Cucurbit[7]uril host–guest complexes of the histamine H_2-receptor antagonist ranitidine†

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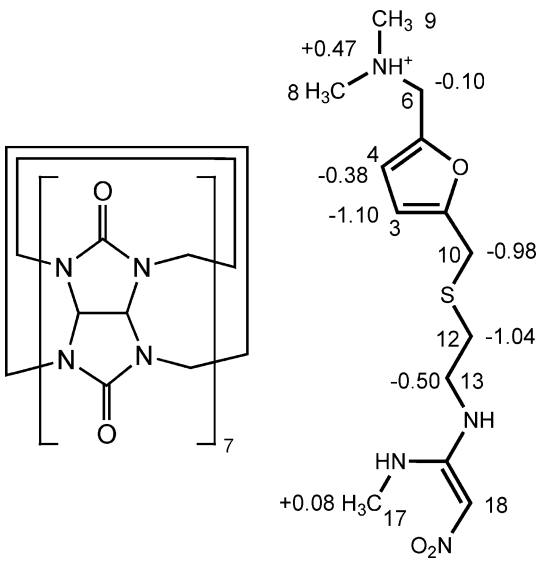
The macrocyclic host cucurbit[7]uril forms very stable complexes with the diprotonated ($K_{CB[7]}^{1} = 1.8 \times 10^8$ dm^3 mol^{-1}), monoprotonated ($K_{CB[7]}^{2} = 1.0 \times 10^7$ dm^3 mol^{-1}), and neutral ($K_{CB[7]}^{3} = 1.2 \times 10^3$ dm^3 mol^{-1}) forms of the histamine H_2-receptor antagonist ranitidine in aqueous solution. The complexation behaviour was investigated using ^{1}H NMR and UV–visible spectroscopy as a function of pH and the pK_a values of the guest were observed to increase ($\Delta pK_{a1} = 1.5$ and $\Delta pK_{a2} = 1.6$) upon host–guest complex formation. The energy-minimized structures of the host–guest complexes with the cationic guests were determined and provide agreement with the NMR results indicating the location of the CB[7] over the central portion of the guest. The inclusion of the monoprotonated form of ranitidine slows the normally rapid (*E*)–(*Z*) exchange process and generates a preference for the (*Z*) isomer. The formation of the CB[7] host–guest complex greatly increases the thermal stability of ranitidine in acidic aqueous solution at 50 °C, but has no effect on its photochemical reactivity.

Introduction

The cucurbit[*n*]uril family (CB[*n*], $n = 5$–8, 10) of macrocyclic host molecules[1] have been of increasing interest since the development of methods for increasing the yields of the minor congeners ($n = 5$, 7, 8, 10),[2,3] compared with the major CB[6] product, at the beginning of the millennium. The CB[6], CB[7], and CB[8] hosts, with hydrophobic cavities comparable in size to α-, β-, and γ-cyclodextrins, respectively, and two restrictive portals lined with ureido carbonyl groups, have been shown to form remarkably stable complexes with a variety of guest molecules in aqueous solution. In addition to the hydrophobic interactions within the cavity, the carbonyl groups are capable of stabilizing the host–guest complex through hydrogen bonding, ion–dipole, and dipole–dipole interactions with appropriate guests. The cucurbit[7]uril (Scheme 1), with its superior solubility in aqueous solution, includes guests such as protonated aminoadamantane cations[4] and substituted cationic ferrocenes[5] with binding constants up to 10^{15} M^{-1}.

