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Studies of the interaction of tetramethylcucurbit[6]uril and 5,5′-dimethyl-2,2′-bipyridyl hydrochloride

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Abstract The interaction between tetramethylcucurbit[6]uril (host) and 5,5′-dimethyl-2,2′-bipyridyl hydrochloride (guest) was studied by ^{1}H NMR, X-ray crystallography, electronic absorption spectroscopy, fluorescence emission spectra and quantum chemistry calculations. This experimental–computational study that indicated the host can orientationally encapsulate the guest with a moderate association constant value. Computation qualitatively explained the split UV–visible absorption peak of the inclusion complex.

Keywords Cucurbiturils · Interaction ·
^{1}H NMR spectroscopy · Electronic absorption spectroscopy ·
Fluorescence emission spectra ·
Quantum chemistry calculations

Abbreviations
TMQ6   Tetramethylcucurbit[6]uril
DMBP+   5,5′-Dimethyl-2,2′-bipyridyl hydrochloride

Introduction

Members of the cucurbit[n]uril family are relatively new synthetic receptors; the crystal structure of cucurbit[6]uril

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(Q[6]) was first characterized with X-rays by Mock and co-workers in 1981 [1]. Interest in the study of cucurbituril chemistry in molecular recognition and supramolecular chemistry has increased dramatically since a series of new cucurbit[n]uril homologs (Q[5], Q[7], Q[8] and Q[10]) were reported by the research groups of Kim and Day in 2000 [2–4]. The strong molecular recognition properties of the Q[n] family towards cations and organic species via noncovalent interactions, including charge-dipole, hydrogen-bonding and hydrophobic interactions, have led to various fundamental and applied studies on the use of Q[n] as the building blocks of supramolecular assemblies, such as rotaxanes, catenanes and molecular machines [5–11].

Like cucurbituril Q[6], its homologs Q[5], Q[7], Q[8] and Q[10] are also weakly soluble in aqueous solution and barely soluble in common organic solvents, such as alcohol, acetone, DMSO, DMF, etc. Consequently, investigation of inclusion complexes involving Q[n]s usually has to be performed in aqueous saline solution or in aqueous acids [12–14]. However, many studies have recently been carried out to improve the solubility and reactivity of Q[n]s. For example, research has shown that the solubility can be improved by introducing methyl, 1,2-cyclohexyl, or phenyl groups at the peripheries of Q[n]s [15]. Perhydroxylated Q[n]s showed not only organic solubility but also reactivity with certain chemical agents [16]. Moreover, the cucumber-shaped Q[n] analogs synthesized by Isaacs and co-workers showed excellent solubility and potential reactivity. They also exhibited special photochemical properties [17–20]. Moreover, new members of the cucurbituril family [21, 22], such as hemicucurbiturils and inverted cucurbiturils, have been synthesized.

In our laboratory, we developed a method for controlled synthesis of a series of symmetrical and unsymmetrical partially substituted cucurbit[n]urils with the methylene-bridged glycoluril dimer [23, 24]. Tetramethylcucurbit[6]

uril (TMQ6) was the first reported symmetrical partially substituted cucurbit[6]uril with an ellipsoid shape [23]. It is not only water soluble, but also easy to crystallize with various metal ions and organic guests. In this work, we studied the interactions of TMQ6 with an organic cation, 5,5′-dimethyl-2,2′-bipyridyl hydrochloride (DMBP$^+$) (Scheme 1) by various methods, including ^{1}H NMR, X-ray crystal structure analysis, and electronic absorption spectroscopy. The experimental results revealed that TMQ6 and DMBP$^+$ formed a 1:1 complex that has an asymmetrical structure with part of DMBP$^+$ protruding from one portal of TMQ6. Quantum chemistry calculations demonstrated that the molecular orbitals of the bound DMBP$^+$ overlap with the molecular orbitals of TMQ6.

Experimental

Materials

TMQ6 was prepared and purified according to the method developed in our laboratory [23]; DMBP$^+$ was obtained from Shenzhen Meryer Chemical Technology (Shenzhen, China) and used without further purification. The corresponding HCl salt was prepared by dissolving DMBP$^+$ in 5 M HCl followed by crystallization with ethanol or acetone, collecting by filtration, and drying.

