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Host–guest complexations of local anaesthetics by cucurbit[7]uril in aqueous solution†

Ian W. Wyman and Donal H. Macartney*

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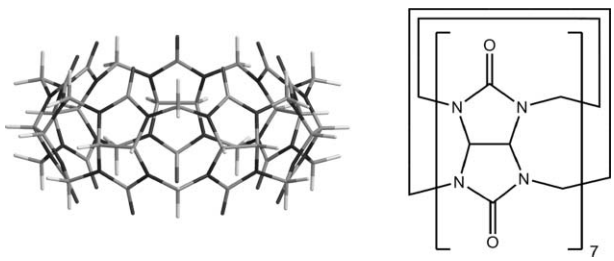
The cucurbit[7]uril (CB[7]) host molecule forms very stable host–guest complexes with the local anaesthetics procaine ($K_{CB[7]} = (3.5 \pm 0.7) \times 10^4$ dm^3 mol^{-1}), tetracaine ($K_{CB[7]} = (1.5 \pm 0.4) \times 10^4$ dm^3 mol^{-1}), procainamide ($K_{CB[7]} = (7.8 \pm 1.6) \times 10^4$ dm^3 mol^{-1}), dibucaine ($K_{CB[7]} = (1.8 \pm 0.4) \times 10^5$ dm^3 mol^{-1}) and prilocaine ($K_{CB[7]} = (2.6 \pm 0.6) \times 10^4$ dm^3 mol^{-1}) in aqueous solution (pD = 4.75). The stability constants are 2–3 orders of magnitude greater than the values reported for binding by the comparably sized β-cyclodextrin host molecule. The inclusion by CB[7] raises the first pK_a values of the anaesthetics by 0.5–1.9 pK units, as the protonated forms are bound more strongly in acidic solution. The complexation-induced chemical shift changes in the guest proton resonances provide an indication of the site(s) of binding and the effects of protonation on the location of the binding sites.

Introduction

The development of ultralong-acting local anaesthetics has been compared to the search for the Holy Grail.[1] These anaesthetic agents, which may be divided into ester (such as procaine and tetracaine) and amide (such as procainamide and prilocaine) groups, act by inhibiting sodium channels in cell membranes, preventing the depolarising of nerve cells.[2] The drugs contain both lipophilic and hydrophilic regions, connected by the ester or amide linkers, and the most common examples of both the ester and amide subgroups of the local anaesthetics have two sites of protonation, an aniline nitrogen with a pK_a of 2–3, and a tertiary amine nitrogen with a pK_a of 8–9.[3] As a result, the molecules can exist in dicationic, cationic, and neutral forms, depending on the pH. The pharmacokinetics of the anaesthetic action is related to the pH of the tissues surrounding the site of injection or application, as the non-ionized form of the drug is able to cross the nerve membrane and bind to the sodium channels. The closer the pH to the tertiary amine pK_a, the faster the onset of the anaesthetic action.

The slow, controlled delivery of anaesthetics by employing liposomes,[4] lipid–protein–sugar microparticles,[5] biodegradable polymers,[6] catanionic gels,[7] bentonite clays[8] and macrocyclic host molecules[9] have been investigated. Among the various host molecules which have been studied, the most attention has been paid to the cyclodextrins.[9] There have been numerous investigations of the β-cyclodextrin (β-CD) inclusion complexes of procaine (novocaine) by a myriad of spectroscopic and other techniques. The strength of the binding depends on the state of protonation of the guest, with cyclodextrins preferring neutral or anionic guests over cationic species. With the anaesthetic procaine, the cationic form binds to β-CD with a stability constant of about 300 dm^3 mol^{-1}, while the neutral form has a stability constant of 1500 dm^3 mol^{-1}.[9h] Extremely weak binding (K = ~1.4 dm^3 mol^{-1}) with the dicationic form in acidic solution is observed with β-CD,[9h] as inclusion results in an increase in the acidity of the guest and formation of the host–guest complex with the monocationic form of procaine.

