Control of the Ketone to gem-Diol Equilibrium by Host–Guest Interactions

Abdel Monem M. Rawashdeh,†‡ Arumugam Thangavel,§ Chariklia Sotiriou-Leventis,*§ and Nicholas Leventis*§

Department of Chemistry, Yarmouk University, Irbid, 211-63, Jordan, Department of Chemistry, Missouri University of Science and Technology,‖ Rolla, Missouri 65409

levent@mst.edu; cslevent@mst.edu

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ABSTRACT

In water, N-methyl-4-(p-substituted benzoyl)pyridinium cations, BP-X, exist in equilibrium with their hydrated forms (gem-diols), whose concentrations depend on the para substituent (-X). In the presence of cucurbit[7]uril (CB[7]), the benzoyl group shows a preference for the CB[7] cavity, and the ketone to gem-diol equilibrium is shifted toward the keto form, meaning that the stabilization realized through hydrophobic interactions of the benzoyl group in the CB[7] cavity exceeds the hydrogen-bonding stabilization of the gem-diols in the aqueous environment.

Host–guest complexes are vehicles for understanding and using supramolecular interactions for purposeful function in sensors, molecular machines, and switches.¹ Cucurbiturils (CB[x], 5 ≤ x ≤ 10), the result of a condensation reaction between glucouril and formaldehyde, are barrel-shaped hosts with a hydrophobic cavity whose mean internal diameter ranges from 4.4 Å (CB[5]) to > 10 Å (CB[10]).²,³ Since the rims are formed by the negative ends of the carbonyl dipoles, they can develop hydrogen bonding and ion–dipole interactions with their environment. Consequently, some members of the CB[x] family are water soluble, and the cavity can bind one or more cationic guests, depending on their size.

This property has been explored recently in conjunction with photosomerization and photodimerization. For instance, only one trans-diaminostilbene dihydrochloride dication (DAS) can be accommodated in CB[7]; irradiation leads to the cis isomer, which is not thermally converted back to trans at room temperature owing to stabilization by interaction of both terminal protonated amines with the two negative rims of CB[7].⁴ CB[8], however, can accommodate two molecules of DAS leading to stereoselective photodimerization.⁵ Similar results have been obtained more recently with 2:1 complexes between trans-1,2-bis(4-pyridyl)ethylene and CB[8],⁶ while CB[7] can accommodate two of the smaller 2-aminopyridine

hydrochloride cations whose irradiation leads to stereo-selective [4 + 4] photodimerization. Modulation of thermal equilibria of the guests are also known, e.g., shifting the 4,4′-bis(dimethylamino)diphenylcarbinol/carbocation equilibrium toward the carbocation with CB[7]. Here, we demonstrate host–guest interactions between CB[7] and a family of guests based on the N-methyl-4-[(p-substituted benzoyl)-pyridinium cation (BP-X, where X = -OCH₃, -CH₃, -H, -Br, -CHO, -NO₂, and -S(CH₃)₂), and we report that the ketone to gem-diol equilibrium in water (eq 1) is controlled by the preference of the keto form for the CB[7] cavity.

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\text{CB}[7] + \text{BP-X} \rightarrow \text{BP-X@CB}[7]
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(1)

In aqueous solution, carbonyl compounds exist in equilibrium with their hydrated forms (gem-diols). The concentration of the latter is usually very low, but it can increase if substitution renders the carbonyl group more susceptible to nucleophilic addition. The position of this equilibrium can be of vital importance in biological systems where reactivity may be either associated with or stereoelectronically controlled by only one of the two forms. Ideally, the carbonyl/gem-diol equilibrium would be controlled with supramolecular additives rather than by modifying the substrate or the environment (e.g., by changing the pH).