Interaction studies

^{1}H NMR spectra were recorded at 20 °C on a VARIAN INOVA-400 spectrometer in D$_2$O. UV–visible (UV-Vis) absorption spectra of the guest and the host–guest complex were recorded on an Unico UV-2102 instrument at 25 °C. An aqueous solution of HCl salt of the guest was prepared with a concentration of 4×10^{-5} mol/L (pH 5.0); this solution was combined with TMQ6 to give a guest/TMQ6 ratio of 0, 4:1, 2:1, 1:1, and 1:2 and so on. The UV-Vis spectrophotometric titrations were carried out at $\lambda_{max} = 248$ nm.

Fluorescence emission spectra titration with a Varian RF-540 fluorescence spectrophotometer was employed to measured association constants at 25 °C. Aqueous solutions of DMBP$^+$ with a fixed concentration of 4×10^{-6} mol/L in the presence of increasing concentrations of TMQ6 were prepared (pH 5.0). The emission spectra at 338 nm with excitation at 310 nm were used to construct titration curves.

pH values of guest and host–guest complex solutions were monitored with a S-3C pH meter.

Scheme 1 Structures of tetramethylcucurbit[6]uril (TMQ6) host and guest 5,5′-dimethyl-2,2′-bipyridyl hydrochloride (DMBP$^+$)
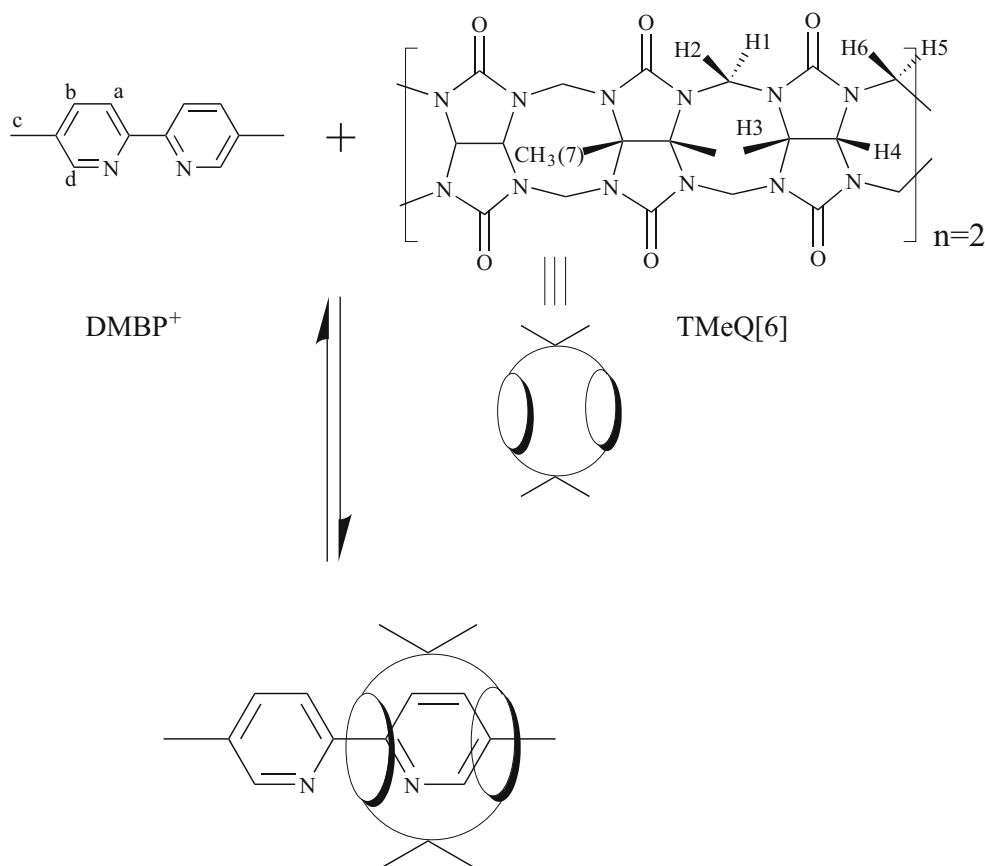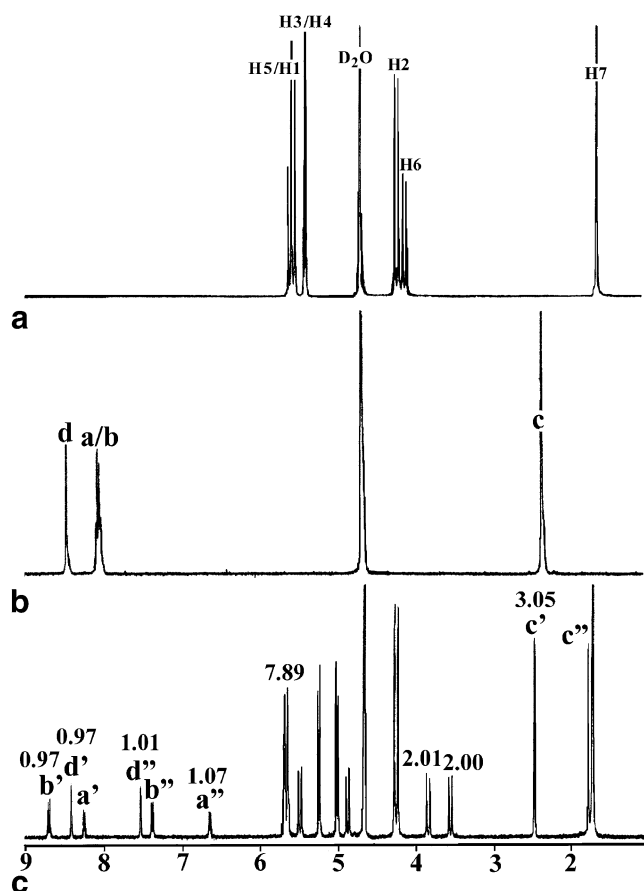
Fig. 1 ^{1}H NMR spectra (400 MHz, D$_2$O) of tetramethylcucurbit[6] uril (TMQ6) (**a**), and 5,5′-dimethyl-2,2′-bipyridyl hydrochloride (DMBP$^+$) in the absence (**b**) and presence (**c**) of 1.0 equivalent of TMQ6

