JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX−XXX
pubs.acs.org/JACS

Alcohols as Latent Hydrophobes: Entropically Driven Uptake of 1,2-Diol Functionalized Ligands by a Porous Capsule in Water

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Supporting Information

ABSTRACT: Alcohols, with hydroxyl groups compositionally identical to water itself, are consummate hydrophiles, whose high solubilities preclude spontaneous self-assembly in water. Nevertheless, the solute−solvent interactions associated with their highly favorable solvation enthalpies impose substantial entropic costs, similar in magnitude to those that drive the hydrophobic assembly of alkanes. We now show that under nanoconfined conditions this normally dormant "hydrophobicity" can emerge as the driving force for alcohol encapsulation. Using a porous molecular capsule, the displacement of endohedrally coordinated formate ligands (HCO_2^-) by 1,2-hydroxyl-functionalized L-glycerate (L-gly, L-$HOCH_2(HO)CHCO_2^-$) was investigated by van't Hoff analysis of variable-temperature ^{1}H NMR in D_2O. At pD 5.8, L-gly uptake is enthalpically inhibited. Upon attenuation of this unfavorable change in enthalpy by cosequestration of protons within the alcoholic environment provided by encapsulated diol-functionalized ligands, $-T\Delta S^\circ$ dominates over ΔH°, spontaneously filling the capsule to its host capacity of 24 L-gly ligands via an entropically driven hydrophobic response.

Water-mediated noncovalent interactions play a central role in numerous biological and chemical processes, and in supramolecular assembly. Among this broad class of interactions, hydrophobic effects control biological processes such as protein folding, substrate recognition and binding, and formation of cell walls from amphiphilic phospholipids.[1] In chemistry, they drive the self-assembly of hydrocarbons and amphiphiles into a wide range of diverse structures, and provide a basis for numerous host−guest phenomena.[2] Moreover, it is now recognized[3] that hydrophobic effects include an increasingly large family of related phenomena, encompassing, for example, entropically driven hydrocarbon aggregation, van der Waals interactions between aromatic (π) and alkane components in supramolecular host−guest chemistry, and the enthalpically driven release of high-energy water upon substrate binding to enzyme active sites.

Alcohols by contrast, including saccharides, whose −OH groups are compositionally identical to water itself, are viewed as consummate hydrophiles.[4] As such, the use of alcohols in supramolecular chemistry is dominated by their enthalpically driven self-assembly in organic solvents, for example, in the formation of numerous cages and containers held together by hydrogen bonds.[5,6] In this context, the binding of saccharides to natural and synthetic lectins[7] is generally attributed to enthalpically favorable van der Waals and related C−H−π interactions,[8−10] involving hydrocarbon components of the alcoholic substrates.

At the same time, the dissolution of polyols in water is accompanied by large *decreases* in entropy,[11] nearly indistinguishable in magnitude (kcal mol^{-1}) from those associated with similarly sized hydrocarbons. As such, correspondingly large gains in entropy would drive polyol sequestration from water, if not prohibited by their even larger enthalpies of hydration. This leads to the intriguing conclusion that attenuation of the unfavorable enthalpy change associated with the removal of polyols from water should trigger their entropically driven sequestration.

We report precisely this phenomenon. Documented for uptake of 1,2-diol-functionalized L-gly ligands by a tunable porous capsule (Figure 1), it represents a new type of reaction under confined conditions. Notably, this finding provides a new perspective on design considerations for hydrophile encapsulation in host−guest chemistry.

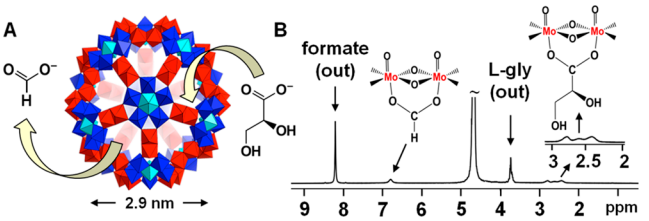

Figure 1. (A) Metal-oxide framework of **1**, shown in polyhedral notation, composed of 12 {(Mo)Mo_5}-type pentagonal units (in cyan and blue) and 30 dimolybdenum {Mo^V_2} linkers (in red). (B) Representative ^{1}H NMR spectrum of {**1**(formate)$_{19}$(L-gly)$_9$}$^{40-}$ at pD 5.8. The broad signals arise from the endohedrally coordinated ligands inside **1**.