We have recently shown that the cationic histamine H_2-receptor antagonist drug ranitidine binds five orders of magnitude stronger with the cucurbit[7]uril host molecule compared with β-cyclodextrin in neutral solution.[10] The cucurbit[n]urils (CB[n], where n = 5–8, 10) are a family of macrocyclic host molecules,[11] comprised of n glycoluril units bridged by n pairs of methylene groups (Scheme 1), whose host–guest behaviour towards cationic and neutral organic and organometallic guests have been of increasing interest recently. The cucurbiturils contain a hydrophobic interior cavity, with polar carbonyl groups surrounding the two restrictive portals. In particular, the cucurbit[7]uril (CB[7]) host[12] has received considerable recent attention because of its solubility in aqueous solution, a capacity to include aromatic[13] and metallocene molecules,[14] and for its molecular recognition of molecules and processes of biological interest.[15]



Scheme 1 Cucurbit[7]uril.

One of the most interesting effects of the complexation of guests by cucurbit[7]uril in aqueous solution is the increase in the pK_a of acidic protons on nitrogen, oxygen and carbon centers, as the host forms more stable host–guest complexes with the protonated forms of the guest, with ion–dipole interactions between the protonated site and the polar carbonyl groups on the

Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, Ontario, K7L 3N6, Canada. E-mail: donal@chem.queensu.ca; Fax: +1 613 533 6669; Tel: +1 613 533 2617

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CB[7] portals.[16] Recently, examples of significant increases in the pK_a values of guests such as the fungicide thiabenzole,[16g] and the 5,6-dimethylbenzimidazole base in vitamin B_{12} and coenzyme B_{12}[16h] have been reported. We have observed that CB[7] inclusion can facilitate a switching in the fluorescence behaviour of protonated 2-aminoanthracene as a result of increases in their ground-state and excited-state pK_a values upon hydrogen bonding between the ammonium group and the portal carbonyl oxygens.[16a]

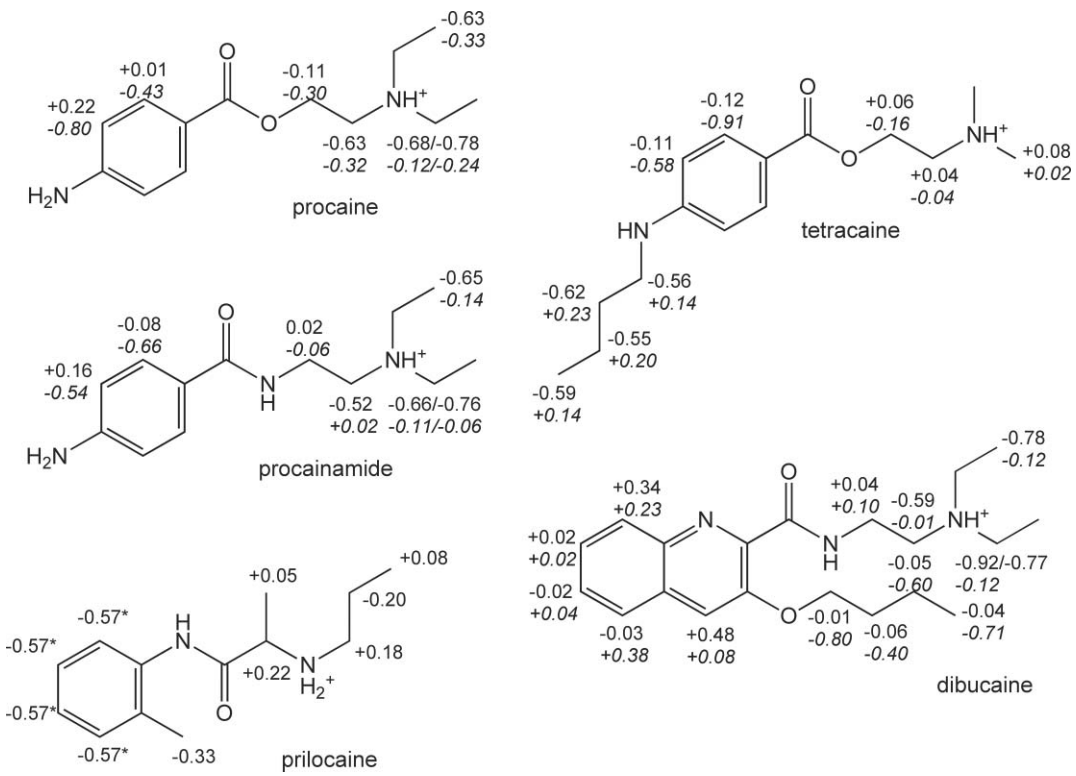
In the same manner as the cyclodextrins, cucurbit[7]uril has been investigated as a potential drug carrier, with anti-tumor platinum(II) complexes for example.[17] With a number of neutral and cationic organic and organometallic guest molecules, including the aforementioned ranitidine, cucurbit[7]uril forms host–guest complexes which have stability constants several orders of magnitude greater than for the corresponding inclusion complexes with β-cyclodextrin. While the cavity dimensions of the two hosts are similar, the somewhat restrictive portals on CB[7], coupled with the potential for stronger dipole–dipole, ion–dipole and hydrogen-bonding interactions between the guest and the polar carbonyl groups, lead to higher stability constants. Examples of stability constant comparisons include a $K_{CB[7]}/K_{\beta\text{-CD}}$ ratio of 7×10^8 for the (trimethylammonio)methylferrocene cation.[13d,14b] Even small neutral molecules such as acetone and other ketones, dimethylsulfoxide and dimethylformamide exhibit binding enhancements of two orders of magnitude with CB[7] over β-CD.[18]

