# 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*

leventis@mst.edu; cslevent@mst.edu

ABSTRACT
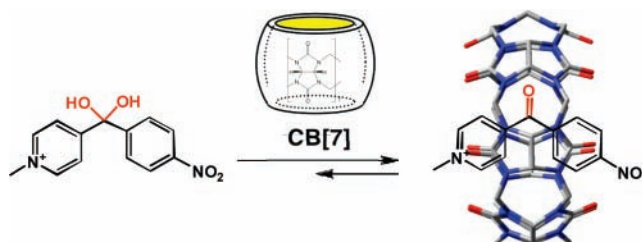
In water, *N*-methyl-4-(*p*-substituted benzoyl)pyridinium cations, BP-X, exist in equilibrium with their hydrated forms (*gem*-diols), whose concentrations depend on the para substituent (-X). In the presence of cucurbit[7]uril (CB[7]), the benzoyl group shows a preference for the CB[7] cavity, and 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]**, $5 \leq x \leq 10$), 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
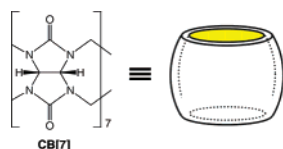
of the **CB[x]** family are water soluble, and the cavity can bind one or more cationic guests, depending on their size.

This property has been explored recently in conjunction with photoisomerization 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

(1) (a) Kaifer, A. E.; Gomez-Kaifer, M. *Supramolecular Electrochemistry*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1999. (b) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348−3391.

(2) (a) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870. (b) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630. (c) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96−107.

(3) Liu, S. L.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 16798−16799.

(4) Choi, S.; Park, S. H.; Ziganshina, A. Y.; Ko, Y. H.; Lee, J. W.; K. K. *Chem. Commun.* **2003**, 2176−2177.

(5) Jon, S. Y.; Ko, Y. H.; Park, S.-H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938−1939.

† Yarmouk University.
‡ Visiting faculty at the University of Missouri−Rolla, Summer 2007.
§ Missouri University of Science and Technology.
|| Formerly, University of Missouri−Rolla.

hydrochloride cations whose irradiation leads to stereo-selective [4 + 4] photodimerization.[7] Modulation of thermal equilibria of the quests are also known, e.g., shifting the 4,4'-bis(dimethylamino)diphenylcarbinol/carbocation equilibrium toward the carbocation with **CB[7]**.[8] 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 = -OCH$_3$, -CH$_3$, -H, -Br, -CHO, -NO$_2$, and -S$^+$(CH$_3$)$_2$), 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.

$$ \text{(1)} $$
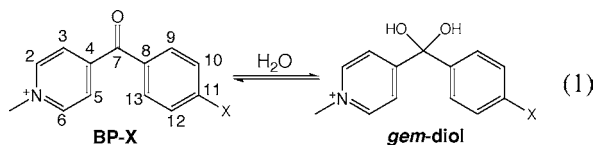
In aqueous solution, carbonyl compounds exist in equilibrium with their hydrated forms (*gem*-diols). The concentration of the latter is usually very low, but it can increase if substitution renders the carbonyl group more susceptible to nucleophilic addition.[9] The position of this equilibrium can be of vital importance in biological systems where reactivity may be either associated with or stereoelectronically controlled by only one of the two forms.[10−13] 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-X**s of this study were available from previous work[14] and were chosen as model ketones because of their water solubility, their relation to the NAD$^+$/NADH coenzyme of dehydrogenases, their expected adjustable aptitude for hydration by para substitution, and their structural similarity to methyl viologen (*N*,*N*'-dimethyl-4,4'-bipyridinium dication, **MV^{2+}**),[15,16] which warrants interaction with **CB[7]**. In this regard, it is noted that **MV^{2+}** fits well in **CB[7]**, and the two positive charges are stabilized by ion−dipole interactions with the carbonyl groups of the rims.[2,15,16] By the same token, however, since **BP-X**s 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:
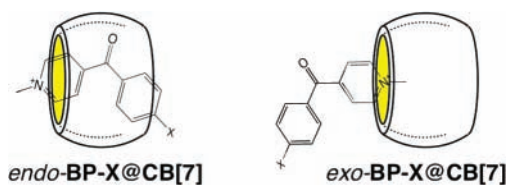
The exo versus endo orientation was elucidated by ^{1}H NMR. As shown in Figure 1 for the aromatic region, in the