Received: April 2, 2019

DOI: 10.1021/jacs.9b03542
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The porous capsule (Figure 1A)[12] is a (pentagon)$_{12}$(linker)$_{30}$-type complex, $[\{Mo^{VI}_6O_{21}(H_2O)_6\}_{12}\{(Mo^{V}_2O_4)_{30}(RCO_2)_{30}\}]^{42-}$,[13−23] abbreviated as $\{\mathbf{1}(RCO_2)_{30}\}^{42-}$, where **1** refers to the soluble capsule's inorganic framework and RCO_2^- are carboxylate ligands, bound via η_2-μ_2 (bidentate) coordination to the $Mo^{V}_2O_4$ (i.e., $\{Mo^{V}_2\}$) linkers (Figure 1B). The structural organization of the pentagons and linkers gives rise to 20 metal-oxide $\{Mo_9O_9\}$ pores that provide access to the capsule's interior. Notably, the interior of **1** is large enough to accommodate 24 L-gly ligands, while it is small enough to allow for stabilizing interactions between them.

In an equilibrated system containing 29 total equivalents of each ligand type ("in" and "out" combined) at 298 K (25 °C) at pD 5.8, 19 formate and 9 L-gly ligands were observed inside **1** by ^{1}H NMR (i.e, $\{\mathbf{1}(formate)_{19}(L\text{-}gly)_9\}^{40-}$; Figure 1B). As the temperature was decreased to 283 K, the number of internally bound L-gly ligands decreased to ca. 3, while upon increase of the temperature to 323 K (50 °C) the capsule was filled to near capacity with ca. 24 L-gly and only 4 formate ligands (Figure 2A).

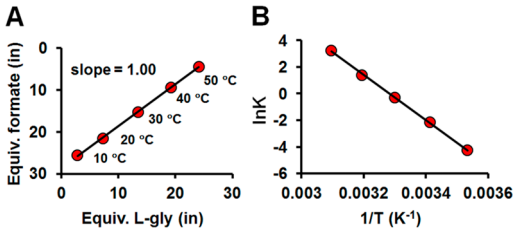

Figure 2. (A) Equivalents of formate and L-gly ligands inside **1** as the temperature is increased from 10 to 50 °C at pD 5.8. (B) van't Hoff plot of the temperature dependence of K (for the data in panel A; K is defined below).

This temperature-induced uptake of L-gly demonstrates the positive (favorable) change in entropy associated with its removal from bulk water. Moreover, the slope of the plot in Figure 2A is effectively unity, indicating that the associated change in populations of internally bound ligands occurs via one-to-one exchange. As such, the equilibrium constant, K, is defined by a mass balance expression (eq 1):

$$K = [\text{formate}_{(out)}][\text{L-gly}_{(in)}]/[\text{formate}_{(in)}][\text{L-gly}_{(out)}] \quad (1)$$

Importantly, the exchanging carboxylate ligands are conjugate bases of acids with nearly identical pK_a values, 3.7 and 3.5, respectively, for formic and L-glyceric acid, such that the difference in the Gibbs free energies associated with their coordination to $\{Mo^{V}_2\}$ linkages in **1** is very small. (For experiments in D_2O, pK_a values of 3.5 and 3.3, respectively, were used.) van't Hoff analysis[24−26] of the temperature dependence of K (Figure 2B) thus reveals the changes in entropy and enthalpy associated with solvation of the two ligand types in bulk water, versus within the ca. 15 000 Å^3 host domain[27] inside **1**. At pD 5.8, $\Delta H°$, $-T\Delta S°$, and $\Delta G°$ for the displacement of formate from **1** by L-gly were found to be +33.7, −33.0, and 0.7 kcal mol^{-1}, respectively, giving K = 0.29. Notably, without the favorable change in entropy, K (based on $\Delta H°$ alone) would be ca. 10^{-25}!

