Acyclic Cucurbit[n]uril-type Molecular Containers: Influence of Aromatic Walls on their Function as Solubilizing Excipients for Insoluble Drugs

Ben Zhang and Lyle Isaacs*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States

Supporting Information

ABSTRACT: We studied the influence of the aromatic sidewalls on the ability of acyclic CB[n]-type molecular containers (1a−1e) to act as solubilizing agents for 19 insoluble drugs including the developmental anticancer agent PBS-1086. All five containers exhibit good water solubility and weak self-association ($K_s \leq 624 \text{ M}^{-1}$). We constructed phase solubility diagrams to extract $K_{rel}$ and $K_a$ values for the container-drug complexes. The acyclic CB[n]-type containers generally display significantly higher $K_a$ values than HP-$\beta$-CD toward drugs. Containers 1a−1e bind the steroidal ring system and aromatic moieties of insoluble drugs. Compound 1b displays highest affinity toward most of the drugs studied. Containers 1a and 1b are broadly applicable and can be used to formulate a wider variety of insoluble drugs than was previously possible with cyclodextrin technology. For drugs that are solubilized by both HP-$\beta$-CD and 1a−1e, lower concentrations of 1a−1e are required to achieve identical [drug].

INTRODUCTION

Molecular container compounds have been extensively studied over the years by synthetic, supramolecular, materials, and medicinal chemists by virtue of their ability to alter the properties of compounds bound within their interior. Some of the best-investigated classes of molecular container compounds include crown ethers, cryptands, carcerands, calixarenes, cyclophanes, cyclodextrins, and complexes self-assembled by metal-ligand and H-bonding interactions as well as reversible covalent bonds. For example, encapsulation inside molecular containers can reduce the reactivity of highly reactive species like $P_4$, reduce the odor of malodorous compounds, promote the reactions of included substrates, provide the basis of stimuli responsive molecular machines, enhance the photophysical properties of encapsulated dyes, and even reverse the toxic effects of certain compounds. We, and others, have been studying an alternative class of molecular containers known as cucurbit[n]urils (CB[n], $n = 5, 6, 7, 8, 10$, Figure 1). CB[n] compounds are particularly attractive because of the remarkably high affinity, selectivity, and stimuli responsiveness that they display toward their guests in aqueous solution. For these reasons, CB[n] compounds have been used as key components in the construction of functional supramolecular systems including affinity separation phases, supramolecular velcro, surface enhanced Raman scattering sensing, and for biomembrane assays.

An urgent problem facing the pharmaceutical industry is that a high percentage of new chemical entities with documented target affinity are so poorly soluble that formulation is challenging. A number of techniques and tools have been developed to address the drug solubility issue including the generation of nanocrystalline solid forms of the drug, salt formation, solid dispersions, and higher solubility prodrugs. Of highest relevance to supramolecular chemists, however, is the...
use of the cyclodextrin derivatives hydroxypropyl-\(\beta\)-cyclodextrin (HP-\(\beta\)-CD) and sulfobutyl ether-\(\beta\)-cyclodextrin (SBE-\(\beta\)-CD, Figure 1) to improve the solubility of insoluble drugs by encapsulation inside the molecular containers.\(^8\) A number of drugs are formulated for administration to humans by encapsulation inside HP-\(\beta\)-CD and SBE-\(\beta\)-CD. Accordingly, researchers in the CB\([n]\) area are exploring their use in this class of applications. For example, CB\([n]\) have been used to increase the solubility of a number of insoluble drugs (e.g., albendazole, chlorambucil, camptothecin), to retard degradation reactions, and for targeted drug delivery.\(^9\)

The Isaacs group has been interested in understanding the mechanism of CB\([n]\) formation and using that information to prepare CB\([n]\)-type receptors with new structural features and recognition properties.\(^10\) In 2012, we reported the synthesis of acyclic CB\([n]\)-type receptor 1a and its use as a solubilizing excipient for insoluble drugs. Compound 1a and relatives have three main structural features: (1) a central glycoluril oligomer to impart curvature and the ability to bind to hydrophobic and cationic species, (2) terminal aromatic walls to promote \(\pi-\pi\) interactions between container and insoluble drug, and (3) solubilizing sulfonate arms that result in high solubility.\(^11\)

In this Article we explore the influence of the nature of the aromatic sidewalls on the ability of the acyclic CB\([n]\)-type container 1b and relatives to act as solubilizing agents for insoluble drugs and found that sulfonate groups are particularly well-suited for this application because they impart high solubility in water and do not promote self-folding and complexation (e.g., as NH\(_3^+\) does).\(^12\)
containers (1a–1e, Scheme 1) to act as solubilizing agents for insoluble drugs.

## RESULTS AND DISCUSSION

This Results and Discussion section is organized as follows. First, we describe the synthesis and solubility of two new acyclic CB[n]-type receptors 1d and 1e. Next, we investigate the self-association properties of 1a–1e. Subsequently, we create phase solubility diagrams (PSDs) for 1a–1e toward a range of well-known poorly soluble pharmaceutical agents (Figure 2) and analyze trends in the solubilization data.

**Design and Synthesis of Acyclic CB[n]-type Containers 1a–1e.** Previously, we reported the synthesis and application of acyclic CB[n] type receptors 1a–1c by the double electrophilic aromatic substitution reaction of glycoluril tetramer bis(cyclic ether) building block 2 with the corresponding dialkoxyaromatic sidewalls 3 in hot CF₂CO₂H. Compounds 1a–1e differ in the nature of their aromatic sidewalls (e.g., benzene, naphthalene, tetrahydropyridazine). These structural differences impact the conformation of the uncomplexed container (e.g., smaller, larger, taller cavity) and the type and balance of noncovalent interactions (e.g., π–π, π–cation versus dispersion interactions) that form in the container-drug complexes. For example, the X-ray crystal structures of 1a show that the tips of the substituted benzene sidewalls are in close contact with one another. Therefore, to accommodate the longer naphthalene sidewalls of 1b, the glycoluril tetramer backbone of 1b flexes which results in a larger cavity that is defined in larger part by the aromatic naphthalene sidewalls. Compound 1c is an isomer of 1b; in this case the sidewalls are shorter and deeper by virtue of the attachment at the naphthalene 1,8 positions.

To prepare new acyclic CB[n] type receptors 1d and 1e which possess alkyd substituted sidewalls we needed to prepare compounds 3d and 3e. Accordingly, we reacted 2,3-dimethylhydroquinone with 1,3-propane sulfone (4) under basic conditions (NaOH) in dioxane at room temperature to give 3d in 73% yield (Scheme 1a). Sidewall 3e was prepared by a multistep procedure (Scheme 1b). First, we performed the Diels–Alder reaction between benzoquinone and 1,3-butadiene in toluene to give 5 in 92% yield. Next, we aromatized 5 by treatment with HBr to give 6 in 82% yield. Subsequently, we reduced the double bond of 6 under standard conditions to give 7 in 85% yield. Finally, 7 was reacted with 4 under basic conditions to give the required aromatic wall 3e in 60% yield. The reaction of glycoluril tetramer 2 with sidewall 3d (4 equiv) in a 1:1 (v:v) mixture of TFA:Ac₂O at 70 °C gave acyclic CB[n] type container 1d in 43% yield. Similarly, the reaction of 2 with 3e (4 equiv) gave container 1e in 30% yield.

**Solubility Properties of the Acyclic CB[n]-type Containers 1a–1e.** An important property of a container that is to be used as a solubilizing excipient for insoluble drugs is the inherent solubility of the container alone. Previously, we have reported the solubility of 1a and 1b in 20 mM sodium phosphate buffered D₂O at pH 7.4 as 105 and 14 mM, respectively. We used the methodology reported previously. 1H NMR assay in the presence of 1,3,5-benzene tricarboxylic acid as internal standard of known concentration, to determine the inherent solubilities of 1c (115 mM), 1d (353 mM), and 1e (145 mM). The high solubilities of 1a, 1c, 1d, and 1e make them particularly attractive as solubilizing exipients for insoluble drugs.

**Self-Association Properties of Acyclic CB[n]-type Containers 1a–1e.** Previously, we have investigated the self-association of 1a and 1b by dilution experiments monitored by 1H NMR spectroscopy. We found that the observed changes in chemical shift for each container fit well to a 2-fold self-association model and extracted the corresponding self-association constants (1a, K_s = 47 M⁻¹; 1b, K_s = 624 M⁻¹). Because 1a and 1b have a low propensity to self-associate, they are well-suited to act as solubilizing excipients for insoluble drugs. In a similar manner, we performed the 1H NMR dilution experiment (15–0.1 mM) for 1d and measured the corresponding value of K_s for 1d as 130 M⁻¹. When we performed similar 1H NMR dilution experiments for 1c, we unexpectedly observed two sets of resonances that were in slow exchange on the chemical shift time scale. We measured the diffusion coefficients for these two species by diffusion ordered NMR spectroscopy (D = 2.058 and 1.751 × 10⁻¹⁰ m²/s), Supporting Information) which allows us to conclude that the two species correspond to monomer 1c and dimer (1c)₂. Accordingly, we integrated the resonances for the two species at several different concentrations and determined the value of K_s (372 M⁻¹) in the usual manner. Finally, we performed a dilution experiment for 1e (35–0.2 mM) and observed both broadening and changes in 1H NMR chemical shifts. Unfortunately, the changes in chemical shift could not be fitted to the standard 2-fold self-association model, and we believe that 1e undergoes more complex higher order aggregation. The generally weak self-association observed for 1a–1e is advantageous toward their use as solubilizing excipients for insoluble drugs because the container is free to associate with drug without having to overcome strong self-association.