In this paper, we report the properties of the host–guest complexes formed in aqueous solution between cucurbit[7]uril and five local anaesthetics: the esters procaine and tetracaine, and the amides procainamide, dibucaine and prilocaine (Scheme 2). The formation of host–guest complexes has been observed by UV-visible absorbance and emission spectroscopy, ^{1}H NMR spectroscopy, and electrospray mass spectrometry.[19] The stability constants and complexation-induced pK_a shifts of the guests have been determined, and compared with the values observed with the β-cyclodextrin host.

Results and discussion

^{1}H NMR Spectroscopy

The formation of stable 1 : 1 host–guest complexes and, in some cases, weaker 2 : 1 host–guest complexes between cucurbit[7]uril (Scheme 1) and the local anaesthetics (Scheme 2) has been observed by UV absorbance and emission spectroscopy, ^{1}H NMR spectroscopy, and electrospray mass spectrometry.[19] In the ^{1}H NMR spectra of cucurbituril host–guest complexes, the limiting chemical shifts of the proton resonances of the guests ($\Delta\delta_{lim} = \delta_{bound} - \delta_{free}$) provide an indication of the preferred orientation of the guest in the cucurbituril host cavity. Upfield shifts ($\Delta\delta_{lim} < 0$) are associated with guest protons located within the shielding hydrophobic cavity, whilst guest protons located at the deshielding carbonyl-laced portals result in downfield shifts ($\Delta\delta_{lim} > 0$). All of the guests in the present study, in both acidic and neutral solution, exhibit fast exchange on the NMR timescale, such that the observed chemical shifts represent an average of the unbound and bound guest states. The limiting chemical shift changes are presented in Scheme 2.



Scheme 2 Local anaesthetic guest molecules (structures at pH 7). The upper numbers represent the CB[7] complexation-induced chemical shift changes ($\Delta\delta_{lim}$) in the proton resonances in D_2O (pD = 5), and the lower values in italics are for the shifts observed in D_2O containing 0.10 mol dm^{-3} DCl. For prilocaine, significant overlap in the aromatic region prevented determinations of individual $\Delta\delta_{lim}$ values and an average value is given.

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We have recently shown that tetraalkylammonium ions (NR_4^+, R = Me, Et, ^{n}Pr or ^{n}Bu) form very stable inclusion complexes with CB[7] in aqueous solution, with the hydrophobic cations residing partially or fully within the cavity of the host,[20] rather than outside at the portals, as observed for alkali and transition metal cations, and primary ammonium groups on RNH_3^+ or $NH_3RNH_3^{2+}$.[11,13] The upfield chemical shift changes in the triethylammonium groups on the monocationic forms of the procaine, procainamide and dibucaine guests (Fig. 1) indicate that the entire group may be encapsulated in the CB[7] cavity, leaving the aromatic portion outside of the cavity near the portal. This may be contrasted with the behaviour of procaine with β-cyclodextrin, in which the neutral or monocationic forms of the guest are postulated to bind with the aromatic amine and ester groups within the cavity, leaving the triethylamine group outside.[9h] The two resonances for the non-equivalent diastereotopic CH_2 protons of the terminal ethyl groups on the prochiral protonated nitrogen further separate upon CB[7] inclusion of these guests, as these protons also likely experience non-equivalent local environments within the cavity. We have previously observed this phenomenon with methylene protons in the case of the CB[7] inclusions of more rigid guests, such as substituted adamantanes.[13e]