When L-glyceric *acid* (rather than its Na$^+$ salt) was added to the formate form of **1**, uptake of the L-gly anion was surprisingly favorable. First, formate buffer (pD 4.1) was added to the formate form of **1**, to give $\{\mathbf{1}(HCO_2)_{25}\}^{37-}$ plus 20 equiv of formate in bulk solution. Then, L-glyceric acid was added incrementally (up to 44 equiv), and its uptake was followed by ^{1}H NMR in D_2O. (Although pD values are reported throughout the text, deuterons are referred to for simplicity as protons.) Dramatically favorable uptake was observed (red squares in Figure 3A), very similar to that

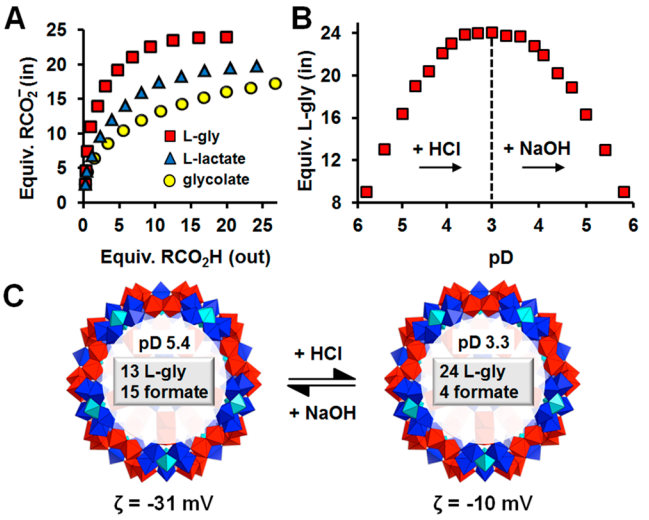

Figure 3. (A) Equivalents of glycolic, L-lactic and L-glyceric acids outside **1**, and of their conjugate anions bound inside **1**, as each acid was added to $[\mathbf{1}(formate)_{25}]^{37-}$. (B) Equivalents of L-gly ligands inside **1** (initially at pD 5.8) as HCl was added to decrease the pD to 3.0 (left side), after which NaOH was added to return the pD to 5.8 (right side). (C) Shift in the zeta potential (ζ) of **1** as the pD was decreased from 5.4 to 3.3.

reported for the entropically driven uptake of *n*-butyrate anions by **1**, which give an encapsulated micelle-like aggregate comprised of 24 ligands (with 72 CH_3- and $-CH_2-$ groups).[24] To assess the role of the two OH- groups on L-gly, glycolic and L-lactic acids ($HOCH_2CO_2H$ and L-$CH_3(HO)$-$CHCO_2H$, respectively), were also investigated. Uptake of L-gly anions was preferred over both (Figure 3A) (section S1.1 and Figures S1−S4).

The highly favorable uptake observed upon addition of L-glyceric acid was investigated by incrementally adding HCl to a pD 5.8 solution of $\{\mathbf{1}(formate)_{19}(L\text{-}gly)_9\}^{40-}$, which contained 29 equiv, each (total of "in" and "out"), of formate and L-glycerate anions (Na$^+$ forms). As the pD was decreased to 3.0, the capsule became populated by 24 L-gly ligands, the maximum number found to fit inside **1** (left side of Figure 3B). The process was also reversible: subsequent return to pD 5.8 (via addition of NaOH) led to a decrease in the number of internally bound L-gly ligands, from 24 back to 9 (right side of Figure 3B and section S1.2). These observations suggested that added H$^+$ might be cosequestered inside **1**.