There has been increasing recent interest in using cucurbit[*n*]urils to aid in the delivery of molecules of biological and medicinal interest, through host–guest formation. Cucurbit[7]uril and cucurbit[8]uril molecules have been used to form host–guest complexes with mononuclear (*cis*-$Pt(NH_3)_2Cl_2$ and *cis*-$Pt(NH_3)_2(OH_2)Cl^+$), dinuclear (*trans*-[{$PtCl(NH_3)_2$}$_2$(μ-NH_2-$(CH_2)_8NH_2$)]$^{2+}$ and *trans*-[{$PtCl(NH_3)_2$}$_2$μ-dpzm]$^{2+}$ (dpzm = 4,4′-dipyrazolylmethane)) and trinuclear (*trans*-[*trans*-{$PtCl(NH_3)_2$}$_2$-*trans*-{$Pt(dpzm)_2(NH_3)_2$}]$^{4+}$) platinum(II) complexes.[6] While the hydrolyzed $Pt(NH_3)_2(OH_2)Cl^+$ appears to bind to the portals of CB[7], the other species are included in the cavities of CB[7] and CB[8]. The inclusion of *trans*-[{$PtCl(NH_3)_2$}$_2$(μ-$NH_2(CH_2)_8NH_2$)]$^{2+}$ in CB[7] and CB[8] reduces the rate of its reactions with cysteine and glutathione. Urbach and co-workers have used 1 : 1 host–guest complexes of CB[8] and methylviologen to form ternary complexes with tripeptides with specific recognition of the N-terminus aromatic amino acids such as tryptophan.[7] Nau's group have recently employed CB[7] in assays for amino acid decarboxylase and studied the effects of CB[7] on the activity of trypsin and related enzymes.[8] The very stable complexation of ferrocenes with CB[7] (10^{10}–10^{15} dm^3 mol^{-1}) has led to the development of a method for the non-covalent immobilization



Scheme 1 Structures of cucurbit[7]uril (CB[7], left) and monoprotonated ranitidine (RH^+ (*Z* isomer) right). The numbers on ranitidine indicate the complexation-induced shifts ($\Delta\delta_{lim}$) in the proton resonances upon binding in acidic solution (RH_2^{2+}, pD = 2).

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of ferrocenylated proteins to a CB[7]-modified gold surface, as a potential replacement for the biotin–avidin pair in biological assays.[9]

Ranitidine hydrochloride (*N*,*N*-dimethyl-5-[2-(1-methylamino-2-nitrovinylamino)ethylthiomethyl]furfuryl-amine hydrochloride (RH^+), Scheme 1) is one of a number of molecules used as a histamine H_2-receptor antagonist in the treatment of excess stomach acid production, in connection with peptic ulcers and related diseases.[10] The acid–base[11–15] and degradation chemistry[16,17] and the ^{1}H NMR spectroscopy[18–20] of ranitidine in aqueous solution have been well studied.

There has been considerable interest in the use of host–guest complexes for improving the stability of drugs and facilitating their delivery and release.[21] Among the strategies explored has been the inclusion of drugs in macrocyclic host molecules such as cyclodextrins.[22] Another concern is the environmental fate of drug molecules and in the case of ranitidine, photochemical degradation has been investigated in both natural waters[23] and in the presence of TiO_2.[24] In this study, we have investigated the host–guest chemistry of cucurbit[7]uril with ranitidine in aqueous solution, determining the stability constants and pK_a values of the included diprotonated and monoprotonated forms, and studied the thermal stabilization and photochemical degradation of the CB[7]-included ranitidine in aqueous solution.

Results and discussion

UV–visible and ESI-MS spectra of the host–guest complexes

The inclusion of the ranitidine in cucurbit[7]uril can be conveniently monitored using UV–visible spectroscopy. The addition of CB[7] to a solution of ranitidine at pH 2.5 results in decreases in the peaks at 228 and 313 nm (peaks for the furan and nitroethylenediamine chromophores, respectively) up to a 1 : 1 host–guest ratio (Fig. 1), and this stoichiometry is also confirmed by a Job's plot.[25] The UV–visible spectrum of the ranitidine guest molecule in this study is very dependent on its state of protonation in aqueous solution (Scheme 2).[11]

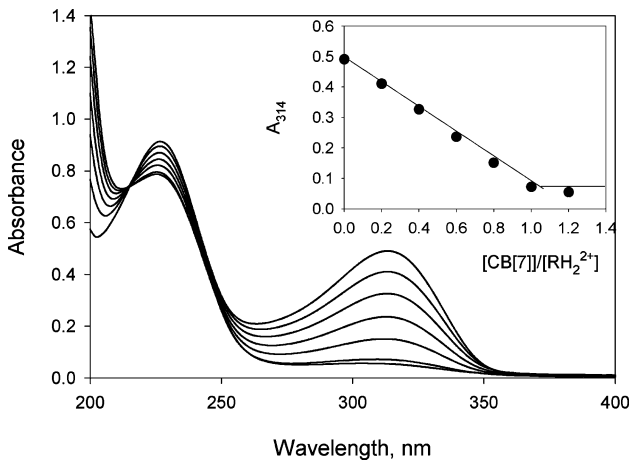
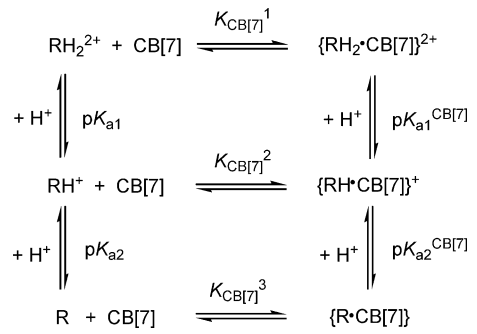


