24) Wu, W.-Y.; Wang, J.-Y.; Du, L.-M.; Wu, H.; Li, C-F. Spectrochim. Acta A 2011, 79, 418–422.
(25) Li, C.F.; Du, L.M.; Zhang, H.M. Spectrochim. Acta A 2010, 75, 912–917.
(26) Miskolczy, Z.; Megyesi, M.; Tarkanyi, G.; Mizei, R.; Biczok, L. Org. Biomol. Chem. 2011, 9, 1061–1070.
(27) Li, C.F.; Du, L.M.; Wu, W.Y.; Sheng, A.Z. Talanta 2010, 80, 1939–1944.
(28) Sheppard, T.; Petti, M.A.; Dougherty, D.A. J. Am. Chem. Soc. 1988, 110, 1983–1985.
(29) Petti, M.A.; Sheppard, T.J.; Barrans, J.R.; R.E.; Dougherty, D.A. J. Am. Chem. Soc. 1988, 110, 6825–6840.
(30) Stauffer, D.A.; Barrans, J.R.; Dougherty, D.A. J. Org. Chem. 1990, 56, 2762–2767.
(31) Kearney, P.C.; Mizoue, L.S.; Kumpf, R.A.; Forman, J.E.; McCurdy, A.; Dougherty, D.A. J. Am. Chem. Soc. 1993, 115, 9907–9919.
(32) Forman, J.E.; Barrans, J.R.; R.E.; Dougherty, D.A. J. Am. Chem. Soc. 1995, 117, 9213–9228.
(33) Ngola, S.M.; Dougherty, D.A. J. Org. Chem. 1998, 63, 4566–4567.
(34) Ngola, S.M.; Kearney, P.C.; Meccozzi, S.; Russell, K.; Dougherty, D.A. J. Am. Chem. Soc. 1999, 121, 1192–1201.
(35) Otto, S.; Furlan, R.L.E.; Sanders, J.K.M. Science 2002, 297, 590–593.
(36) Sukai, C.; Figueiras Gómez, S.; Chhabra, A.; Liu, J.; Skepper, J.N.; Tuntulani, T.; Otto, S. Langmuir 2006, 22, 5994–5997.
(37) Corbett, P.T.; Sanders, J.K.M.; Otto, S. Chem. Eur. J. 2008, 14, 2153–2166.
(38) Mansfeld, F.M.; Feng, G.; Otto, S. Org. Biomol. Chem. 2009, 7, 4289–4295.
(39) Collier, H.O.; Potter, M.D.; Taylor, E.P. Br. J. Pharm. Chemother. 1953, 8, 34–37.
(40) Collier, H.O.; Potter, M.D.; Taylor, E.P.; Smith, G.K.A. Br. J. Pharm. Chemother. 1955, 10, 343–348.
(41) Babb, M.; Collier, H.O.J.; Austin, W.C.; Potter, M.D.; Taylor, E.P. J. Pharm. Pharmacol. 1956, 8, 110–119.
(42) Tischer, M.; Pradel, G.; Ohlsen, K.; Holzgrabe, U. ChemMedChem 2012, 7, 22–31.
(43) Binder, J.; Paar, M.; Jun, D.; Pohanka, M.; Hrabinova, M.; Opletalova, V.; Kuca, K. Lett. Drug. Des. Discov. 2010, 7, 1–4.
(44) Musilek, K.; Komloova, M.; Holas, O.; Hrabinova, M.; Phanka, M.; Doňal, V.; Nachon, F.; Doležal, M.; Kuca, K. 
Eur. J. Med. Chem. 2011, 46, 811–818.
(45) Zheng, G.; Zhang, Z.; Lockman, P.R.; Geldenhuys, W.J.; Allen, D.D.; Dwoškin, L.P.; Crooks, P.A. Bioorg. Med. 
Chem. Lett. 2010, 20, 3208–3210.
(46) Kassa, J.; Musilek, K.; Komloova, M.; Bajgar, J. Basic Clin. 
Pharmacol. 2012, 110, 322–326.
(47) Lava, K.; Evrard, Y.; Van Hecke, K.; Van Meervelt, L.; Binnemans, K. RSC Adv. 2012, 2, 8061–8070.
(48) St-Jacques, A.D.; Wyman, I.W.; Macartney, D.H. Chem. 
Commun. 2008, 4936–4938.
(49) Yuan, L.; Wang, R.; Macartney, D.H. J. Org. Chem. 2007, 
72, 4539–4542.
(50) Wyman, I.W.; Macartney, D.H. J. Org. Chem. 2009, 
74, 8031–8038.
(51) Wyman, I.W.; Macartney, D.H. Org. Biomol. Chem. 2009, 
7, 4045–4051.
(52) Gamal-Eldin, M.A.; Macartney, D.H. Org. Biomol. Chem. 
2013, 11, 1234–1241.
(53) MacGillivray, B.C.; Macartney, D.H. Eur. J. Org. Chem. 
2013, 2573–2582.
(54) Ni, X.-L.; Yi, J.-M.; Song, S.; Zhang, Y.-Q.; Xue, S.-F.; 
Zhu, Q.-J.; Tao, Z. Tetrahedron 2013, 69, 6219–6222.
(55) Pességo, M.; Moreira, J.A.; Rosa da Costa, A.M.; Corrochano, P.; Poblete, F.J.; Garcia-Rio, L. J. Org. 
Chem. 2013, 78, 3886–3894.
(56) Moon, K.; Kaifer, A.E. Org. Lett. 2004, 6, 185–188.
(57) Sindelar, V.; Moon, K.; Kaifer, A.E. Org. Lett. 2004, 6, 
2665–2668.
(58) Hettiarachchi, D.S.N.; Macartney, D.H. Can. J. Chem. 
2006, 84, 905–914.
(59) Wang, R.; Yuan, L.; Macartney, D.H. Chem. Commun. 
2006, 2908–2010.
(60) Day, A.I.; Arnold, A.P.; Blanch, R.I.; Snushall, B. J. Org. 
Chem. 2001, 66, 8094–8100.
(61) Schlütler, E.; Muller, J. Helv. Chim. Acta 1948, 31, 
914–924.
(62) Austin, W.C.; Potter, M.D.; Taylor, E.P. J. Chem. Soc. 
1958, 1489–1495.
(63) Liu, S.; Ruspic, C.; Mukhopadhyay, P.; Chakrbarti, S.; 
Zavalij, P.Y.; Isaacs, L. J. Am. Chem. Soc. 2005, 127, 
15959–15967.
(64) Ercolani, G. J. Am. Chem. Soc. 2003, 125, 16097–16103.