Computational methods

All calculations were processed on an Intel Pentium 3.0G PC with a Gaussian 03W (Revision C.02) software package [25]. The initial geometries of all structures were constructed with the aid of the Hyperchem package, release 7.52 [26]. TMQ6 and the title complex were constructed based on crystal structures obtained by our laboratory (see Electronic supplementary material). Becke's three-parameter hybrid function with the correlation function of Lee, Yang, and Parr (B3LYP) [27–29] was used for full geometry optimization, solvent effect [30–32][1], and basis set superposition error (BSSE)-corrected [33, 34] binding energy with a 3–21G* basis set [35–38].

Results and discussion

Figure 1 shows the ^{1}H NMR spectra of TMQ6 alone (a), and DMBP$^+$ in the absence (b) and presence of TMQ6 (c). Compared with free DMBP$^+$, the ^{1}H NMR spectrum of the bound DMBP$^+$ indicates that the two pyridine rings are in different magnetic environments. One-ring protons marked as a′, b′, and d′ shifted upfield by 0.5–1.4 ppm, and the other ring protons marked as a″, b″, d″ shifted downfield by 0.2–0.6 ppm. Similarly, the methyl protons on the two pyridine rings experienced an upfield shift of 0.57 ppm and a downfield shift of 0.12 ppm, respectively. These data clearly indicate that one ring of DMBP$^+$ was encapsulated
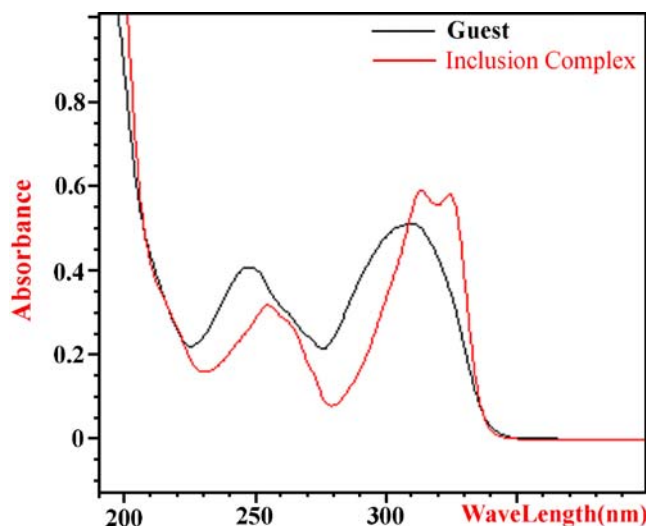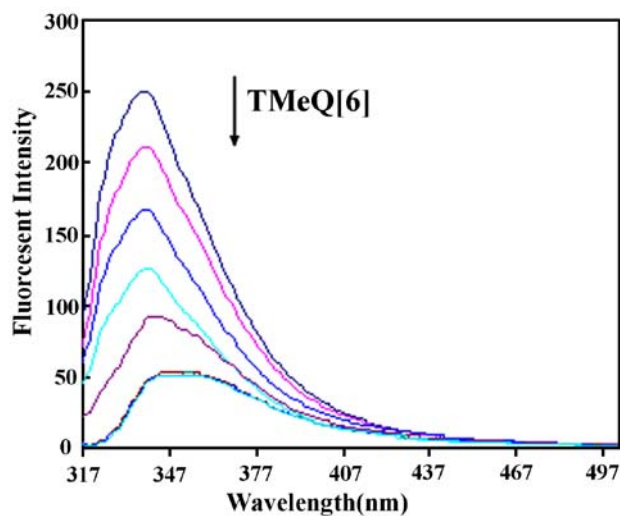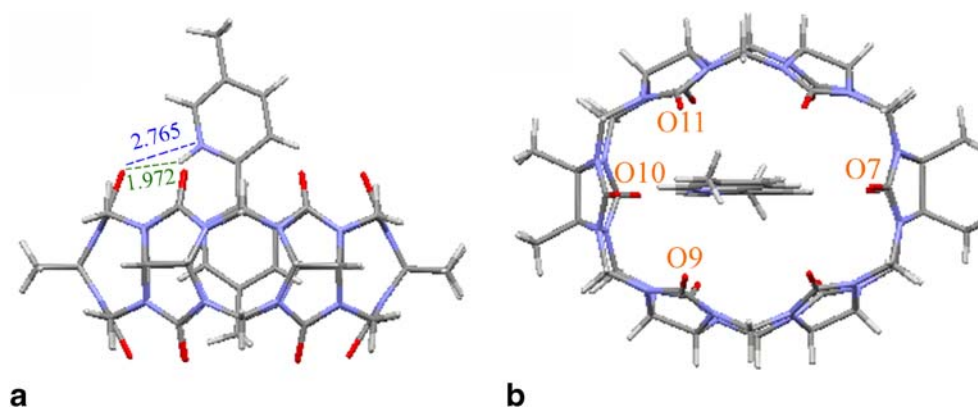