Fig. 1 UV–visible titration of ranitidine (2.0×10^{-5} M^{-1}) with cucurbit[7]uril in aqueous solution at pH 2.5. Inset: dependence of the absorbance at 314 nm on the host–guest ratio.



Scheme 2 The host–guest and acid dissociation equilibria in the complex formation between CB[7] and ranitidine (R) in aqueous solution.

The free ranitidine exists as a monocationic species in neutral solutions with protonation at the terminal dimethylamino group. In acidic solutions, the diaminovinyl group undergoes protonation and the pK_{a1} value for the diprotonated ranitidine (RH_2^{2+}) has been reported as 1.95 ± 0.01,[11] 2.19 ± 0.04,[13] and 2.3.[12] The second acid dissociation to form the neutral guest occurs with pK_{a2} values reported as 8.13 ± 0.05,[11] 8.20,[12] and 8.35 ± 0.01.[20] We[26] and others[27] have shown that the pK_a values of protonated guest molecules included in the cavity of cucurbiturils may be modulated through non-covalent interactions with the polar carbonyl-lined portals. The effect of the inclusion of RH_2^{2+} in CB[7] on the first acid dissociation constant was investigated with a UV pH titration (Fig 2), monitoring the changes in the absorbances at 228 and 308 nm with pH in the range of 1–6. The titration gives a value of $pK_{a1}^{CB[7]} = 3.48 \pm 0.02$. The titration of the $\{RH{\cdot}CB[7]\}^+$ with base in the pH range of 8–12 results in an increase in the peak at 228 nm, corresponding to a release of the guest upon its deprotonation. From the pH dependent UV spectral changes (Fig. 2), the value of $pK_{a2}^{CB[7]}$ is estimated to be 9.8 ± 0.2.

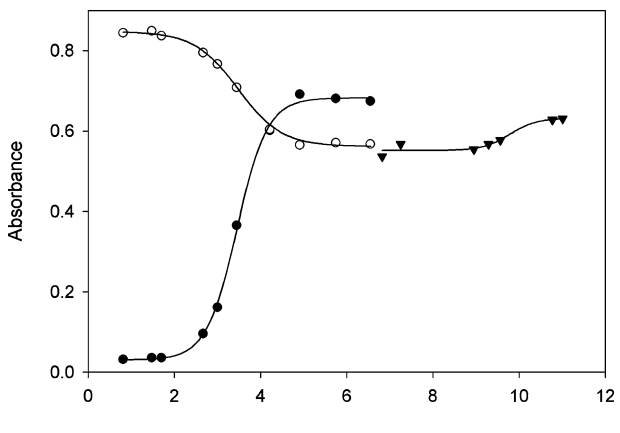


Fig. 2 pH titrations of the $\{RH_2{\cdot}CB[7]\}^{2+}$ host–guest complex monitored at 228 (○) and 308 (●) nm (curves correspond to a pK_a of 3.48), and the $\{RH{\cdot}CB[7]\}^+$ host–guest complex at 228 nm (▼) (curve corresponds to a pK_a of 9.8).

The increases in the pK_a values for the ranitidine guest upon its inclusion in CB[7] are comparable to several other pK_a shifts reported for the inclusion of amine guests, such as 2-aminoanthracene ($\Delta pK_a = 3.0$)[26] and acridine orange ($\Delta pK_a = 2.6$)[27b] in CB[7]. The decrease in the acidity of the protonated amine

groups is attributed to stabilization of the N–H bond through hydrogen-bonding and ion–dipole interactions with the carbonyl groups on the CB[7] portals.