Figure 1. Room temperature (23 °C) ^{1}H NMR of the aromatic region of **BP-H** (X = H; 16.1 mM) in D$_2$O/0.1 M KCl before (A) and after (B) addition of 1.25 mol equivalents of **CB[7]**. The upfield shift of all protons supports the *endo*-orientation. The small "impurities" in the baseline is the *gem*-diol form of **BP-H** in equilibrium with the dominant keto form.

presence of **CB[7]** (purchased from Aldrich), the ^{1}H NMR of **BP-H** (X = H) in D$_2$O 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*'-dihexyl-4,4'-bipyridinium dication; refer to the Supporting Information).[16] 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 **MV^{2+}**.[17] 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 (K_{eq} = (6.2 ± 2.1) × 10^3 M^{-1} by analysis of the UV titration data of Figure 2; see the Supporting Information).[18]

(6) Maddipatla, M. V. S. N.; Kaanumalle, L. S.; Natarajan, A.; Pattabiraman, M.; Ramamurthy, V. *Langmuir* **2007**, *23*, 7545−7554.

(7) Wang, R.; Yuan, L.; Macartney, D. H. *J. Org. Chem.* **2006**, *71*, 1237−1239.

(8) Wang, R.; Macartney, D. H. *Tetrahedron Lett.* **2008**, *49*, 311−314.

(9) See for example: Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749−756.
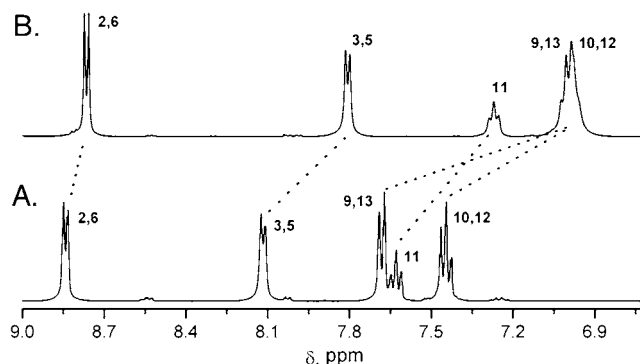
(10) Silva, A. M.; Cachau, R. E.; Sham, H. L.; Erickson, J. W. *J. Mol. Biol.* **1996**, *255*, 321−346.

(11) Eisses, K. Th. *Bioorg. Chem.* **1989**, *17*, 268−274.

(12) Likar, M. D.; Taylor, R. J.; Fagerness, P. E.; Hiyama, Y.; Robins, R. H. *Pharm. Res.* **1993**, *10*, 75−79.

(13) Hanessian, S.; Roy, R. *Tetrahedron Lett.* **1981**, *22*, 1005−1008.

(14) Leventis, N.; Rawashdeh, A.-M. M.; Zhang, G.; Elder, I. A.; Sotiriou-Leventis, C. *J. Org. Chem.* **2002**, *67*, 7501−7510.

(15) Kim, H.-J.; Jeon, W. S.; Ko, Y. H.; Kim, K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5007−5011.

(16) Moon, K.; Kaifer, A. E. *Org. Lett.* **2004**, *6*, 185−188.

(17) Ong, W.; Gómez-Kaifer, M.; Kaifer, A. E. *Org. Lett.* **2002**, *4*, 1791−1794.