The tetracaine guest displays interesting behaviour with respect to the site of binding (Scheme 2). It might be expected in neutral solution, with protonation of the tertiary amine group in the free guest, that binding might occur at this site. The ^{1}H NMR spectra of the 1 : 1 complex, however, clearly reveals large upfield shifts in the protons of the butyl group, with smaller shifts in the aromatic protons, suggesting that CB[7] prefers to bind to the larger, hydrophobic butylanilinium end of the molecule. While the protonated triethylammonium site is encapsulated by CB[7] on procaine, procainamide and dibucaine, binding to the protonated trimethylammonium group on tetracaine would be expected to be much weaker, by analogy to the weaker binding of NMe_4^+ compared with NEt_4^+.[20] This is much more thermodynamically plausible than the possibility that the binding to the secondary aromatic amine end causes it to become preferentially protonated over the tertiary amine, despite the fact that the pK_a value for the secondary aromatic amine is much lower (2.24) than the tertiary amine group (8.48).[3b] The prilocaine appears to bind exclusively to the phenyl ring and its methyl substituent (Scheme 2), with only a small upfield shift in the resonance for the protons on the middle carbon of the propyl group. The lack of binding to the propylammonium group is again unusual, especially in terms of the binding to the butylamine group in the case of the tetracaine guest.

The effects of CB[7] complexation on the proton resonances of the guests in acidic media (0.10 mol dm^{-3} DCl in D_2O) reveal different binding sites on some of the anaesthetic molecules than observed in neutral solution. With procaine, tetracaine and procainamide, the aromatic amine center becomes protonated and the CB[7] complexation of the aromatic ring induces significant upfield shifts in these protons (Scheme 2). With procaine and to a lesser extent with procainamide, the protons of the triethylammonium group also shift upfield somewhat, indicating that the CB[7] is spending some time on this portion of the molecule, or a second CB[7] is weakly bound (see below). With tetracaine, the upfield shifts of the aromatic protons are larger, with the butyl proton resonances now shifted significantly downfield.

The dibucaine guest appears to shift its binding site from the triethylammonium group in neutral solution to the butyloxy group in acidic solution upon protonation of the imine nitrogen (Fig. 1 and Scheme 2). Inclusion of the butyloxy group, with significant upfield shifts in the butyl proton resonances, places the protonated nitrogen on the aromatic ring (with a downfield shift in aromatic proton H4) closer to the portal of CB[7] than would binding over the triethylammonium group. The CB[7] otherwise displays no

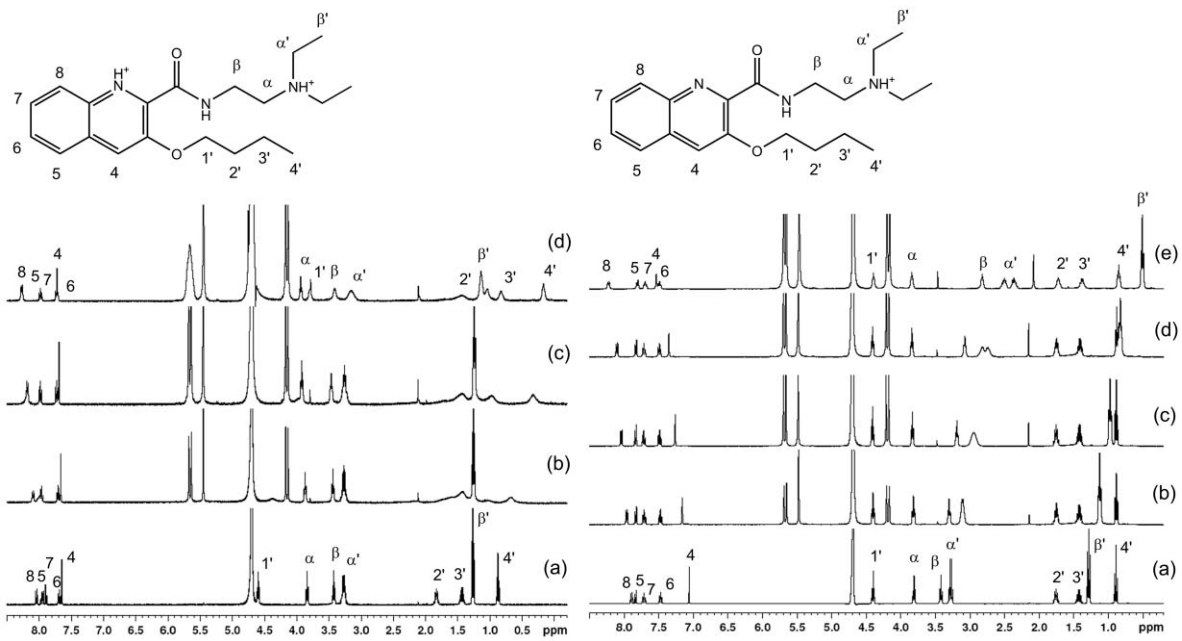

Fig. 1 ^{1}H NMR spectra of dibucaine (1.02 mmol dm^{-3}) with CB[7] in (right) D_2O: (a) 0.0 equiv., (b) 0.21 equiv., (c) 0.44 equiv., (d) 0.68 equiv. and (e) 1.37 equiv. of CB[7], and (left) D_2O containing 0.10 mol dm^{-3} DCl: (a) 0.0 equiv., (b) 0.31 equiv., (c) 0.78 equiv., and (d) 1.24 equiv. of CB[7].

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affinity for the aromatic end of the molecule in either neutral or acidic solution.

Host–guest stability constants

The 1 : 1 host–guest stability constants for the inclusion of the anaesthetics in CB[7] are too large ($> 10^4$ dm^3 mol^{-1}) to determine accurately by conventional UV or ^{1}H NMR titrations. Instead, competitive binding studies, monitored by ^{1}H NMR spectroscopy, have been carried out. Isaacs and co-workers[13d] have recently reported a series of binding constants in the range of 10^4–10^{12} dm^3 mol^{-1} for CB[7] host–guest complexes, which may be used as competitor guests. For the anaesthetics, diprotonated 1,2-phenylenediamine, which has a binding constant of $(8.04 \pm 1.28) \times 10^4$ dm^3 mol^{-1},[13d] was employed as the competitor at pD = 4.75 (0.050 mol dm^{-3} NaOAc-d_3/0.025 mol dm^{-3} DCl), while 3-(trimethylsilyl)propionic acid ($K_{CB[7]} = (1.82 \pm 0.22) \times 10^7$ dm^3 mol^{-1})[13d] was used for dibucaine at pD = 1.0 (0.10 mol dm^{-3} DCl).

The host–guest stability constants for the 1 : 1 complexes formed between CB[7] and the local anaesthetics at 25 °C and pD 4.75 or pD 1.0 are listed in Table 1. At pD 4.75, the values are in the range of $(1.5–18) \times 10^4$ dm^3 mol^{-1}. At pD 1.0, generally higher stability constants are observed, in the range of $(2.2–1100) \times 10^4$ dm^3 mol^{-1}. For the two ester anaesthetics procaine and tetracaine, as well as for dibucaine, there is a significant increase in the binding constant on going to acidic solution, while for the amide anaesthetics procaineamide and prilocaine, the binding constants exhibit small decreases. The host–guest stability constants for the complexes between the anaesthetics and β-cyclodextrin are also listed in Table 1. The values for β-CD are in the range of 10^2–10^3 lower than the corresponding values measured for CB[7] at pD 4.75. While both host molecules have similar cavity sizes, the more polar portals (rimmed with ureido carbonyl groups) of CB[7], compared with β-CD (rimmed with hydroxyl groups), likely account for the tighter binding with the cationic guests. This is probably due to a combination of stronger non-covalent interactions (dipole–dipole, ion–dipole and hydrogen bonding). Recently, the binding constant between an amide anaesthetic agent, bupivacaine, and CB[6] has been reported to be 3×10^3 dm^3 mol^{-1} in aqueous solution.[21] The corresponding values for α-CD and β-CD are 102 ± 10 and 63 ± 5 dm^3 mol^{-1}, respectively.[22]

