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Cucurbit[7]uril stabilization of a diarylmethane carbocation in aqueous solution

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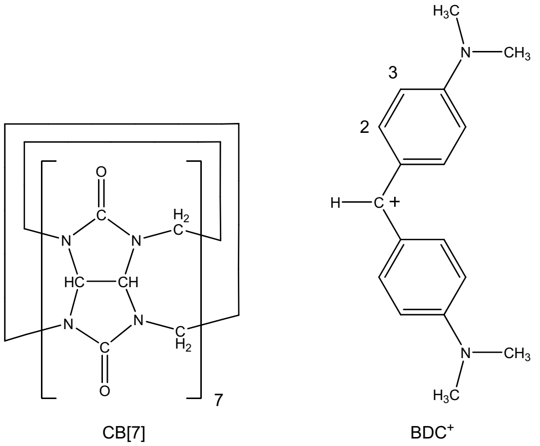
Abstract—The stability of the 4,4′-bis(dimethylamino)diphenylmethane carbocation is significantly enhanced in aqueous solution by its inclusion in the cucurbit[7]uril host cavity. The formation of the host–guest complex ($K_{CB[7]} = 2.0 \times 10^4\ M^{-1}$) shifts the carbinol–carbocation equilibrium, maximizing the formation of the intensely blue carbocation to 90% at pH 5.2.

In aqueous solution, carbocations, such as diaryl- and triarylmethanes, tend to have very short lifetimes as a result of their rapid reactions with the solvent to give the corresponding carbinols.[1] With electron-donating substituents on the aryl rings, such as dialkylamino groups, the lifetimes can be increased substantially.[2,3] The 4,4′-bis(dimethylamino)diphenylmethane carbocation (BDC^+, Michler's Hydrol Blue) has a half-life of 10–20 s, about ten orders of magnitude greater than the parent compound.[2,3] Harrison and co-workers have shown that in the presence of 4 M guanidinium hydrochloride, the blue carbocation ($\lambda_{max} = 612$ nm, $\varepsilon = 128{,}000\ M^{-1}\ cm^{-1}$) is stabilized compared to a solution containing only 0.1 M sodium acetate.[4] They have utilized this species in the detection of sulfhydryl groups in amino acids and peptides.[4]

The cucurbit[*n*]urils (CB[*n*], $n = 5$–8, 10) are a family of cyclic host molecules comprised of *n* glycoluril units bridged by 2*n* methylene groups.[5] The symmetrical CB[*n*] hosts possess hydrophobic cavities and restrictive polar portals lined with ureido carbonyl groups. The CB[7] host has been of particular interest in recent years because of its superior solubility in aqueous solution compared to other CB[*n*] members and its remarkable ability to form host–guest complexes with organic and ferrocene cations, with some exhibiting exceedingly large stability constants (up to $10^{12}\ M^{-1}$).[6,7]

The cucurbiturils have been successfully employed in the stabilization of organic and organometallic molecules such as rhodamine and other dye molecules,[8,9] and vinylferrocenes,[9c] protecting them from photobleaching and photoisomerization reactions, respectively. Nau and co-workers have recently shown that the dye Brilliant Green, a bis(diethylamino)-substituted triarylmethane carbocation, binds to CB[7], resulting in moderate enhancement of its fluorescence emission.[8g] In this Letter, the effects of inclusion of the 4,4′-bis(dimethylamino)diphenylmethane carbocation in the cavity of cucurbit[7]uril on its pH dependent stability and spectroscopic properties (UV–visible, NMR and ESI-MS) are reported (see Scheme 1).



Scheme 1. Structures of cucurbit[7]uril (CB[7]) and the 4,4′-bis(dimethylamino)diphenylmethane carbocation (BDC^+).

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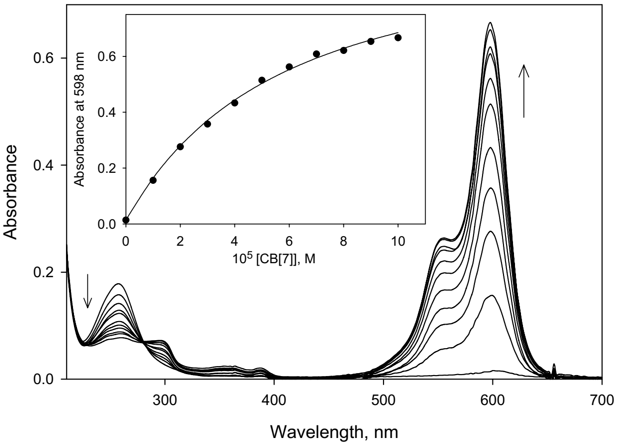


Figure 1. UV–visible spectra of BCD (10 μM) in the presence of increasing amounts of CB[7] (from 0 to 10 equiv in 1 equiv intervals in the direction indicated on spectra) in aqueous solution at pH 7. Inset: dependence of the absorbance at 598 nm on [CB[7]], with the solid line representing a fit of the data to a binding constant of 2.0×10^4 M^{-1}.