In line with this, the zeta potential of **1** shifted from −31 to −10 mV as added HCl decreased the pD from 5.4 to 3.3 (Figure 3C). Importantly, the acid-induced uptake of L-gly ligands led to a one-to-one displacement of formate anions, so that at each pD value 28 anionic ligands were bound inside **1** (Figures 3C and S5). As such, the ligand-exchange process itself did not alter the total charge of the capsule. Rather, the shift to less negative ζ values points to H$^+$ sequestration. The process was reversible, with ζ returning to −31 mV as NaOH

DOI: 10.1021/jacs.9b03542
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addition shifted the mix of ligands inside **1** back to original values of 13 L-gly and 15 formate (Figure 3C). (In a control experiment involving Na_{34}**1**$(acetate)_{22}$, the decrease in the pD from 5.4 to 3.3 caused no change in ζ; see section S1.3.)

Quantitative support for H^+ sequestration was provided by using the Henderson–Hasselbalch equation[28−30] to calculate concentrations of the carboxylic acids and their conjugate-base anions in bulk water outside **1**. As HCl was added, leading to larger numbers of L-gly ligands inside **1**, the added protons (left in Figure 4A) could not be accounted for by hydronium ions

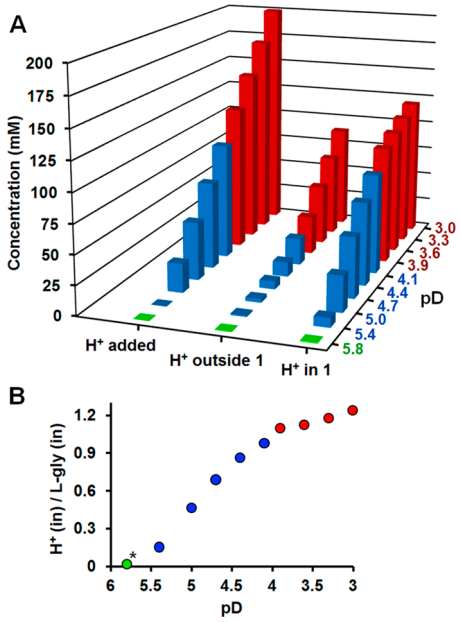

Figure 4. (A) Proton allocations from Henderson–Hasselbalch analysis. The leftmost and central sets of values are concentrations of added HCl and protons in formate and L-glycerate buffers outside **1**. Unaccounted for protons (far-right) were sequestered by **1**. (At pD 5.4, 13, L-gly inside **1**, the capsule acts as a polyprotic aqua acid, supplying two protons per capsule; see ref 31.) (B) Ratios of $H^+_{(in)}$ to L-$gly_{(in)}$ as a function of pD. Colors of the filled circles match identically color-coded regions in panel (A). The value at pD 5.8 (asterisk) was estimated.

and carboxylic acids in bulk solution (Figure 4A, center). These "missing" protons were allocated to sequestered H^+ ions (right in Figure 4A).

At pD 5.8, the total H^+ concentration was small, and only nine L-gly ligands were found within **1**. As the pD was decreased, the number of L-gly ligands inside **1** increased, as did the H^+:L-gly ratio (Figure 4B), which increased to ca. 1:1 (red-filled circles), as the capsule approached its host capacity of 24 L-gly ligands (section S1.4 and Figures S6–S7).

Crystallographic data were consistent with the presence of excess protons within the aqueous-alcoholic environment provided by encapsulated L-gly ligands and proximal water molecules. Dark brown rhombohedral crystals of **1** ($Me_2NH_2^+$ salt; space group $R\bar{3}$, CCDC-1878439) were grown in the presence of a large excess of pH-3 L-glycerate buffer. In line with ^{1}H NMR signal intensities, X-ray crystallographic data[32,33] indicated the presence of 24 L-gly ligands, each coordinated to one of the capsule's 30 $\{Mo^V_2\}$ linkers[19,34,35] (Figure 5A). Crystallographically defined conformations of L-gly ligands and water gave hydroxyl-to-water and hydroxyl-to-hydroxyl O atom distances between 2.8 and 3.1 Å, indicative of moderate-