The electrospray ionization mass spectrum of a mixture of ranitidine hydrochloride and CB[7] in water revealed peaks at $m/z = 740$ and 1478, with masses and molecular ion patterns consistent with the $\{RH_2{\cdot}CB[7]\}^{2+}$ and $\{RH{\cdot}CB[7]\}^{+}$ host–guest complexes, respectively.[25] The doubly charged ion could involve a second protonation of the guest or protonation of the host in the inclusion complex.

^{1}H NMR spectra of the host–guest complexes

In the ^{1}H NMR spectra of cucurbituril host–guest complexes, the complexation-induced shift changes (CIS, $\Delta\delta = \delta_{bound} - \delta_{free}$) in the proton resonances of the guest molecule are very informative as to the average location of the guest with respect to the CB[7] cavity. Upfield shifts ($\Delta\delta < 0$) are observed for guest protons located in the shielding region of the cavity, while guest protons located near the carbonyl oxygens of the portals experience deshielding and downfield CIS values ($\Delta\delta > 0$). For ranitidine, in each of its states of protonation, slow exchange behaviour in the ^{1}H NMR spectra was exhibited, with resonances for both the free and bound guests observed when less than one equivalent of the host molecule was present (Fig. 3)

The values of $\Delta\delta_{lim}$ (Scheme 1) clearly indicate that the central portion of the ranitidine is located in the CB[7] cavity, while the charged or neutral end units are located outside of the cavity near the carbonyl-lined portals. The complexation is stabilized by ion–dipole and dipole–dipole interactions of the protonated and polar head groups of the guests with carbonyl laced portals. In addition, the CIS values of approximately −1.0 ppm in the vicinity of the –CH_2-S-CH_2CH_2– central linker in the guest suggest that the sulfur atom is located within the CB[7] cavity. With the quadrupolar nature of the cucurbituril cavity, the sulfur may be involved in dipolar–quadrupolar interactions with the CB[7] cavity. We have recently observed that small polar neutral molecules such as ketones bind reasonably strongly to CB[7] (10^3–10^4 dm^3 mol^{-1}), as a result of contributions from dipole–quadrupole interactions, with the oxygen of the guest directed towards the center of the cavity wall.[28] The ^{1}H NMR spectra of ranitidine in the presence of CB[7] at pH 12 reveals smaller changes in the chemical shifts of the proton resonances of the neutral guest, compared with those of the protonated forms, suggesting a much weaker and shallower inclusion of this form.

The nitroethylenediamine group in ranitidine can exist as either the *E* or *Z* isomer, and is observed to crystallize in both forms, depending on the nature of the counter ion and the solvent.[29,30] Crisponi *et al.*[20] have suggested that both forms are in rapid equilibrium in aqueous solution on the NMR timescale at higher pH (monoprotonated form), but upon protonation of the diaminovinyl group, the interconversion of the *E* and *Z* forms is slowed down due to the formation of intramolecularly hydrogen-bonded species, yielding pairs of resonances (equal amounts) for protons H6, H10, and H13.

The CB[7] inclusion of ranitidine in the mono- and diprotonated forms appears to further lock the two isomers through ion–dipole and hydrogen bonding interactions between the protonated nitroethylenediamine group and the carbonyl groups of the CB[7] portals. The ^{1}H NMR spectra of both the $\{RH_2{\cdot}CB[7]\}^{2+}$ and $\{RH{\cdot}CB[7]\}^{+}$ forms of the host–guest exhibit pairs of resonances, indicating that the inclusion has slowed the exchange between the *E* and *Z* forms to such an extent that both are observable on the NMR timescale below pD 8. Coupled with the slow in-and-out guest exchange on the ^{1}H NMR timescale, the two isomers of the included ranitidine guests would have slightly different complexation induced chemical shift changes. As a result, even the resonances for the protons located some distance from the double bond, such as those on the furan ring, show pairs of peaks (Fig. 3), due to slightly different average positions in the CB[7]