All BP-Xs of this study were available from previous work and were chosen as model ketones because of their water solubility, their relation to the NAD⁺/NADH coenzyme dehydrogenases, their expected adjustable aptitude for hydration by para substitution, and their structural similarity to methyl viologen (N,N’-dimethyl-4,4’-bipyridinium dications, MV²⁺). which warrants interaction with CB[7]. In this regard, it is noted that MV²⁺ fits well in CB[7], and the two positive charges are stabilized by ion–dipole interactions with the carbonyl groups of the rings. By the same token, however, since BP-Xs have only one pyridinium ring, their orientation relative to the cavity of CB[7] was not obvious a priori: they could assume either an exo or an endo stereochemistry as illustrated below:

The exo versus endo orientation was elucidated by ¹H NMR. As shown in Figure 1 for the aromatic region, in the presence of CB[7] (purchased from Aldrich), the ¹H NMR of BP-H (X = H) in D₂O shows an upfield shift for all protons, consistent with the endo-BP-H@CB[7]. Identical results were observed for all BP-X of this study. The exo orientation is in fact observed with the corresponding N-hexyl-4-[(p-substituted benzoyl)pyridinium cations, by analogy to that reported for hexylviologen (N,N’-dihexyloxy-4,4’-bipyridinium dications; refer to the Supporting Information). Clearly, the benzoyl group, despite possible H-bonding interactions with the solvent through the carbonyl oxygen, prefers to retreat into the hydrophobic cavity where it must enjoy greater stabilization through hydrophobic interactions.

As shown in Figure 2, upon intercalation in CB[7] the longest wavelength electronic absorption of BP-X decreases in analogy to what has been reported for MV²⁺. The 1:1 stoichiometry of the resulting BP-X@CB[7] complexes is supported by the presence of stable isosbestic points in the UV titration of BP-X with CB[7], and in the case of BP-H, it was confirmed by a peak at m/z = 1361.58 (expected at m/z = 1361.20) in the ESI mass spectrum of the BP-H/CB[7] aqueous solution (see the Supporting Information). The strong binding aptitude of BP-H with CB[7] is reflected in the equilibrium constant for complex formation (Kₑq = (6.2 ± 2.1) × 10¹⁵ M⁻¹ by analysis of the UV titration data of Figure 2; see the Supporting Information).

References:
(18) Connors, K. A. Binding Constants, The Measurement of Molecular Complex Stability; John Wiley and Sons, Inc.: New York, 1987; Chapter 4, p 141.
Similarly, all the other BP-Xs examined showed strong binding aptitudes toward CB[7]. Equilibrium constants, $K_{eq}$, increase with electron-withdrawing substitution (Figure 3, $K_{eq}$ increases with electron-deficient benzoyl groups becoming more electron-deficient, its compatibility with the hydrophobic cavity of CB[7] increases.

$\rho = 0.58 \pm 0.06$ reflecting that as the benzoyl group becomes more electron-deficient, its ability to form H-bonding with the aqueous environment decreases, thus increasing its preference for the hydrophobic interior of CB[7]. The extreme case of BP-S(CH$_3$)$_2$ is noteworthy because it shows an abnormally high affinity for CB[7] ($K_{eq}$ = $(3.6 \pm 1.0) 	imes 10^5$ M$^{-1}$), most probably because that complex is stabilized by two cation-dipole interactions, much like MV$^{2+}$ whose $K_{eq}$ is $2 \times 10^5$ M$^{-1}$.

The effect of substitution is also followed by $^1$H NMR (no CB[7] present), we are able to see that as X- becomes more electron withdrawing (e.g., going from -H to -NO$_2$), in aqueous solutions BP-X exist in equilibrium with progressively increasing amounts of their gem-diol forms, whose identity was confirmed by the $^{13}$C NMR signature resonance of the C(OH)$_2$ carbon at ~94.5 ppm. The relative ratio of the two forms, and therefore the value of each ketone $\approx$ gem-diol equilibrium constant ($K_{dil}$), is extracted directly from the $^1$H NMR spectra. $K_{dil}$ data show a good Hammett correlation (Figure 4) with a reaction constant $\rho = 1.31 \pm 0.02$, which is similar to values reported for substituted benzaldehydes (1.71–1.75).