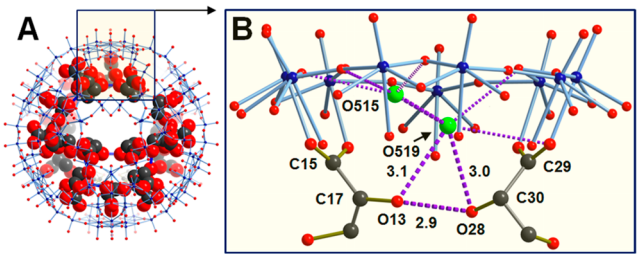

Figure 5. (A) Structure of **1** (in ball and stick notation, with Mo in blue and O in red), with space-filling representations of internally bound L-gly. (B) Side view of a $\{Mo_9O_9\}$ pore, highlighting short H-bonded distances (Å) from α-hydroxyl O atoms of L-gly (in red) to O atoms (in green) of nearby water or hydronium-ion dimers, H_4O_2 or $H_5O_2^+$.

strength H-bonds (Figure 5B) (section S1.5 and Figures S8–S15).

Finally, the effect of cosequestered protons on the energetics of L-gly self-assembly was investigated by van't Hoff analysis at pD values of from 5.8 to 3.0 (Figure 6A). At each pD value,

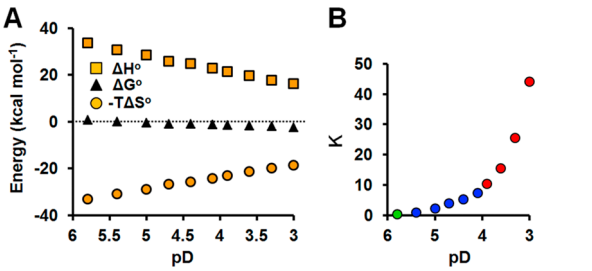

Figure 6. (A) Plot of $\Delta H°$, $-T\Delta S°$, and $\Delta G°$ (kcal mol^{-1}) for L-gly uptake by **1**, at pD 5.8 to 3.0. (B) Corresponding equilibrium constants, K (298 K), for L-gly uptake, determined from the $\Delta G°$ values in panel (A). Data markers are color-coded to match correspondingly colored entries in Figure 4.

temperature variation (10–50 C°) resulted in one-to-one displacements of formate by L-gly, such that K was defined as in eq 1 (section S1.6 and Figures S16–S27).

As the pD was decreased, $\Delta H°$ values were attenuated by proton solvation within the increasingly alcoholic environment within **1**,[36,37] while $-T\Delta S°$ decreased more gradually due (at least in part) to increasingly restricted degrees of freedom of the L-gly ligands as they filled the capsule's interior. At pD 3.0, $-T\Delta S°$ (−18.5 kcal mol^{-1}) dominated over $\Delta H°$ (+16.3 kcal mol^{-1}), triggering the spontaneous uptake of 24 L-gly ligands (in total) via an entropically driven hydrophobic effect, characterized by an overall 150-fold increase in K from 0.29 to 43.9 (Figure 6B; see also Tables S14–15 and Figure S28).

The data reported here show that, under confined conditions, the large entropic costs associated with the dissolution of nominally hydrophilic molecules in water can be utilized to drive their self-assembly. This is achieved using the porous capsule, **1**, as a versatile molecular container for rationally attenuating the enthalpic cost associated with the uptake of 1,2-diol functionalized L-gly ligands and, simultaneously, as a diamagnetic framework for precise ^{1}H NMR analysis of how equilibrated populations of encapsulated ligands change with temperature. The findings shed new light on future prospects for hydrophile self-assembly in water. Namely, creative options for attenuating unfavorable enthalpies of guest-sequestration processes may make it possible to

DOI: 10.1021/jacs.9b03542
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generate entropically driven assemblies of nominally hydrophilic building blocks in other water-soluble cages, containers, and nanostructures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b03542.

Experimental details, NMR spectra, and van't Hoff plots (PDF)

Crystallographic data for L-glycerate (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

I.A.W. thanks the Israel Science Foundation (170/17), S.C. thanks the Kreitman School of Advanced Graduate Studies of Ben-Gurion University of the Negev for a postdoctoral fellowship, and A.M. the European Union for an Advanced Grant.

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DOI: 10.1021/jacs.9b03542
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX