ation of the oxidative Pd(II) adduct with the triple bond followed by trans-oxypalladation to produce 2, and finally (3) reductive elimination to produce 1 and regenerate the palladium catalyst (Scheme I).

The facile hydrolysis[1a,12] of these exocyclic enol ethers in acid or even in dry chloroform-*d* can be prevented by adding 1–10% of Et_3N to their solutions.

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Supplementary Material Available: Experimental section containing procedures and analytical data of starting materials and products (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) For example, *trans*-heptahydro-2(*E*)-(phenylmethylene)-2*H*-cyclohexa[*b*]furan is easily hydrolyzed to *trans*-2-(2-oxo-3-phenylpropyl)cyclohexanol in dry chloroform-*d* within 4 h at room temperature under nitrogen.

Controlled Molecular Aggregation. 1. Cyclic Trimerization via Hydrogen Bonding

Steven C. Zimmerman* and Brook F. Duerr

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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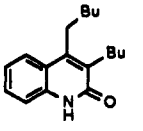
Summary: Vapor pressure osmometric and ^1H NMR dilution studies of quinolone **7**, isoquinolone **8**, and pyrido[4,3-*g*]quinolinedione **1**, indicate that **1** forms an extremely robust cyclic trimer in solution.

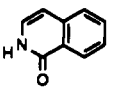
A contemporary challenge in organic chemistry is to develop strategies for controlling molecular aggregation.[1] In addition to providing insight into molecular recognition phenomena, advances in this area are likely to facilitate the creation of new materials and new molecular devices.[2] While numerous approaches to host–guest complexes have been developed, there are surprisingly few strategies available for forming mesomolecular aggregates (e.g., aggregates of 3–20 molecules). Such aggregates can be regarded as a logical first step toward engineering more complicated 3-dimensional assemblies with well-defined architectures. One potentially simple method for forming discrete mesomolecular aggregates in solution involves hydrogen bond mediated cyclic aggregation.[3,4] This strategy is illustrated by compound **1**, a pyrido[4,3-*g*]quinoline that was designed to form cyclic trimer **2** or linear aggregates (e.g., **3**) of any length, including dimers. Although **2** and **3** contain similar contacts, **2** is predicted to be of greater stability because it contains two hydrogen bonds per molecule of **1**, while **3** contains only $(2n + 2)/(n + 2)$ hydrogen bonds per **1**.[5] Herein we show that pyrido[4,3-*g*]quinolinedione **1** forms a robust aggregate in organic solvents and that the properties of the aggregate are consistent with those expected for cyclic trimer **2**.

Pyridoquinoline **1** was synthesized in nine steps as outlined in Scheme II.[6] Acylation of 3-bromoaniline by butyl ketene dimer[7] afforded keto amide **4**.[8] Knorr cyclization,[9] treatment with cuprous cyanide,[10] and DIBALH reduction gave quinolone **5**. Imine formation with aminoacetaldehyde dimethyl acetal and borohydride reduction afforded **6**,[11] which underwent oxidative cyclization with chlorosulfonic acid[12] and subsequent N-7 → C-8 oxidation[13] to form **1**.

The ability of **1** to aggregate in solution was examined both by ^1H NMR and vapor-pressure osmometry (VPO). The ^1H NMR spectra of **1** in chloroform-*d* was notable in that both N–H resonances appeared in the region (13–14 ppm) expected for fully associated (iso)quinolone systems. Furthermore, a striking difference in ^1H NMR dilution shifts was observed for **1** and model compounds **7** and **8**.



7



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While the N–H chemical shifts of **1** were largely unchanged across a broad concentration range ($\Delta\delta < 0.3$ ppm), ca. 70% of the dilution curve could be observed for quinolone

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(5) If a cyclic aggregate contains *n* subunits, its advantage over the analogous linear aggregate will vanish as *n* becomes large.

(6) All new compounds gave correct elemental analysis and had spectroscopic data that were in accord with the reported structures. The (iso)quinolone tautomeric form for **1** and its aggregates is more probable than the hydroxy(iso)quinoline forms: Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186–192. Mirek, J.; Sygula, A. *Z. Naturforsch.* **1982**, *37a*, 1276–1283. Dyke, S. F.; Kinsman, R. G. In *The Chemistry of Heterocyclic Compounds: Isoquinolines*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, Part 1, p 11.

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(9) For a review see: Jones, G. *The Chemistry of Heterocyclic Compounds*, Wiley: New York, 1977; Vol. 32; Part 1, pp 151–159.

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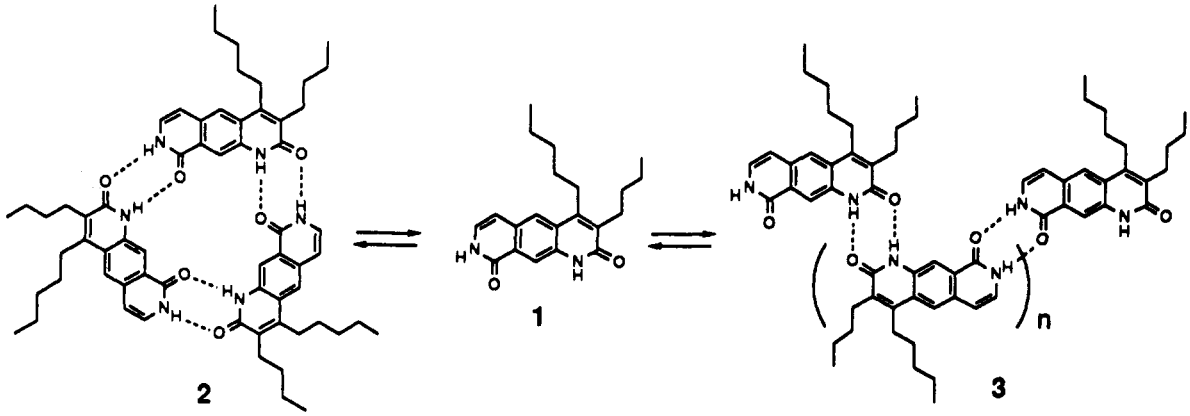
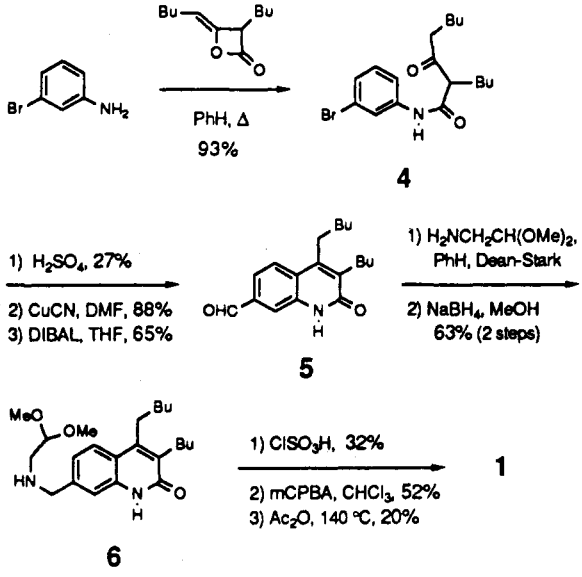
Scheme I



Scheme II



7, representing $\Delta\delta_{obs}$ = 3.45 ppm (Figure 1). These latter data fit a standard dimerization model giving K_2 = 46 M^{-1} for **7**·**7**.[14] Isoquinolone **8** gives a similar dilution curve with K_2 = 50 M^{-1} for **8**·**8** ($\Delta\delta_{obs}$ = 2.83 ppm, data not shown). The K_{assoc} for complex **7**·**8** was estimated to be of the same magnitude, although slightly larger than these K_2 values. These data indicate that **1** aggregates in a highly cooperative manner, which is most easily explained by cyclic as opposed to linear aggregation.

In order to determine the aggregation state of **1**, vapor-pressure osmometry (VPO) was performed in the solvent used for the ^{1}H NMR dilution studies (chloroform-*d*). The molecular weight determined from ca. 9–18 mM at 35 °C was 942 ± 80, which is within experimental error of that calculated for a trimer (MW_{calcd} = 1014).[15] Not withstanding the cooperative nature of the aggregation, this MW could represent a mixture of linear aggregates. At the concentrations used for VPO this would require each K_{assoc} ($3_n + 1 \rightleftarrows 3_{n+1}$) to be 94 M^{-1}, a value similar in magnitude to that seen for quinolone–isoquinolone complexes (vide supra).[16] Thus, it was of importance to independently determine the aggregation state of **1**. Toward this end, additional ^{1}H NMR dilution experiments were carried out in 10% DMSO-d_6/$CDCl_3$. In this more competitive solvent **7** and **8** are fully deaggregated (K_2 < 3 M^{-1}), even at high concentration, as evidenced by their nearly flat dilution curves (Figure 1). Similarly, the K_{assoc} for **7**·**8** is <3 M^{-1}.

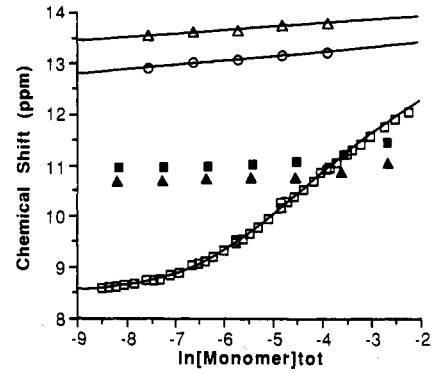


Figure 1. ^{1}H NMR dilution shifts: △, H-1; ○, H-7 for **1**, in $CDCl_3$; □, NH for **7** in $CDCl_3$; ■, N-H for **7** in 10% DMSO-*d*/$CDCl_3$; ▲, N-H for **8** in 10% DMSO-d_6/$CDCl_3$.

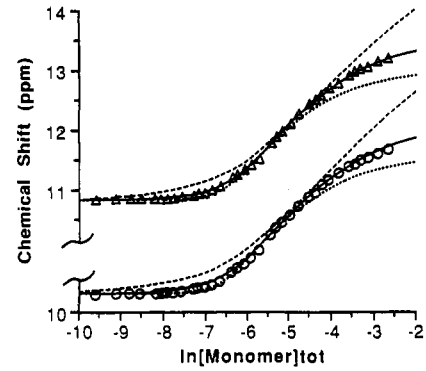


Figure 2. Saunders–Hyne analysis of ^{1}H NMR dilution shift of **1** in 10% DMSO-d_6/$CDCl_3$: △, H-1; ○, H-7, --- dimer model, K_2 = 45 M^{-1}, $\Delta\delta_{max}$ 4.25 (H-1), 4.46 (H-7); — trimer model, K_3 = 2.0 × 10^4 M^{-2}, $\Delta\delta_{max}$ 2.73 (H-1), 2.86 (H-7); ··· tetramer model, K_4 = 1.1 × 10^7 M^{-3}, $\Delta\delta_{max}$ 2.19 (H-1), 2.30 (H-7).

Although **7** and **8** do not self-associate or bind one another in DMSO-d_6/$CDCl_3$, in this solvent **1** still aggregates strongly, and nearly all of its ^{1}H NMR dilution curves could be accessed (Figure 2). As with the chloroform dilution study, this result makes it unlikely that **1** forms dimers or linear aggregates. In order to determine the possible structure of the cyclic aggregate, the dilution curves were fit to models for an *n*-merization process using the Saunders–Hyne method.[17] As can be seen in Figure

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(15) The molecular weights of two standards were determined by VPO in $CDCl_3$ and gave the following results: 2,4,5-trinitrofluorenone, MW_{obs} = 355, MW_{calc} = 315; 4-*tert*-butylcalix[8]arene, MW_{obs} = 1327, MW_{calc} = 1297.

(16) Implicit in this calculation is the assumption that only linear aggregates are present and each K_n is identical.

2, the best-fit trimer model fits well across the entire concentration range. In contrast, the best-fit dimer and tetramer models deviate substantially from the experimental data. Combined, these data suggest that 1 strongly aggregates in solution and that the aggregation state is that of cyclic trimer 2.

The trimerization constant, $K_3 = 20\,000\ M^{-2}$, obtained from the Saunders-Hyne analysis of 1, is very large, particularly given that quinolone 7 and isoquinolone 8 negligibly associate in 10% DMSO-d_6/$CDCl_3$.[18] For comparison, phenol is believed to form a cyclic hydrogen-bonded trimer in carbon tetrachloride with $K_3 = 4.78\ M^{-2}$.[17a] The robustness of the cyclic trimer under conditions where the individual binding contacts are weak provides strong support for the hydrogen bond mediated cyclic aggregation strategy. Efforts are underway to generate higher order cyclic aggregates and to stack these disk-shaped assemblies into tubes.

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(18) The equilibrium constant K_3 in the Saunders-Hyne analysis is the equilibrium constant for formation of the trimer from three monomers, not the equilibrium constant for addition of a third monomer onto an existing dimer.

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Synthesis of Enantiomerically Pure (2′*R*,5′*S*)-(−)-1-[2-(Hydroxymethyl)oxathiolan-5-yl]cytosine as a Potent Antiviral Agent against Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV)

J. Warren Beach,† Lak S. Jeong,† Antonio J. Alves,† Douglas Pohl,[1,†] Hea O. Kim,† Chien-Neng Chang,‡ Shin-Lian Doong,‡ Raymond F. Schinazi,§ Yung-Chi Cheng,‡ and Chung K. Chu*,†

Department of Medicinal Chemistry, College of Pharmacy, The University of Georgia, Athens, Georgia 30602, Department of Pharmacology, Yale School of Medicine, New Haven, Connecticut 06510, and Emory University School of Medicine/VA Medical Center, Atlanta, Georgia 30033

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Summary: The synthesis of the enantiomerically pure 2′*R*,5′*S*-(−) form of BCH-189 from L-gulose has been accomplished, and this isomer has been found to exhibit the most potent anti-HIV and anti-HBV activities among the four possible isomers. This is the first example of an "L-like" nucleoside which is more potent than its "D-like" isomer.

BCH-189[2] 1 is an interesting nucleoside which exhibits a potent anti-HIV activity in vitro and is undergoing clinical trials in patients with AIDS and AIDS related complex. It is a member of an unusual class of nucleosides in which the 3′-CH_2 group has been replaced by a heteroatom such as sulfur[2-4] or oxygen.[2,5,6]

Since the β-D-isomers of nucleosides are in general the biologically active isomers, we have recently synthesized the 2′*S*,5′*R*-(+) 2 and 2′*S*,5′*S*-(−) 4 isomers of BCH-189 (Table I) from 1,6-thioanhydro-D-mannose[3a] and more recently from 1,6-thioanhydro-D-galactose.[3b] Surprisingly, it was found that the "D-like" isomer 2 was less potent than racemic BCH-189 1 in human peripheral blood mononuclear (PBM) cells. Furthermore, compound 2 was also less potent against hepatitis B virus (HBV) than the racemic BCH-189 1. Thus, it was of great interest to synthesize the antipodes ("L-like" isomers) and compare their activities to those of the compounds 2 and 4. Doong et al.[7] reported that racemic BCH-189 was a potent anti-HBV compound in 2.2.15 cells (clonal cells derived from HepG2 cells transfected with a plasmid containing HBV DNA that secrete hepatitis B virons). It was therefore important to determine if this unexpected result also applied to HBV. We now wish to report the enantiomeric synthesis of the (2′*R*,5′*S*)-(−)-BCH-189 3 and its α isomer, (2′*R*,5′*R*)-(+) 5 and their anti-HBV and anti-HIV[8] activities.

Since we had successfully utilized D-mannose as the starting material for the key intermediate, 1,6-thioanhydro-D-mannose in the synthesis of 2′*S*,5′*R*-(+)-BCH-189 2,[3a] L-mannose was considered as a carbohydrate template for the 2′*R*-isomers. However, it was found that L-mannose is too expensive to use as the starting sugar for a practical synthesis of the 2′*R*-isomers. In search of a more useful L-series sugar, it was determined that L-gulose (6) would serve well as a starting material. L-Gulose (6) can easily be prepared from the commercially available

† The University of Georgia.
‡ Yale School of Medicine.
§ Emory University School of Medicine/VA Medical Center.

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