With β-CD, the binding constant decreases for the diprotonated form of procaine (1.4 dm^3 mol^{-1}), while it increases for the neutral forms of procaine (from 3.0×10^2 to 1.5×10^3 dm^3 mol^{-1})[9h] and tetracaine (from 1.36×10^3 to 6.60×10^3 dm^3 mol^{-1}).[9j] With α-CD, only the neutral form of procaine binds, with a stability constant of 120 dm^3 mol^{-1} at pH 10.4.[9i] The complexation of tetracaine has also been investigated with the hydroxypropyl-β-cyclodextrin[9d] and *p*-sulfonated calix[6]arene hosts,[9j] and stability constants of 1.31×10^3 and 3.89×10^3 dm^3 mol^{-1}, respectively, were determined for the monocationic guest species. The stability constant for prilocaine with the smaller α-CD host molecules has been reported to be < 5 dm^3 mol^{-1}, compared with the value of 96 dm^3 mol^{-1} for β-CD.

For some of the local anaesthetics, there is evidence from the ^{1}H NMR and UV spectroscopic titrations of much weaker 2 : 1 host–guest binding with CB[7] at higher concentrations of the host. Plots of UV absorbance against [CB[7]]/[guest] for procaine, for example, suggest a very strong 1 : 1 complex is formed initially, followed by a much weaker inclusion by a second CB[7]. With amine groups at each end of the molecule, a second CB[7] could bind at the opposite end to that of the 1 : 1 complex, although the electrostatic repulsions between the polar carbonyl groups on each host would be expected to reduce the stability constant of the second CB[7] substantially.

UV absorbance and emission spectroscopy

The changes in the UV spectra of tetracaine upon addition of CB[7] at pH 5 are illustrated in Fig. 2. The complexation of the guest results in a bathochromic shift of the peak from 310 to 322 nm, with an isosbestic point at 314 nm. The spectrum of procaine is also affected by CB[7] complexation, with a shift from 290 to 286 nm.[19] The fluorescence spectrum of procaine is significantly enhanced by the encapsulation by CB[7] (Fig. 3), with

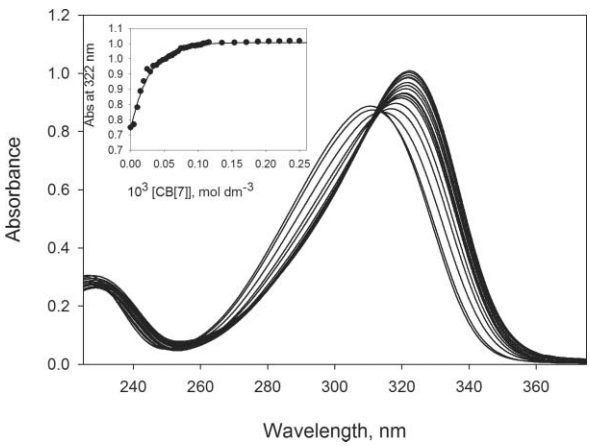

Fig. 2 UV titration of tetracaine (50 μmol dm^{-3}) with CB[7] in water. Inset: dependence of the absorbance at 322 nm on the concentration of CB[7].