**Theoretical Treatment of Phase Solubility Diagrams.** PSDs are plots of [Drug] as a function of [Container] that are commonly used to study the ability of molecular containers to increase the solubility of insoluble drugs. These PSDs can assume a variety of shapes, but linear PSDs (AL-type) are most common and occur when container and guest form soluble complexes. Such PSDs behave according to eq 1 where S₀ is the solubility of drug alone and Kₛ is the binding constant for the container-drug complex. The slope of an AL-type PSD simply reflects the ratio of the increase in concentration of drug obtained relative to the concentration of container used. Container-drug systems that display larger PSD slopes (e.g., slope ≥0.5) are advantageous because larger concentrations of drug can be obtained with smaller concentrations of container. Figure 3 shows the results of two simulations that were performed on a hypothetical container-drug system that obeys eq 1 to stimulate the discussion and analysis of the experimental PSDs created for containers 1a–1e and HP-β-CD with drugs 8–26 shown in Figure 2. Figure 3a shows the calculated PSDs for five different containers and a single drug with S₀ = 1 × 10⁻⁶ M which form well-defined 1:1 container-drug complexes of high solubility. The different Kₛ values for the different container-drug complexes translate into PSDs with different slopes. For example, a change in slope from 0.1 to 0.5 and from 0.5 to 0.9 each corresponds to a 9-fold increase of Kₛ. Importantly, a precise knowledge of S₀ is not necessary in order to calculate relative Kₛ values (Kₛ₁/Kₛ₂) from the PSDs obtained with two different containers (e.g., C1 and C2) toward a common drug (e.g., D1) because the S₀ values cancel as shown in eq 2. If S₀ is known precisely, then absolute Kₛ...
2. Of these, 18 are drugs currently used in practice along with HP-β-CD of comparable slope. As a special case of eq 1, consider the insoluble drug by container until equilibrium is achieved, then remove remaining excess of insoluble drug with a known concentration of spectroscopy. Our 1H NMR assay relies on the addition of a 0.5) with an inherent solubility of 10 S of drug complex for (B) Plot of slope of the PSD versus K values for five different values of S (1 mM, 10 μM, 1 μM, 100 nM, 100 nM).

values can be calculated using eq 1. Figure 3b shows a plot of the slope of the PSD as a function of the Ks for the container-drug complex for five different values of S (1 mM, 100 μM, 10 μM, 1 μM, 0.1 μM). Clearly, the lower the inherent solubility of the drug (S), the higher the value of Ks needed to result in a PSD of comparable slope. As a special case of eq 1, consider the situation when (Ks/S) = 1; under this constraint, then slope = 0.5 (Figure 3b). From a practical point of view this means that to efficiently solubilize an insoluble drug (e.g., slope of PSD = 0.5) with an inherent solubility of 10 μM (100 nM) requires a Ks value of 105 M−1 (107 M−1). In theory, the high values of Ks that are typically observed for CB[n]-type receptors promise to enable the solubilization of drugs whose solubilities are too low to be solubilized by lower affinity hosts (e.g., cyclodextrins).

\[
K_a = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)
\]

\[
K_{rel} = \frac{K_{a,C1,D1}}{K_{a,C2,D1}} = \frac{\frac{\text{slope}_{C1,D1}}{h_0(1 - \text{slope}_{C1,D1})}}{\frac{\text{slope}_{C2,D1}}{h_0(1 - \text{slope}_{C2,D1})}} = \frac{(\text{slope}_{C1,D1})(1 - \text{slope}_{C2,D1})}{(\text{slope}_{C2,D1})(1 - \text{slope}_{C1,D1})} \quad (2)
\]