(18) Connors, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; John Wiley and Sons, Inc.: New York, 1987; Chapter 4, p 141.
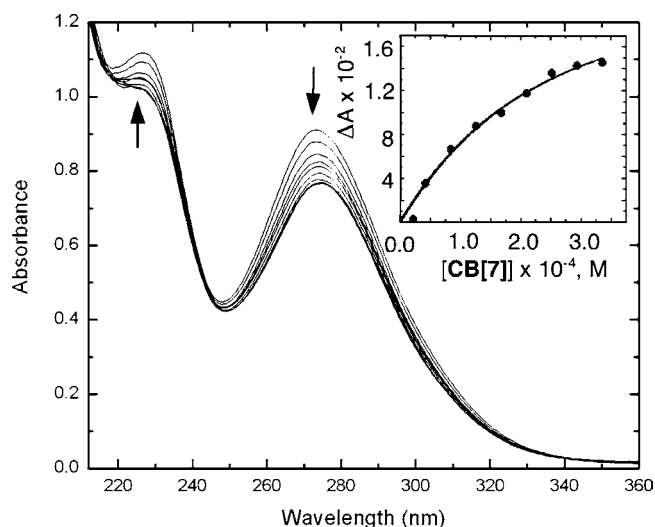
Figure 2. Room-temperature (23 °C) titration of **BP-H** (9.88×10^{-5} M) in $H_2O/0.1$ M KCl with **CB[7]**. (Initial pH ~6.0; after addition of **CB[7]**, pH~4.0. Results identical in phosphate buffer at pH = 7.0.) Inset curve: by nonlinear regression (see the Supporting Information).

Similarly, all the other **BP-X**s examined showed strong binding aptitudes toward **CB[7]**. Equilibrium constants, K_{eq}, increase with electron-withdrawing substitution (Figure 3,
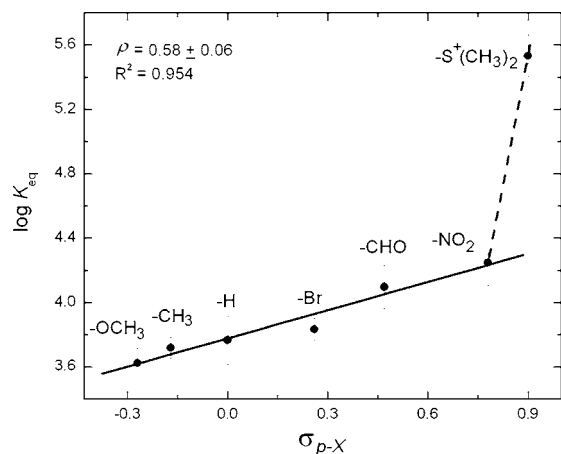

Figure 3. Substitution effects for the **BP-X** + **CB[7]** ⇌ **BP-X@CB[7]** equilibrium in $D_2O/0.1$ M KCl showing that as **BP-X** becomes more electron deficient, its compatibility with the hydrophobic cavity of **CB[7]** increases.

$\rho = 0.58 \pm 0.06$) 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⁺(CH₃)₂** is noteworthy because it shows an abnormally high affinity for **CB[7]** ($K_{eq} = (3.6 \pm 1.0) \times 10^5$ M^{-1}), most probably because that

complex is stabilized by two cation-dipole interactions, much like **MV²⁺** whose $K_{eq} \sim 2 \times 10^5$ M^{-1}.[15−17]

If 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 -NO₂), 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 ⇌ *gem*-diol equilibrium constant (K_{diol}), is extracted directly from the ^{1}H NMR spectra. K_{diol} data show a good Hammett correlation (Figure 4) with a reaction constant $\rho = 1.31 \pm$
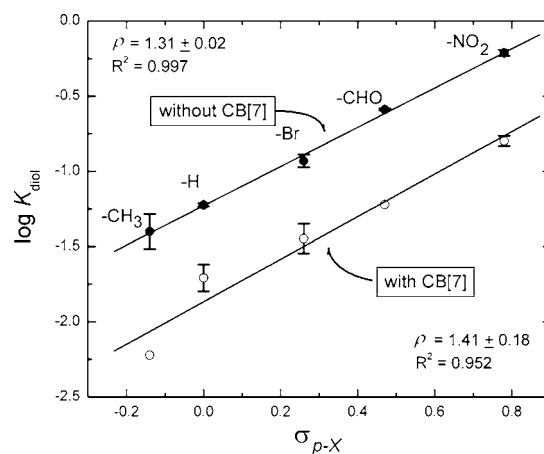