The addition of 1 equiv of CB[7] to aqueous solutions of the 4,4′-bis(dimethylamino)diphenyl carbinol (BCD-OH) at pD = 5 results in the disappearance of the proton resonances of the free compound and the appearance of new peaks for the included guest, indicating exchange which is slow on the NMR timescale. The ^{1}H NMR proton resonances of the carbocation guest exhibit complexation-induced chemical shifts ($\delta_{complex} - \delta_{free}$) in the presence of CB[7]. One of the aromatic protons (H3) shifts downfield ($\Delta\delta = 0.39$ ppm), while the other (H2) shifts upfield ($\Delta\delta = -0.45$ ppm). The methyl proton resonance shifts downfield by 0.30 ppm in the presence of CB[7]. These shifts are consistent with the carbocation being included in the CB[7], with the center part of the guest spending the most time in the cavity. The electrospray mass spectrum of a mixture of BDC-OH and CB[7] in distilled water gives a peak at $m/z = 1415$, which is consistent with the $\{BDC{\cdot}CB[7]\}^+$ complex.

The addition of CB[7] to an aqueous solution of the BDC-OH species results in the formation of a blue coloured complex, with a maximum absorbance at 598 nm (Fig. 1). A shoulder also appears at 558 nm, while the peak at 260 nm decreases. The complexation of the BDC^+ by CB[7] thus results in a slight hypochromic shift in λ_{max}, while the stabilization of BDC^+ in the presence of high concentrations of guanidinium hydrochloride was reported to result in a slight bathochromic shift to 612 nm.

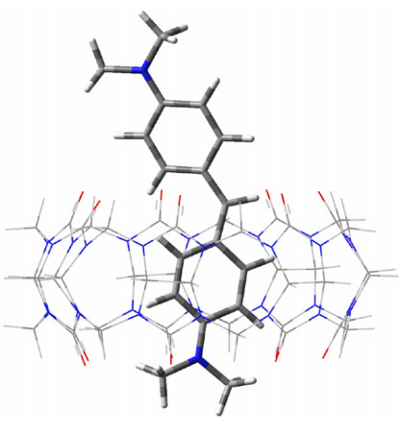


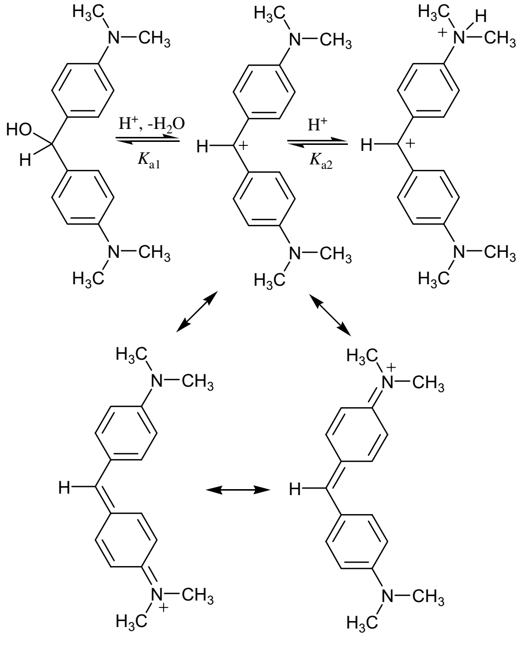
Figure 2. Energy-minimized structure of the $\{BDC{\cdot}CB[7]\}^+$ complex in the gas phase (HF/3-21G** basis set).

The apparent stability constant for the $\{BDC{\cdot}CB[7]\}^+$ host–guest complex is calculated to be $(2.0 \pm 0.5) \times 10^4$ M^{-1} at pH 7 from the titration in Figure 1. This is very similar to the value of 1.7×10^4 M^{-1} determined for CB[7] complexation of the triarylmethane carbocation Brilliant Green, in which a *p*-diethylaminophenyl group is included in the CB[7] cavity.[8g]

The structure of the $\{BCD{\cdot}CB[7]\}^+$ host–guest complex (Fig. 2) has been calculated by ab initio energy-minimization methods (HF/3-21G** basis set) using the GAUSSIAN 03 program.[10] The structure shows the inclusion of half of the carbocation, placing the central CH^+ and one dimethylamine group near the two portals of the CB[7].

The carbocation has been shown to be resonance stabilized by two additional contributors in which the positive charge is located on one of the dimethylamine groups.[11] The three resonance structures would be stabilized by inclusion in the cavity of CB[7] with either the central $-CH^+$ or a $=N(CH_3)_2{}^+$ group near a portal, which would result in ion–dipole interactions. The CB[7] is likely moving back and forth along the axis of the carbocation, which would be consistent with complexation-induced chemical shifts observed in the ^{1}H NMR spectrum.