Use of 1α–1ε as Solubilizing Agents for Insoluble Drugs. In order to more fully understand the correlation between container structure (e.g., 1α–1ε), drug structure and properties, and the ability of the containers to solubilize insoluble drugs, we created PSDs for containers 1α–1ε and HP-β-CD with the 19 insoluble drugs (8–26) shown in Figure 2. Of these, 18 are drugs currently used in practice along with PBS-1086 (17) which is a developmental compound with documented anticancer activity.18 To create these PSDs we stir an excess of insoluble drug with a known concentration of container until equilibrium is achieved, then remove remaining insoluble drug by filtration or centrifugation, and measure the concentration of drug in the supernatant by 1H NMR spectroscopy. Our 1H NMR assay relies on the addition of a known concentration of 1,3,5-benzene tricarboxylic acid as a nonbinding internal standard of known concentration which allows us to use the ratio of the integrals for drug versus internal standard to measure drug concentration. We have measured full PSDs for all 19 drugs with the six containers (Supporting Information). In nearly all cases, linear PSDs were observed at low [container] indicative of well-defined 1:1 complex formation, although some of the PSDs display plateau regions at higher [container] which indicates that the solubility of the container-drug complex is lower than that of the uncomplexed container. Table 1 gives the initial slopes of the PSDs determined by linear regression for all container–drug combinations. Table 1 also presents the Krel values calculated using eq 2 referenced to the weakest binding host (usually HP-β-CD with Krel = 1). The uncertainties in Krel are generally ≈10–20%, although larger uncertainties are noted for PSDs with slope greater than or equal to 0.8. Figure 4 presents the PSDs measured for three drugs (estradiol (18), development anticancer agent 17, camptothecin (14)) with the 6 different containers. In the sections below, we analyze the data presented in Table 1 to ascertain key features of the use of acyclic CB[n]-type containers as solubilizing excipients for insoluble drugs.

Container 1β Is the Most Potent Solubilizing Agent. Of the 19 drugs tested, compound 1β is the most efficient solubilizing agent (e.g., largest slope, highest Krel) for 12 drugs, and is nearly the best for one additional drug [slopes for ziprasidone (26): 1b ≈ 0.432 versus 1ε = 0.458]. For five drugs [melphalan (10), amiodarone (13), camptothecin (14), 17α-ethynylestradiol (19), voriconazole (24)], 1β forms such tight complexes (slope ≈1) that it is not possible to calculate a Krel value using eq 1. Acyclic CB[n]-type containers including 1a and 1b are known to be relatively flexible11,19 and often exhibit an out-of-plane distortion (e.g., helical twist) as they wrap around their guests. Accordingly, each container-drug complex will exhibit a different geometry based on the size, shape, and functionality of the drug. However, we offer some rationale for the observed superior performance of 1b. Figure 5 shows the previously reported X-ray structures of 1a and 1b as their CF3CO2H solvates.11 First, the size of the cavity of 1b is larger than that of 1a as measured by the distance between the opposing quaternary C atoms (1a, 10.93 and 11.44 Å; 1b, 11.99 and 12.90 Å) of the dimethylglycoluril units. The increased size of 1b is caused by its longer naphthalene sidewalls (relative to 1a) which would clash sterically in a more compact geometry. Second, the naphthalene walls of 1b engage in edge-to-face π–π interactions with one another that creates a large hydrophobic π-surface that should allow it to simultaneously engage in edge-to-face and offset face-to-face π–π interactions with insoluble aromatic drugs. Containers 1d and 1e which feature Me and cyclohexyl substituted o-xyleneyl sidewalls should possess larger cavities than 1a; however, the alkyl substitution reduces the available π-surface area which should decrease their affinity toward insoluble aromatic compounds. For container 1c, the isomeric naphthalene sidewalls are of comparable length to 1a and result in a narrow and deep cavity. Accordingly, we surmise that the length of the naphthalene walls of 1b and their ability to define a hydrophobic box of large π-surface area makes 1b a superior solubilizing agent relative to containers 1a and 1c–1ε.