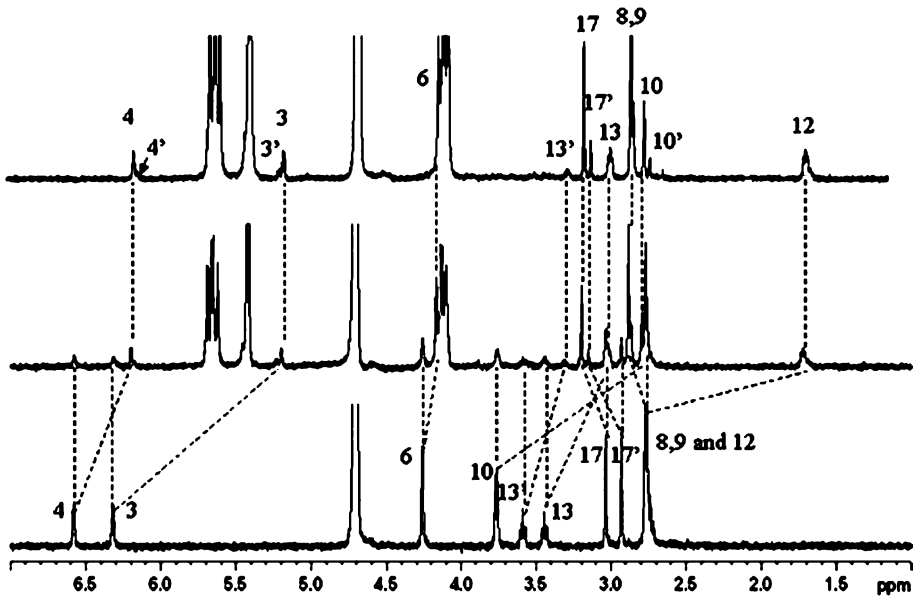


Fig. 3 ^{1}H NMR spectra of diprotonated ranitidine (RH_2^{2+}) in the absence (bottom) and presence of 0.7 equivalents (middle) and 1.4 equivalents (top) of cucurbit[7]uril in D_2O (pD = 2). The proton resonances are numbered as in Scheme 1, with the primed numbers in the top spectrum indicating the *E* isomer.

cavity. While the free ranitidine exhibits equal amounts of the *E* and *Z* isomers, the inclusion in CB[7] shifts the equilibrium towards the *Z* isomer, with only about 20% *E* form observed for $\{RH_2{\cdot}CB[7]\}^{2+}$ (as shown in Fig. 3) and approximately 40% *E* for $\{RH{\cdot}CB[7]\}^{+}$. In the former species, the *Z* isomer appears to allow for more favourable ion–dipole interactions between the guest and the host portal.

Host–guest stability constants

Cucurbit[7]uril has been shown to form exceedingly stable host–guest complexes with cationic and dicationic guest molecules in aqueous solution. The large stability constants preclude measurements by standard spectroscopic titrations, and require the use of competitive binding experiments using techniques such as isothermal calorimetry or UV–visible, fluorescence, or ^{1}H NMR spectroscopy. The stability constants of the host–guest complexes of CB[7] with diprotonated (pD = 1.5) and monoprotonated (pD = 4.7) ranitidine were measured in this study by using ^{1}H NMR competitive binding measurements with 3-trimethylsilylpropionic-2,2,3,3-d_4 acid, whose binding constant has been reported previously ($K_{CB[7]} = (1.82 \pm 0.22) \times 10^7$ dm^3 mol^{-1}) as the competing guest. The values of $K_{CB[7]}{}^1 = (1.8 \pm 0.3) \times 10^8$ dm^3 mol^{-1} and $K_{CB[7]}{}^2 = (1.0 \pm 0.3) \times 10^7$ dm^3 mol^{-1} for the di- and monoprotonated ranitidines, respectively, are comparable to values reported for other cationic guests of similar size.[31,32] The value of $K_{CB[7]}{}^3$ for the neutral ranitidine was determined to be $(1.2 \pm 0.1) \times 10^3$ M^{-1} from a UV spectrophotometric titration at pH 13. Host–guest stability constants for CB[7] with neutral guest molecules in the range of 10^2–10^5 M^{-1} have been reported previously.[28,33]

The host–guest stability constants for CB[7] and β-cyclodextrin (β-CD) have been compared because of the similarity in their cavity volumes. Jicsinszky and Kolbe have reported a stability constant of 134 M^{-1} for ranitidine with β-cyclodextrin at 30 °C in neutral D_2O.[34] Energy-minimization calculations suggested that for $\{RH{\cdot}\beta\text{-}CD\}^{+}$, only a shallow inclusion complex is formed. With CB[7], the ability to form much stronger ion–dipole and dipole–dipole interactions with the carbonyl-lined portals gives rise to the much more stable host–guest complexes with cationic guests, such as the protonated ranitidine species, compared with β-CD.