The blue 4,4′-bis(dimethylamino)diphenylmethane carbocation exists in equilibrium (Scheme 2) with the



Scheme 2. The equilibria between the BDC^+, $BDCH^{2+}$, and BDC-OH species and the resonance structures of the BDC^+ carbocation.

colourless carbinol BDC-OH (K_{a1}) and with its conjugate acid $BDCH^{2+}$ (K_{a2})

$$BDC^+ + H_2O \overset{K_{a1}}{\rightleftharpoons} BDC\text{-}OH + H^+ \tag{1}$$

$$BCDH^{2+} \overset{K_{a2}}{\rightleftharpoons} BCD^+ + H^+ \tag{2}$$

The pK_{a1} and pK_{a2} values were determined by Harrison and coworkers to be 4.12 and 5.48, respectively, in the presence of 0.1 M sodium acetate, which change to 5.53 and 4.70, respectively, when 4 M guanidinium hydrochloride is also added.[4b] The increase in the value of pK_{a1} and decrease in pK_{a2} results in the greater amount of BDC^+ in the presence of the guanidinium hydrochloride, perhaps due to ionic strength effects (favouring the reverse process in Eq. 2 at high ionic strength). The optimum pH for the BDC^+ in the presence of the guanidinium hydrochloride is 5.10, while the optimum pH in the sodium acetate alone is 4.80. The addition of CB[7] also stabilizes the BDC^+ carbocation, with respect to $BDCH^+$ and BDC-OH. Using buffers containing 0.1 M sodium acetate, the amount of BDC^+ was determined at several pH values in the range of 4–7 in the presence of a slight excess of CB[7] (Fig. 3).

The relationship between the concentrations of BDC^+ and the total BDC species (Fig. 3), and the equilibrium constants is given by Eq. 3.

$$[BCD^+] = \frac{[BCD]_{total}}{(1 + K_{a1}/[H^+] + [H^+]/K_{a2})} \tag{3}$$

The best fit of Eq. 3 to the data (Fig. 3) yields values of $pK_{a1} = 6.46 \pm 0.10$ and $pK_{a2} = 3.96 \pm 0.10$. As with the addition of 4 M guanidinium hydrochloride, the inclusion of the carbocation in the CB[7] cavity stabilizes it with respect to both the dication $BDCH^{2+}$ and the BDC-OH. A ^1H NMR spectrum of the $BDCH^{2+}$ in the presence of excess CB[7] (pD = 2) reveals substantially less complexation-induced shifts of the aromatic proton resonances (exchange is fast on the NMR timescale), suggesting a weaker binding of $BDCH^{2+}$ with CB[7] than observed with the BDC^+ carbocation. The lower binding strength results in a reduction in pK_{a2} with respect to the value measured in 0.1 M sodium acetate.

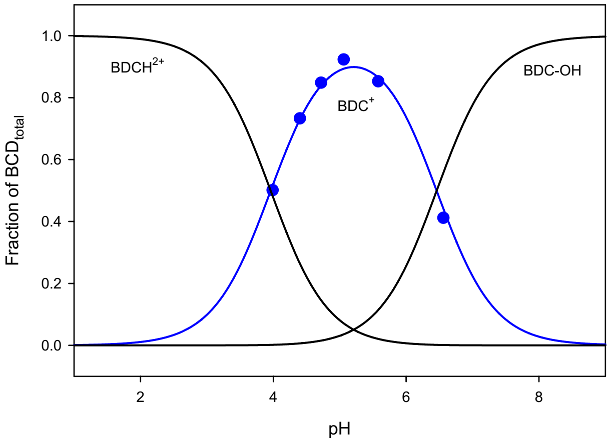


Figure 3. Speciation pH diagram for the 4,4′-bis(dimethylamino)diphenylmethane carbocation (BDC^+, blue) and dication ($BDCH^{2+}$) and the carbinol (BDC-OH) in aqueous solution (containing 0.1 M sodium acetate) in the presence of CB[7]. The blue circles represent the BCD^+ fraction determined from the spectra in the presence of an excess of CB[7] and the curves are fit to Eq. 3.

The relative fractions of BDC^+, $BDCH^{2+}$, and BDC-OH in the presence of CB[7], as a function of pH, are shown in Figure 3, and demonstrates that at pH 5.2 the maximum amount of BDC^+ (about 90% of the total BDC species) is produced. This may be compared to the previously reported maxima of about 10% in the presence of 0.1 M sodium acetate alone and 60% in the presence of added 4 M guanidinium hydrochloride.[4b]

In summary, the 4,4′-bis(dimethylamino)diphenylmethane carbocation can be stabilized in aqueous solution upon inclusion in the cavity of cucurbit[7]uril. Investigations of the stabilization of other diphenylmethane and triphenylmethane carbocations in aqueous solution by inclusions in cucurbit[*n*]uril host molecules are in progress.

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Supplementary data

The ^1H NMR and ESI-MS spectra and procedures for the calculations of the acid–base equilibrium and host–guest stability constants are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.052.

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