Solubilization of Steroids. The test panel of insoluble drugs contained three steroids [estradiol (18), 17α-ethynylestradiol (19), and fulvestrant (25)]. Steroids can often be solubilized with HP-β-CD, which allows a head-to-head comparison with
Table 1. Inherent Solubility ($S_\text{sol}\, \mu M$) of Selected Drugs and Values of Slope Calculated from the Linear Region of the PSDs for Containers 1a–1e and HP-β-CD with Drugs 8–26<sup>±</sup>

|   | 1a |   | 1b |   | 1c |
|---|---|---|----|---|----|
| $S_\text{sol}$ (μM) | Slope | $K_{\text{eq}}$ | $K_{\text{v}}$ | Slope | $K_{\text{eq}}$ | $K_{\text{v}}$ | Slope | $K_{\text{eq}}$ | $K_{\text{v}}$ |
| 8 | n.d. | 0.12 ± 0.0041 | 9.4 ± 0.45 | 0.48 ± 0.076 | 62 ± 13 | 0.026 ± 0.0032 | 1.8 ± 0.23 |
| 9 | 2.7 ± 0.34 | 10 | 1.2 ± 0.0080 | TL | 1.1 ± 0.072 | TL | 0.81 ± 0.10 | 34 ± 19 |
| 10 | n.d. | 12 ± 1.9 | 0.040 ± 0.0031 | 1.5 ± 0.15 | 0.10 ± 0.0071 | 3.9 ± 0.39 | 0.46 ± 0.010 | 30 ± 2.2 |
| 11 | 14 ± 1.7 | 0.59 ± 0.0095 | 6.3(±0.30) × 10³ | 0.0 ± 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 12 | 66 ± 2.7 | 0.080 ± 0.0074 | 0.89 ± 0.11 | 1.03 ± 0.15 | TL | 0.14 ± 0.0074 | 1.6 ± 0.18 |
| 13 | 54 ± 3.9 | 0.14 ± 0.0070 | 1.0 ± 0.073 | 1.1 ± 0.059 | TL | 0.26 ± 0.019 | 2.2 ± 0.20 |
| 14 | 57 ± 1.1 | 0.024 ± 0.0017 | 1.8 ± 0.14 | 0.47 ± 0.037 | 67 ± 7.3 | 0.022 ± 0.0022 | 1.69 ± 0.17 |
| 15 | 1.9 ± 0.41 | 0.043 ± 0.0037 | 5.5 ± 1.2 | 0.54 ± 0.017 | 1.6(±0.35) × 10³ | 0.052 ± 0.0023 | 4.0(±0.87) × 10³ |
| 16 | 4.5 ± 0.90 | 0.71 ± 0.027 | 15 ± 2.0 | 0.89 ± 0.0043 | 50 ± 5.0 | 0.14 ± 0.013 | 2.9(±0.63) × 10³ |
| 17 | 8.8 ± 0.42 | 0.35 ± 0.019 | 6.2(±0.48) × 10³ | 0.92 ± 0.053 | 51 ± 33 | 0.38 ± 0.015 | 2.7 ± 0.14 |
| 18 | 24 ± 2.4 | 0.35 ± 0.016 | 1.0 | 1.0 | 2.2(±0.24) × 10³ | 0.41 ± 0.071 | 1.25 ± 0.27 |
| 19 | n.d. | 0 | — | 0 | — | 0.12 ± 0.0098 | 8.6 ± 1.8 |
| 20 | 23 ± 3.1 | 0.066 ± 0.0034 | 2.0 ± 0.16 | 0.31 ± 0.027 | 13 ± 1.4 | 0.034 ± 0.0020 | 1.0 |
| 21 | n.d. | 0 | — | n.d. | — | 0.0 | 0.0 |
| 22 | n.d. | 0.079 ± 0.0092 | 1.0 | 0 | — | 0.0 |
| 23 | 38 ± 1.6 | 0.50 ± 0.047 | 3.4 ± 0.54 | 1.0 ± 0.026 | TL | 0.40 ± 0.037 | 2.3 ± 0.32 |
| 24 | n.d. | 0 | — | 0 | — | 0.0 |
| 25 | 63 ± 3.5 | 1.1 ± 0.19 | TL | 0.43 ± 0.052 | 29 ± 5.0 | 0.18 ± 0.018 | 8.2 ± 1.1 |