The effect of CB[7] upon the keto/gem-diol equilibrium is best illustrated with the N-methyl-4-(p-formylbenzoyl)-pyridinium cation (BP-CHO), which in CH$_3$CN appears as a pure compound (Figure 5A), while in D$_2$O consists of a mixture of three forms (Figure 5B).

Upon addition of increasing amounts of CB[7] (Figures 5C and 5D), the fate of the individual forms in equilibrium can be followed separately: the dicarbonyl form, BP-CHO, shows an evolution-pattern similar to that of BP-H in Figure 1, underscoring the preference of the benzoyl group for the CB[7] cavity. A similar case is made for the hydrated aldehyde: BP-CH(OH)$_2$. However, when the gem-diol is on the benzoyl group only small chemical shift changes are observed with increasing the concentration of CB[7].

(20) The bis gem-diol of BP-CHO is not detectable, reflecting the change in the electronic properties of carbonyls converted to gem-diols.
ing that this form is oriented mostly outside the cavity. Starting with similar geometries (the carbonyl or the gem-diol groups inside the cavity), PM3-optimized structures of BP-NO₂@CB[7] and of the corresponding gem-diol support that the gem-diol of the benzoyl group prefers to stay outside the cavity, where presumably it can be further stabilized by hydrogen bonding with the aqueous environment.21 The most significant observation in Figure 5, however, is that upon addition of increasing amounts of CB[7], the relative amount of BP-CHO increases at the expense of both hydrated forms. After addition of 1.25 mol equivalent of CB[7] into the aqueous solution of BP-CHO, the ¹H NMR spectrum (Figure 5A) looks similar to that in CD₃CN (Figure 5A), while the relative ratios of the three forms BP-CHO/gem-diol/hydrated aldehyde change from 1.0:0.26:0.20 to 1.0:0.06:<0.01 after addition of one equivalent of CB[7].22 The new keto ↔ gem-diol equilibrium constants after addition of CB[7], still show a good Hammett correlation (Figure 4). The new line runs almost parallel to (ρ = 1.41 ± 0.18), but below the one representing the keto/gem-diol equilibrium before the addition of CB[7] reflecting similar stereoelectronic factors but much lower equilibrium concentrations of gem-diols. Clearly, the stabilization realized by H-bonding of the gem-diols in water is still less than the stabilization realized through hydrophobic interactions of the benzoyl groups in the interior of the cavity.23 It is noteworthy that in systems where the benzoylpyridinium group assumes the exo-configuration (the case of N-hexyl-4-benzoylpyridinium cations), the keto to gem-diol equilibrium is affected less by the presence of CB[7] (see the Supporting Information).

The results described herewith have been possible because all BP-X@CB[7] complexes seem to include strong hydrophobic interactions with the CB[7] cavity and are oriented endo in water. Our results viewed together with those reported in recent and current literature suggest that the broader scope of exerting control on potentially useful homogeneous reactions of the guest via host–guest interactions should be explored further.2,4–7 Finally, BP-X@CB[7] having one redox center, the benzoyl group, inside the cavity invites further studies of the electron transfer through the cage wall.

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Supporting Information Available: Data analysis and data tables; ¹H NMR spectra (in D₂O) of (a) N-hexyl-4-benzoylpyridinium, (b) N-methyl-4-(p-nitrobenzoyl)pyridinium, and (c) N-hexyl-4-(p-nitrobenzoyl)pyridinium tetrafluoroborate with/without CB[7]; ESI mass spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) DFT-optimized structures (by the B3LYP/6-31G* method) were used as inputs of the PM3 optimizations for all three: CB[7], BP-NO₂, and the gem-diol of the latter.

(22) It is emphasized that in the presence of CB[7] the concentration of BP-CH(OH)₂ is extremely small; hence, the point for BP-CHO in the Hammett plot of Figure 3 falls in line with the rest of the substituents.

(23) Apparently, CB[7] can intercalate even neutral aromatic ketones.24 Equilibrium constant data in the presence of K⁺ are about 1 order of magnitude less than the values plotted in Figure 3, probably reflecting the lack of positive charge.