Table 1 Host–guest stability constants for complexes of local anaesthetics with CB[7] and β-CD, and pK_a values for the guest and CB[7] host–guest complexes in D_2O at 25 °C

Guest	$K_{CB[7]}$/dm^3 mol^{-1} (pD 4.75)	$K_{CB[7]}$/dm^3 mol^{-1} (pD 1.0)	$K_{β\text{-}CD}$/dm^3 mol^{-1}	pK_a	p$K_a^{CB[7]}$
Procaine	$(3.5 \pm 0.7) \times 10^4$	$(4.4 \pm 1.6) \times 10^5$	3.3×10^2 [a] 1.4[c]	2.28[b]	3.50 ± 0.05
Tetracaine	$(1.5 \pm 0.4) \times 10^4$	$(1.1 \pm 0.3) \times 10^6$	1.1×10^3 [a]	2.24[b]	4.15 ± 0.05
Procainamide	$(7.8 \pm 1.6) \times 10^4$	$(5.5 \pm 1.1) \times 10^4$		2.83[b]	3.38 ± 0.05
Dibucaine	$(1.8 \pm 0.4) \times 10^5$	$(1.1 \pm 0.2) \times 10^7$	6.6×10^2 [a]	1.77[d]	3.55 ± 0.05
Prilocaine	$(2.6 \pm 0.6) \times 10^4$	$(2.1 \pm 0.4) \times 10^4$	9.6×10^1 [e]		

[a] Ref. 9*a*. [b] Ref. 3*b*. [c] For diprotonated form, ref. 9*h*. [d] Ref. 3*c*. [e] Ref. 9*b*.

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an increase in intensity at 354 nm by about 2.5-fold and a slight decrease in the wavelength of the emission maximum from 354 to 346 nm. Cucubiturils have been shown previously to cause significant changes in the fluorescence of guest molecules,[16b,23] either enhancements or quenching as a result of the formation of 1 : 2 host–guest complexes. A similar change in emission wavelength and intensity has been reported by Iglesias for procaine in the presence of β-CD, and the increase in the emission upon host–guest complex formation is attributed to an increase in molecular rigidity of the guest and the decreased polarity of the environment in the cavity of the host.[9h] A fit of the change in the fluorescence intensity (F/F_0) as a function of the CB[7] concentration yielded a 1 : 1 binding constant of $(1.0 \pm 0.3) \times 10^5$ dm^3 mol^{-1} in water (no added electrolytes). The value is larger than that determined from the ^{1}H NMR competition measurement, likely due to the lack of competing Na^+ ions used in the buffer for the NMR experiment (0.050 mol dm^{-3}). A previous report of the effects of Na^+ on the CB[7] host–guest's stability constant for acetophenone, for example, found a decrease of about seven-fold on going from no added Na^+ to 0.20 mol dm^{-3} Na^+.[18]

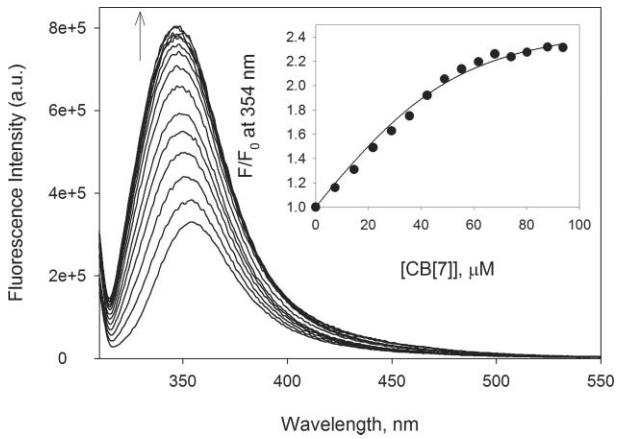

Fig. 3 Emission spectra of procaine (50 μmol dm^{-3}) in the presence of increasing amounts of CB[7] (7 mmol dm^{-3} additions) in water. Inset: dependence of F/F_0 at 354 nm as a function of [CB[7]], with a solid curve fit to F_∞/F_0 of 2.5 and $K_{CB[7]} = 1.0 \times 10^5$ dm^3 mol^{-1}.

Effect of CB[7] encapsulation on anaesthetic pK_a values

The pH of the tissue surrounding the site of injection has a significant effect on the pharmacokinetics of local anaesthetics, as non-ionized forms are able to diffuse across nerve membranes and block the sodium channels. The greater the proportion of the non-ionized portion, the faster the onset of action. In the presence of inflammation (acidosis), a more acidic environment is created, slowing the onset of action. The modulations of the pK_a values of local anaesthetics in the presence of micelles, vesicles, and membranes has also been reported. For tetracaine, for example, ΔpK_a values (compared with $pK_{a2} = 8.26$ in aqueous solution) of −1.38, −0.68 and +1.66 were found in the presence of cationic, neutral and anionic micelles, respectively.[24–26] Absorption of the monoprotonated tetracaine to neutral phosphatidylcholine membranes reduces the pK_{a2} value by 0.3–0.4 units, with the protonated tertiary amine group placed near the phosphate of the lipid headgroup.