|   | 1d |   | 1e |   | HP-β-CD |
|---|---|---|----|---|---|
| $S_\text{sol}$ (μM) | Slope | $K_{\text{eq}}$ | $K_{\text{v}}$ | Slope | $K_{\text{eq}}$ | $K_{\text{v}}$ | Slope | $K_{\text{eq}}$ | $K_{\text{v}}$ |
| 8 | n.d. | 0 | — | 0 | — | 0 | — | 0 | — |
| 9 | 2.7 ± 0.34 | 0.10 ± 0.0057 | 8.0 ± 0.51 | 0.43(±0.60) × 10³ | 0.0 | — | 0.04 ± 0.0057 | 10 |
| 10 | n.d. | 0.80 ± 0.071 | 32 ± 12 | 0.47 ± 0.053 | 69 ± 1.3 | 0.11 ± 0.012 | 10 |
| 11 | 12 ± 1.9 | 0.060 ± 0.0046 | 2.2 ± 0.23 | 0 | — | 0.028 ± 0.0019 | 10 |
| 12 | 14 ± 1.7 | 0 | — | 0.057 ± 0.0011 | 27 ± 1.1 | 0.0020 ± 0.000086 | 2.4(±0.41) × 10³ |
| 13 | 66 ± 2.7 | 0.13 ± 0.0039 | 1.5 ± 0.14 | 0.13 ± 0.0050 | 1.6 ± 0.16 | 0.089 ± 0.0083 | 1.6(±0.22) × 10³ |
| 14 | 54 ± 3.9 | 0.50 ± 0.010 | 6.4 ± 0.38 | 0.13 ± 0.0070 | 1.0 | 0 | — |
| 15 | 57 ± 1.1 | 0.017 ± 0.0018 | 1.3 ± 0.14 | 0 | — | 0.013 ± 0.00040 | 1.0 |
| 16 | 1.9 ± 0.41 | 0.033 ± 0.0045 | 4.4 ± 1.0 | 0 | — | 0.0080 ± 0.0015 | 1.0 |
| 17 | 4.5 ± 0.90 | 0.52 ± 0.023 | 6.4 ± 0.73 | 0.16 ± 0.017 | 1.1 ± 0.16 | 0 | — |
| 18 | 8.8 ± 0.42 | 0.61 ± 0.056 | 6.8 ± 1.2 | 0.52 ± 0.064 | 4.7 ± 0.86 | 0.18 ± 0.0025 | 2.6(±0.13) × 10³ |
| 19 | 24 ± 2.4 | 0.38 ± 0.026 | 1.1 ± 0.11 | 0.44 ± 0.014 | 1.4 ± 0.094 | 0.47 ± 0.048 | 1.6 ± 0.24 |

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The corresponding $K_\text{s}$ (M$^{-1}$) and $K_{\text{rel}}$ values were calculated using eqs 1 and 2. n.d. = not determined, n.l. = nonlinear PSD; $-$ = could not be determined because PSD is nonlinear or slope = 0; TL = too large to be determined from PSD.

![Figure 4. PSDs constructed for mixtures of containers (1a, ■; 1b, ●; 1c, ▲; 1d, ▼; 1e, ◆; HP-β-CD, ▼) with selected insoluble drugs: (a) estradiol (18), (b) 17, (c) camptothecin (14). Conditions: 20 mM sodium phosphate buffered D$_2$O (pH = 7.4, rt). The red data points were not used in the linear regression.](image)

![Figure 5. Cross-eyed stereoscopic representations of the X-ray crystal structures of (a) 1a and (b) 1b. Solvating CF$_3$CO$_2$H molecules have been omitted for clarity. Color code: C, gray; H, white; N, blue; O, red; S, yellow.](image)
Me-substituted sidewalls of 1d makes it intermediate in size (Figure S) between 1a and 1b.

**Acyclic CB[n]-type Containers Are Good Solubilizing Agents for Insoluble Drugs Containing Aromatic Rings.** The X-ray crystal structures of 1a and 1b (Figure S) show that the aromatic sidewalls are oriented roughly perpendicular to the aromatic rings would be good guests for acyclic CB[n]-type containers. The majority of drugs studied in this paper contain aromatic rings within their structure, and we generally observed upfield shifting of the $^1$H NMR resonances of these aromatic rings upon complexation with 1a−1e. Those aromatic rings with attached ammonium functional groups (e.g., anilines, benzimidazoles, N-arylpyrazines) constitute preferred binding sites. In only one case (amiodarone, 13) was complexation at an aliphatic ammonium (Pr$_2$NH$^+$) moiety predominant. The observed upfield shifting of the aromatic protons confirms that the aromatic residues of the drugs are encapsulated within the hydrophobic box that is defined by the two aromatic walls and the methylene bridged glycoluril tetramer backbone. For example, Figure 6d−f shows the $^1$H NMR spectra recorded for camptothecin (14) alone in DMSO-$d_6$ and in water in the presence of containers 1d and 1b. Obviously, the protons on the aromatic rings of camptothecin (H$_a$−H$_j$) undergo substantial upfield shifts upon complexation. Larger upfield shifts are observed upon complexation with 1b probably because of the larger anisotropic shielding effect of the naphthalene walls of 1b relative to the o-xylene walls of 1d. Figure 4c shows the PSDs created for mixtures of camptothecin (14) with containers 1a−1e and HP-β-CD which display A$_2$-type PSDs indicative of 1:1 complexation. All five acyclic CB[n]-type containers (1a−1e) solubilize camptothecin (14) nicely, with 1b doing so in equimolar amounts whereas HP-β-CD is unable to solubilize camptothecin under these conditions. Among containers 1a−1e, container 1e displays the narrowest scope of solubilizing abilities with 9 out of 19 drugs displaying no solubilization. We attribute the poor solubilization abilities of 1e to the half-chair conformation of its tetrahydronaphthalene walls which sterically impede π−π interactions. We believe that the strategic merging of the structural features of CB[n]-type receptors (to deliver strong hydrophobic binding and ammonium binding) with the aromatic walls of cyclophanes to impart affinity toward the wide variety of insoluble aromatic drugs positions acyclic CB[n]-type receptors as a powerful alternative to cyclodextrins that expands the scope of insoluble drugs that can be formulated with molecular container technology.