Fig. 2 a The UV-vis spectra of DMBP$^+$ (4×10^{-5} mol L^{-1}) in the absence (*black line*) and presence (*red line*) of TMQ6 (4×10^{-5} mol L^{-1}) in aqueous solution. **b** The fluorescence emission spectra of an aqueous solution containing a fixed concentration (4×10^{-6} mol L^{-1}) of DMBP$^+$ and variable concentrations (from 0 to 8×10^{-6} mol L^{-1} along the direction of the *arrow*) of TMQ6

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[1] The IEF-PCM (polarizable continuum model based an integral equation formalism) model was used to calculate the solvent effect, as part of G03.

in the cavity of TMQ6 with the other located in the deshielding portal zone of TMQ6.

In addition, dramatic chemical shifts of the protons of TMQ6 were also observed upon formation of the TMQ6-DMBP⁺ inclusion complex. Particularly, the protons of H(5) and H(6) were not only shifted upfield, but also divided into two sets of doublets, with H(6)″ at 3.54 and H(6)′ 3.84, H(5)″ at 4.76 and H(5)′ 5.49. The appearance of these two sets of doublets is indicative of an unsymmetrical inclusion complex, where the H(5)″ protons near one portal are shielded by the protruding pyridine ring at that portal, and the H(5)′ protons at the opposite portal are shielded to a lesser degree by the pyridine ring encapsulated within the cavity. Moreover, the magnitude of separation in chemical shift between H(5) and H(6) compared with that of H(1) or H(2) suggested that the pyridine rings were situated close to the four methylene bridges found between the two unsubstituted glycoluril moieties. Furthermore, the protons of H(3) and H(4) were clearly separated into two coupled resonances at 5.01 and 5.24, further supporting the proposed structure of the complex. The hydrogen integration areas of bound DMBP⁺ relative to TMQ6 showed that a 1:1 inclusion complex was formed.