The pK_{a1} values for the CB[7]-included anaesthetic guests were determined by UV pH titrations at 25.0 °C (Fig. 4), and were found to increase between 0.5 and 1.9 pK units compared to the literature values for the free guests in aqueous solution. The raising of the pK_a values, due to stabilization of the dication in the CB[7] host, has been observed previously for a number of *N*- and *C*-centered organic acids, and is attributed to the greater stabilization of the diprotonated forms of the guests through cation–dipole interactions with the polar carbonyl groups on the host portals.

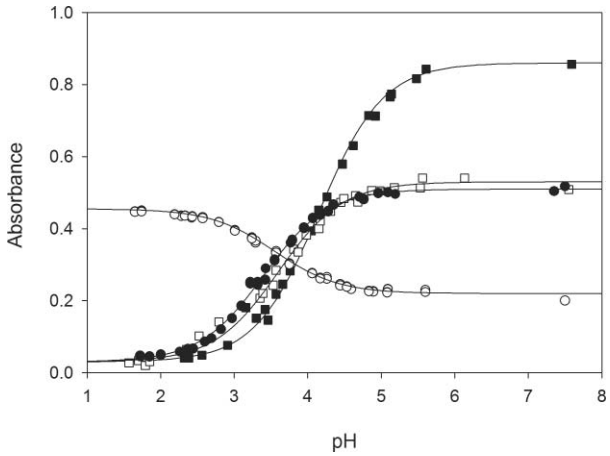

Fig. 4 UV pH titrations of CB[7] host–guest complexes of (□) procaine (288 nm), (■) tetracaine (312 nm), (○) dibucaine (318 nm) and (●) procainamide (378 nm) at 25 °C.

Experimental

Materials

Cucurbit[7]uril was prepared and characterized by the method of Day and coworkers.[12b] The hydrochloride salts of procaine, tetracaine, dibucaine, procainamide and prilocaine, 3-(trimethylsilyl)propionic acid-d_4, and 1,2-phenylenediamine were used as received (Sigma-Aldrich).

Methods

The 1D and 2D ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 and 500 instruments in D_2O using the residual HOD signal as the internal reference. The UV-visible spectra were recorded on a Hewlett-Packard 8452A diode-array spectrometer. Fluorescence measurements were preformed on a Photon Technologies International QuantaMaster C-60 spectrometer. Mass spectra were collected on a QStar XL MS/MS system with an electrospray ionization source. The host–guest stability constants were determined from ^{1}H NMR competition experiments using diprotonated 1,2-phenylenediamine ($K_{CB[7]} = (8.04 \pm 1.28) \times 10^4$ dm^3 mol^{-1})[13d] as the competitor guest in D_2O containing a 0.050 mol dm^{-3} NaOAc-d_3–0.025 mol dm^{-3} DCl buffer mixture (pD = 4.75). For dibucaine at pD = 1.0 (0.10 mol dm^{-3} DCl), 3-(trimethylsilyl)propionic acid ($K_{CB[7]} = (1.28 \pm 0.22) \times 10^7$ dm^3 mol^{-1})[13d] was used as the competitor. The stability constants and error limits were calculated using the methods of Isaacs and coworkers.[13d]

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Conclusions

The local anaesthetics procaine, tetracaine, prilocaine and dibucaine, along with procainamide form stable guest-host complexes with cucurbit[7]uril in aqueous solution, as the result of ion–dipole interactions between the protonated amine groups on the guests and the carbonyl-rimmed portals of the host molecules. The portion(s) of the guest molecules included in the host cavity depend on the solution pH and the relative sites of protonation. The inclusion of the local anaesthetic drugs in the cavity of CB[7] results in small increases in the first pK_a values of the guests.

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