**Some Drugs Are Solubilized by a Narrow Set of Containers.** Four drugs are solubilized by only one acyclic CB[n]-type container: paclitaxel (8) and docetaxel (23) by 1a, fenofibrate (22) and fulvestrant (25) by 1b. Cinnarizine (12) is only solubilized by two containers; it is best solubilized by 1a and less well by 1e. On the basis of this data we believe that containers 1a and 1b are the most versatile and general purpose solubilizing agents and that these containers are best positioned for further development as novel solubilizing excipients for practical applications.

**Container 1d Is Structurally and Functionally Intermediate between 1a and 1b.** The dimethyl substituted o-xylene walls of container 1d are intermediate in length between 1a and 1b which feature benzene and naphthalene derived sidewalls. Compound 1d is also intermediate between 1a and 1b in terms of its self-association properties but possesses superior solubility characteristics (353 mM) in buffered water. Accordingly, and perhaps unsurprisingly, we find that 1d exhibits solubilization abilities that are similar to those of 1a and 1b. For example, for albendazole (9), melphanal (10), amiodarone (13), indomethacin (15), and toltenamic acid (16), the slopes and $K_{rel}$ values for 1d are comparable to those of 1a but significantly smaller than the corresponding values measured for 1b. For other drugs, namely voriconazole (24) and ziprasidone (26), the slope and $K_{rel}$ values measured for 1d are more comparable to those of 1b than 1a.

**Comparison of the Binding Affinity of 1a−1e with HP-β-CD toward Insoluble Drugs.** It is also possible to determine the absolute $K_s$ value for container-drug complexes from the PSDs if the solubility of the uncomplexed drug ($S_0$) is known. Accordingly, we measured the inherent solubility for 13 of the 19 drugs studied and used these $S_0$ values to determine the absolute $K_s$ values for this selection of drugs as given in Table 1. The binding constants for these 13 drugs toward HP-β-CD span the range 160−36 000 M$^{-1}$ which is in line with the well-known low affinity ($K_s = 2.5 ± 1.1$ M$^{-1}$) and low selectivity of cyclodextrins toward their guests.$^{21}$ In contrast, the $K_s$ values measured for these 13 drugs toward 1a−1e fall in the range 1300 to 1.9 $×$ 10$^6$ M$^{-1}$ with three additional complexes too tight to measure using the PSD. For drugs that are solubilized by HP-β-CD, the best acyclic container (e.g., 1a−1e) always forms significantly stronger container-drug complexes (29- to 630-fold stronger) than HP-β-CD. In many cases the acyclic containers bind to and solubilize drugs [e.g., camptothecin (14) and aripiprazole (21)] that cannot be solubilized at all with HP-β-CD under these conditions. The ability of 1a−1e to solubilize drugs that cannot be solubilized with HP-β-CD and to do so more efficiently (larger slope and...
In summary, we have compared the ability of 1a–1e to solubilize insulin drugs relative to HP-β-CD. Compounds 1a–1e do not undergo strong self-association (K ≤ 624 M⁻¹) in buffered water and possess good solubility characteristics. We created PSDs for mixtures of containers 1a–1e and HP-β-CD with 19 drugs. We find that the solubilizing ability of the best container (1a–1e) is superior to HP-β-CD in all cases; 1a–1e even solubilize 8 drugs that are completely insoluble with HP-β-CD. The superior solubilizing ability can be traced to the 29- to 630-fold higher binding affinity of the best acyclic CB[6]-type container toward the drugs compared to HP-β-CD. Less container is needed, therefore, to achieve a given drug. A notable achievement was the solubilization of the developmental anticancer agent 17. The acyclic CB[6]-type containers display an affinity for the steroid ring system, aromatic moieties of insoluble drugs, and cationic ammonium groups. Compound 1b is generally the most potent (K up to and exceeding 10⁶ M⁻¹) container whereas both 1a and 1b display excellent solubility enhancement toward a broad range of insoluble drugs. The broad scope of insoluble drugs that can be formulated with 1a and 1b, in many cases where HP-β-CD fails completely, makes acyclic CB[6]-type containers particularly advantageous alternatives to cyclodextrins as solubilizing excipients for practical applications.