Energy-minimized structures of the host–guest complexes

The gas-phase structures of the CB[7] host–guest complexes with the diprotonated and monoprotonate forms of ranitidine (Fig. 4) have been determined from energy-minimization calculations (HF/3-21G** basis set).[35] The resulting locations of the guests in the CB[7] cavity are consistent with the ^{1}H NMR spectra and the complexation-induced chemical shifts ($\Delta\delta_{lim}$) of the guest protons, with the furan ring and its methyl substituents residing in the cavity, leaving the end groups outside near the portals. The main differences between the structures of the host–guest complexes of the mono- and diprotonated are the portions of the guest included in the cavity and the orientation of the nitroethylenediamine end unit. With the diprotonated guest, both charged ends of the molecule are located adjacent to the carbonyl-lined portals, while in the mono-protonated guest, the nitroethylenediamine group is less closely associated with the portal.

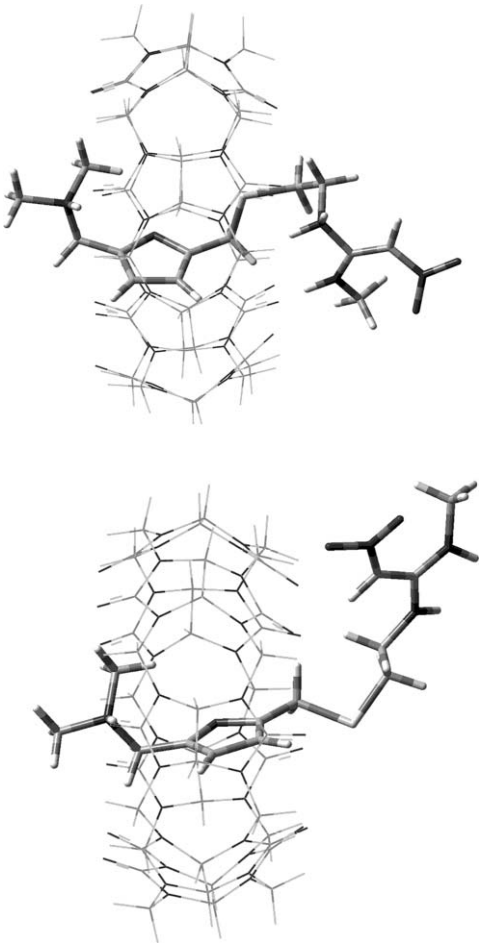


Fig. 4 Energy minimized structures of the cucurbit[7]uril–ranitidine host–guest complexes $\{RH_2{\cdot}CB[7]\}^{2+}$ (top) and $\{RH{\cdot}CB[7]\}^{+}$ (bottom) calculated in the gas-phase (HF/3-21G** basis set).

Thermal and photochemical stability of included ranitidine

As a result of the instability of the solid drug formulations containing ranitidine hydrochloride towards humidity, several investigations of its stability in aqueous solution have been carried out.[15–17] It has been reported by Hayward *et al.*[16] that ranitidine is particularly susceptible to decomposition in acidic solutions (pH 2–4) at elevated temperatures. The main products of the reaction are 5-*N*,*N*-dimethylaminomethyl-2-furylmethanol and 3-methylamino-5,6-dihydro-2*H*-1,4-thiazin-2-one. A proton induced shift in the double bond followed by ring closure between the sulfur and the carbon bearing the original nitro group leads to the formation of the dihydrothiazin-2-one oxime, with nucleophilic attack of the solvent resulting in the furylmethanol product. At 50 °C and pH = 1.5, the degradation reaction has a half-life of about 4 days (monitored by UV (Fig. 5) and ^{1}H NMR spectroscopy), whereas in the presence of a slight excess of CB[7], no observable degradation products are observed in the ^{1}H NMR spectrum, after 2 weeks. The stabilization of the ranitidine under these conditions likely results from the prevention of attack of