UV-vis spectrophotometric analysis was employed to determine the association constant of the inclusion complex of TMQ6 and DMBP⁺ (Fig. 2a). Decrease in absorbance at 248 nm versus increase in concentration of TMQ6 was fitted to a 1:1 binding model to determine the association constant, which was found to be $(2.14\pm0.58)\times10^6$ L mol⁻¹. The electronic absorption spectrum of DMBP⁺ exhibited a red shift in the presence of TMQ6. It was noticed that the absorption band of DMBP⁺ at 310 nm was split into two absorption bands, at 314 and 325 nm, respectively. Changes in the fluorescence intensity at 338 nm were also used to determine the association constant of the 1:1 inclusion complex of TMQ6 and DMBP⁺. The association constant was determined to be $(2.82\pm0.83)\times10^6$ L mol⁻¹, which is consistent with the value obtained from UV-vis data (Fig. 2b).

Structural determination by single crystal X-ray diffraction confirmed the interaction model of TMQ6 and DMBP⁺ that had been inferred based on the information from ¹H NMR and electronic absorption spectroscopies[2]. The unprotonated ring of DMBP⁺ was encapsulated deep in the cavity of TMQ6, while the protonated ring of DMBP⁺ was at the portal of TMQ6. Thus, as expected, the partially bound DMBP⁺ formed an unsymmetrical inclusion complex (Fig. 3). The preferential orientation of DMBP⁺ followed the ellipsoid shape of the cavity of the host TMQ6, which led to differential shielding and separation of the chemical shifts between H(5) and (6) compared with those of H(1) or (2). At the portal of TMQ6, the intermolecular distances between the protonated nitrogen atom of DMBP⁺ and the nearby carbonyl oxygen atoms are 2.93 nm (H⁺–N...O9), 2.76 nm (H⁺–N...O10), and 2.84 nm (H⁺–N...O11). Also, the distances between the proton on DMBP⁺ and latter oxygen atoms are 2.70 nm (N–H⁺...O9), 1.97 nm (N–H⁺...O10), and 2.73 nm (N–H⁺...O11). Moreover, the bond angles are 96.85° (O9...H⁺–N), 152.63° (O10...H⁺–N), and 88.50° (O11...H⁺–N), respectively. Because of bond angles close to 90°, only one hydrogen bond (N–H⁺...O10) formed, which may be the cause of the somewhat distorted structure of the guest in the cavity of host (Fig. 3a). Furthermore, it is noteworthy that the guest DMBP⁺ inserted into the TMQ6 cavity with the molecular plane oriented co-planar to the long ellipsoid axis. The orientational effect is probably due to the anomalous ellipsoid-like cavity of TMQ6. The distance between the portal oxygens O7 and O10 is about 8.00 nm,

² CCDC (Cambridge Crystallographic Data Centre) number: CCDC 641150. The crystal structure of the title host-guest inclusion complex is triclinic, $a=11.853(3)$nm, $b=12.821(3)$nm, $c=24.055(6)$nm; $\alpha=104.868(5)°$, $\beta=93.557(5)°$, $\gamma=91.906(4)°$; $V=3521.5(16)$ nm³, Dc=1.274 g / cm³, $Z=7$, F000=1414, R=0.0918, Rw=0.2571 (see CIF file).
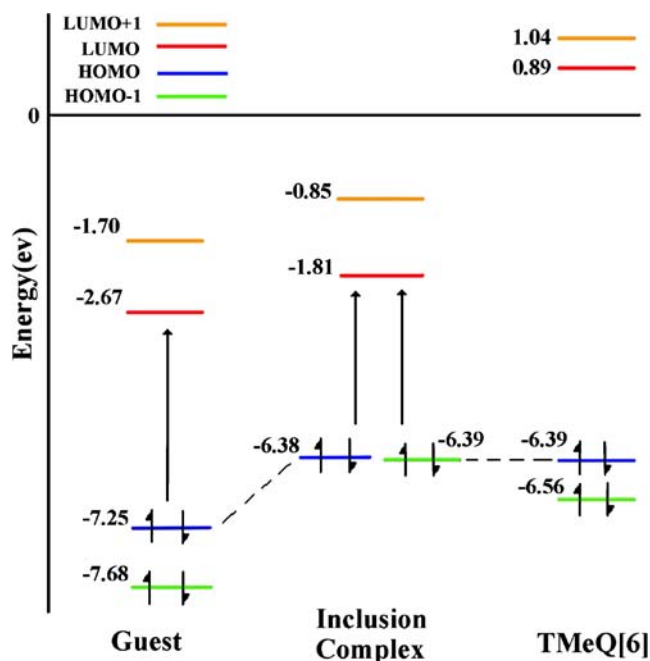
Fig. 4 Schematic representations of HOMO-1, HOMO, LUMO, and LUMO+1 of DMBP[+], TMQ6, and the inclusion complex TMQ6@DMBP[+]