**EXPERIMENTAL SECTION**

**General Experimental.** Starting materials were purchased from commercial suppliers and were used without further purification. Compounds 1a–1c, 2, 5, and 6 were prepared according to literature procedures.11–13 Melting points were measured on a Melttemp apparatus in open capillary tubes and are uncorrected. IR spectra were measured on a JASCO FT/IR 4100 spectrometer by attenuated total reflectance (ATR) and are reported in cm⁻¹. HRMS spectra were measured at 400 or 600 MHz for ¹H and 125 MHz for ¹³C. Integration of the ¹H NMR spectra indicates that the new compounds have a level of purity ≥ 95%. Mass spectrometry was performed using a JEOL Acquity TOF electrospray instrument using the electrospray ionization technique.

1-[Propanesulfonic Acid, 2,3,3,3′,3″,3‴-(1,2,3-trimethyl-1,4-phenylene)bis(oxy)]bis(propyl-1-sulfonate) (3d). A solution of 4 (18 g, 0.15 mol) in 1,4-dioxane (130 mL) was added to a solution of 2,3-dimethylhydroquinone (8.0 g, 58 mmol) in aqueous NaOH solution (1.0 M, 10.0 L). The mixture was stirred at rt for 12 h and then filtered to collect the crude solid. The solid was stirred with acetone (0.20 L) and then dried under high vacuum to yield 3d as a pale red solid (18 g, 73%). 1H NMR (CDCl₃, δ): 7.39–7.34 (m, 8H), 7.12–7.08 (m, 4H), 6.99 (d, J = 8.0, 4H), 6.64 (d, J = 8.0, 4H), 6.38 (d, J = 8.0, 4H), 3.99 (d, J = 8.0, 4H), 3.94 (s, 12H), 3.88 (s, 12H), 3.82 (s, 12H), 3.74 (s, 12H), 3.68 (s, 12H), 3.64 (s, 12H), 3.60 (s, 12H), 3.55 (s, 12H), 3.52 (s, 12H), 3.49 (s, 12H), 3.43 (s, 12H), 3.25 (s, 12H), 2.90 (s, 12H), 2.69 (s, 12H), 2.52 (s, 12H), 2.48 (s, 12H), 2.42 (s, 12H), 2.39 (s, 12H), 2.33 (s, 12H), 2.28 (s, 12H), 2.22 (s, 12H), 2.17 (s, 12H), 2.11 (s, 12H), 2.05 (s, 12H), 2.00 (s, 12H), 1.98 (s, 12H), 1.94 (s, 12H), 1.88 (s, 12H), 1.80 (s, 12H), 1.79 (s, 12H), 1.75 (s, 12H), 1.69 (s, 12H), 1.60 (s, 12H), 1.28 (s, 12H), 1.19 (s, 12H), 1.03 (s, 12H), 0.87 (s, 12H), 0.82 (s, 12H), 0.78 (s, 12H), 0.74 (s, 12H), 0.69 (s, 12H), 0.66 (s, 12H), 0.63 (s, 12H), 0.60 (s, 12H), 0.57 (s, 12H), 0.54 (s, 12H), 0.51 (s, 12H), 0.48 (s, 12H), 0.45 (s, 12H), 0.42 (s, 12H), 0.40 (s, 12H), 0.37 (s, 12H), 0.35 (s, 12H), 0.32 (s, 12H), 0.29 (s, 12H), 0.27 (s, 12H), 0.24 (s, 12H), 0.22 (s, 12H), 0.20 (s, 12H), 0.18 (s, 12H), 0.16 (s, 12H), 0.14 (s, 12H), 0.12 (s, 12H), 0.10 (s, 12H), 0.08 (s, 12H), 0.06 (s, 12H), 0.04 (s, 12H), 0.02 (s, 12H), 0.00 (s, 12H). MS (ESI): m/z 381.0694 ([M – 2Na + H⁺], C₂₈H₄₅NO₁₆S₄O₂, calc for 381.0678).


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