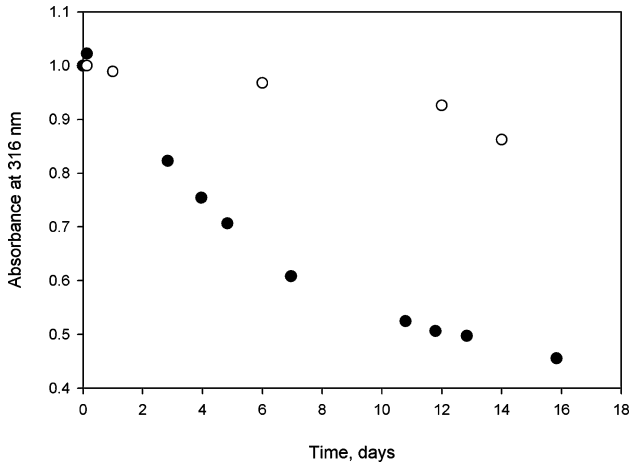


Fig. 5 Change in absorbance (normalized) at 316 nm for (●) ranitidine (RH_2^{2+}) and (○) $\{RH_2{\cdot}CB[7]\}^{2+}$ (5.0×10^{-5} mol dm^{-3}) as a function of time at 50 °C and pH 1.5.

the solvent and steric hindrance of the formation of the cyclic intermediate.

The irradiation of ranitidine in aqueous solution (254 nm, pH 1.5) is unaffected by the presence of CB[7], which is consistent with the proposed degradation involving the nitroacetamidine portion of the guest,[23,24] which resides outside of the CB[7] cavity. This is of importance in environmental remediation of natural waters containing the excreted ranitidine drug, for which photochemical degradation has been demonstrated.[23]

Conclusions

The cucurbit[7]uril host molecule forms very stable complexes with the histamine H_2-receptor antagonist ranitidine over a wide pH range in aqueous solution. The stability constants diminish as the charge on the guest is reduced through deprotonation, while the acid dissociation constants increase by about 1.5 pK units upon guest inclusion. The E to Z interconversion of the mono- and diprotonated ranitidine is slowed upon inclusion in the CB[7], with the Z isomer preferred. The inclusion significantly stabilizes ranitidine from thermal degradation at 50 °C, but has no effect on the photochemical reactivity.

Experimental section

Materials

The cucurbit[7]uril was synthesized and characterized according to the method of Day *et al*.[2b] The ranitidine hydrochloride (99%, Sigma) and sodium 3-trimethylsilylpropionate-2,2,3,3-d_4 (Aldrich) were used as received.

Methods

The ^{1}H and 2D COSY NMR spectra were recorded on a Bruker Avance 400 spectrometer in D_2O. The electrospray ionization mass spectra were recorded on a Waters 2Q Single Quadrupole spectrometer equipped with a ESI/APcI multiprobe. The UV–visible spectra were acquired on a Hewlett-Packard 8452A diode-array spectrometer. The modeled structures of the host–guest complexes were computed by energy-minimizations using Gaussian 03 programs[35] run on the computing facilities of the High Performance Virtual Computing Laboratory (HPVCL) at Queen's University.

The structures of the complexes were originally constructed using ChemDraw and Chem3D (ChemOffice 7.0, CambridgeSoft) programs and thereafter imported into Gaussian 03.[35] The basis set used for the calculations was HF/3-21G**.

The host–guest stability constants for the cucurbit[7]uril complexes with the diprotonated and monoprotonated ranitidine ($K_{CB[7]}^1$ and $K_{CB[7]}^2$, respectively) were determined by competitive ^{1}H NMR binding studies using 3-trimethylsilylpropionic-2,2,3,3-d_4 acid ($K_{CB[7]} = (1.82 \pm 0.22) \times 10^7$ M^{-1}) as the competing guest as described by Isaacs and co-workers.[4] The $K_{CB[7]}^3$ value for the neutral ranitidine at pH 13 was determined from a UV spectrometric titration with CB[7]. The change in the absorbance at 312 nm with [CB[7]] was subjected to a non-linear least squares fit to a 1 : 1 binding isotherm.[36]

Acknowledgements

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