Figure 4. Substitution effect for the keto/*gem*-diol equilibrium in $D_2O/0.1$ M KCl with and without 1.0 molar equiv of **CB[7]**. ([**BP-X**] = 16.0 ± 0.6 mM.) Equilibrium constants, K_{diol}, directly from ^{1}H NMR data: spectra recorded 15 min and 24 h after dissolving **BP-X** in $D_2O/0.1$ M KCl were identical. Data for **BP-S⁺(CH₃)₂** are not included because the $t_{1/2}$ of the ketone to *gem*-diol equilibrium was a few hours.

0.02, which is similar to values reported for substituted benzaldehydes (1.71−1.75).[19]

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_3CN appears as a pure compound (Figure 5A), while in D_2O consists of a mixture of three forms (Figure 5B).[20]

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]** indicat-

(19) Baymak, M. S.; Vercoe, K. L.; Zuman, P. *J. Phys. Chem. B* **2005**, *109*, 21928−21929.

(20) The bis *gem*-diol of **BP-CHO** is not detectable, reflecting the change in the electronic properties of carbonyls converted to *gem*-diols.
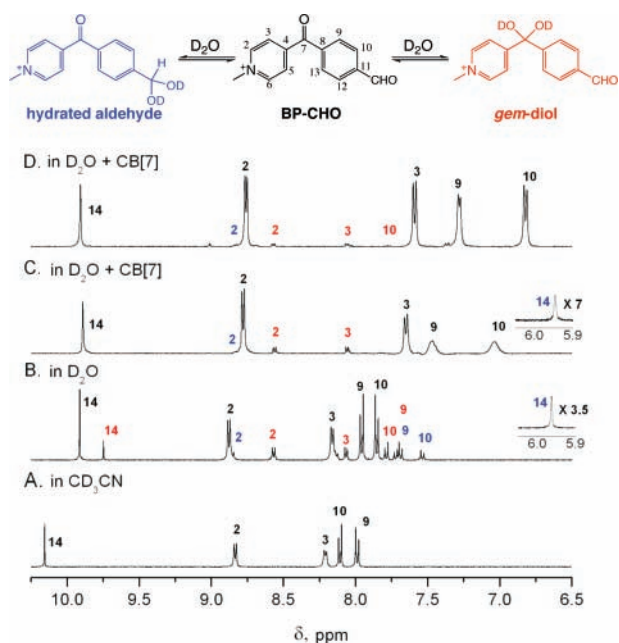
Figure 5. ^{1}H NMR data of **BP-CHO** in CD_3CN (A) and in D_2O/ 0.1 M KCl without **CB[7]** (B), with 0.75 molar equiv **CB[7]** (C), and 1.25 molar equiv of **CB[7]** (D). Peak assignment by COSY 2D NMR and simulation; blue and red color coding to match structures on top.

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]

BP-NO₂@CB[7]   ***gem*-diol_of_BP-NO₂@CB[7]**
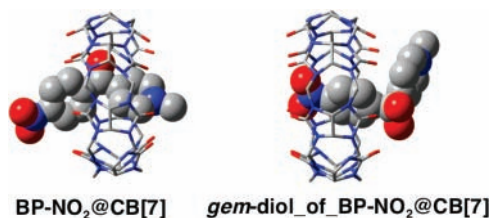
The most significant observation in Figure 5, however, is that upon addition of increasing amounts of **CB[7]**, the

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 ^{1}H NMR spectrum (Figure 5D) looks similar to that in CD_3CN (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 $\rightleftharpoons$ *gem*-diol equilibrium constants after addition of **CB[7]**, still show a good Hammett correlation (Figure 4). The new line runs almost parallel to ($\rho = 1.41 \pm 0.18$), 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.

Supporting Information Available: Data analysis and data tables; ^{1}H NMR spectra (in D_2O) 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.

OL800021R

(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.

(24) Mezzina, E.; Cruciani, F.; Pedulli, G. F.; Lucarini, M. *Chem. Eur. J.* **2007**, *13*, 7223−7233.