which is 0.66 nm longer than that in free TMQ6; while the distance between the portal oxygens O9 and O11 is 5.37 nm, which is 0.03 nm shorter than that in free TMQ6 [23].

Quantum chemistry calculations based on density functional theory (DFT, B3LYP/3–21G* basis set) for the optimized geometry of the inclusion complex were performed with the Gaussian 03W (Revision C.02) software package. The results of the calculation revealed that interactions between TMQ6 and DMBP[+] can occur in either gas phase or aqueous solution, and the BSSE-corrected binding energies were −171 KJ mol^{-1} in gas phase and −135 KJ mol^{-1} in liquid phase. There was
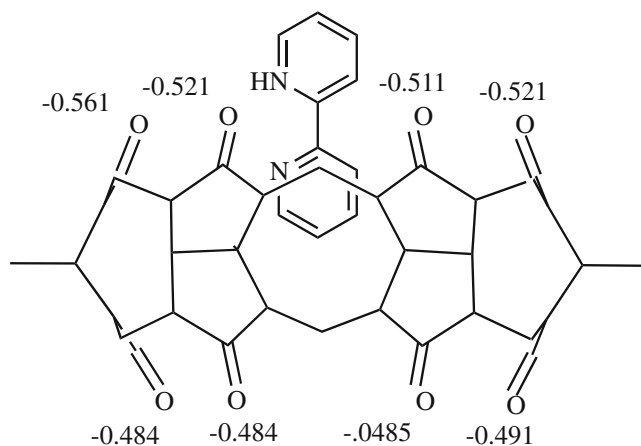
consistent agreement between the optimized geometry result and with the single crystal structural data. For example, differences in the distances of the portal diameter between the experimental and calculated results are only −2.0% for O7...O10 and −2.4% for O9...O11.

The HOMO-LUMO (H-L) energy gap of TMQ6 was calculated at 7.28 ev, which was so large that the direct functionality of cucurbiturils was thought of as being hindered [39] (Fig. 4). This is consistent with the fact that no electronic absorption in the range >210 nm was observed. The H-L energy gap of the inclusion complex was calculated to be 4.57 ev, similar to that of guest DMBP[+] (4.58 ev). The similarity in H-L energy gaps for the guest and the complex suggests that this method may be determining the gap for the guest, and that binding has little effect on this property. Therefore, the frontier electrons of the complex and the guest could be excited by similar energies. Furthermore, the inclusion complex was found to have two nearly degenerate occupied molecular orbitals; the highest occupied molecular orbital (HOMO) at −6.38 ev and HOMO-1 at −6.39 ev could be generated by interactions between TMQ6 and DMBP[+]. The electrons on these two occupied molecular orbitals can be excited by continuous electronic absorption—qualitatively consistent with the split absorption bands of the bound DMBP[+].

In addition, the most negative Mulliken atomic charge of the carbonyl oxygens on TMQ6 of the complex was on O10 (−0.561). The atomic charge on O9 or O11 was −0.521. Before complex formation, however, the Mulliken atomic charge on all of carbonyl oxygens of TMQ6 was −0.489 (Fig. 5). These changes in the oxygen atomic charges indicated that the strongest hydrogen binding was involved with the O10, consistent with the results obtained from hydrogen bond length. Static electricity is also an important driver for the interaction of TMQ6 with DMBP[+].

Conclusion

In summary, we have studied the interaction of a substituted cucurbituril, TMQ6, with DMBP[+] in neutral aqueous solvent. The formation of a 1:1 inclusion complex has been affirmed by ^{1}H NMR, crystal structure, and UV-vis spectra. The DFT calculation predicted the formation of the inclusion complex, and qualitatively explained the split UV-Vis absorption peak of the inclusion complex.

Fig. 5 Calculated Mulliken atomic charges on the carbonyl of TMQ6 @DMBP[+] at the B3LYP/3–21G* level

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