hedral angle (28.8°) between the two least-squares mean planes O(6)-C(16)-O(16)-C(17) with a maximum deviation of 0.006 Å and C(16)-C(17)-C(18)-C(19) with a 0.010 Å maximum deviation.

An intermolecular hydrogen bond exists between the hydroxyl oxygen, O(9), and the lactone carbonyl oxygen, O(12), of a neighboring molecule related by the twofold screw axis. The overall crystalline structure appears as spirals of molecules interconnected by intermolecular hydrogen bonds. The intermolecular O(9)-O(12) distance, 2.85 Å, is within range (2.55-2.96 Å) normally observed for hydroxyl donor to oxygen acceptor bonds.[15] The hydrogen was found to lie between the two oxygen atoms at distances of 1.07 Å from O(9) and 1.81 Å from O(12), with O-H···O angle of 164°.

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Supplementary Material Available: Structure factor tables (16 pages). Ordering information is given on any current masthead page.

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2-Deoxypentoses. Stereoselective Reduction of Ketene Dithioacetals

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Abstract: A new, general method for the synthesis of 2-deoxypentoses is described. 2-Deoxy-D-*erythro*-pentose and 2-deoxy-D-*threo*-pentose have been prepared from D-arabinose and D-xylose, respectively, by a route involving the formation and reduction of ketene dithioacetal derivatives. The key step in the synthesis is the use of lithium aluminum hydride to reduce ketene dithioacetals containing a free allylic hydroxyl group. Deuterium labeling experiments demonstrate that hydride transfer occurs stereoselectively at C-2, via intramolecular delivery from an alkoxyaluminum hydride salt, with water added during work-up serving as the proton source at C-1. This method also provides an efficient synthesis of deuterium- and tritium-labeled compounds.

Interest in the synthesis of deoxy sugars is prompted by the rapidly increasing number found as components of natural products, and by their increased utilization in the synthesis of antibiotics. To date, most methods of synthesis have involved selective deoxygenation of the parent sugars, which, in general, are more readily available. Although methods have been developed for the replacement of both primary and secondary hydroxyl by hydrogen,[2-5] no general method has been developed for the specific replacement of the C-2 hydroxyl of aldoses by hydrogen. Because of the ubiquitous occurrence of 2-deoxyaldoses, such a method would be of great synthetic utility.

In a recent communication, Wong and Gray[6] described a potential general method for the synthesis of 2-deoxyaldoses and their isotopically labeled derivatives, as illustrated in Scheme I for the conversion of D-arabinose (**1**) to 2-deoxy-D-*erythro*-pentose (**5**). It is the purpose of this article to elaborate this synthesis and to establish the mechanism and stereochemistry of the crucial reduction step (**3** → **4**).

Results

Synthesis of 2-Deoxy-D-*erythro*-pentose and 2-Deoxy-D-*threo*-pentose. Treatment of 2,3:4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (**2**, prepared in 70-80% yield from D-arabinose by published procedures[7-9]) with 1.5 equiv of *tert*-BuOK in Me_2SO-THF (1:3 v/v) resulted in abstraction of the acidic C-1 hydrogen and concomitant elimination of acetone to give 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (**3**) in 82% yield. The elimination was also accomplished under the conditions described by other workers, including potassium hydroxide in anhydrous THF,[10] sodium methylsulfinyl carbanion in Me_2SO,[11] and *n*-butyllithium in THF,[11] but the conditions reported herein gave much higher yields of the ketene dithioacetal.

Because of the instability of **3** in acid,[12] reduction could not be accomplished by the known protonation-hydride transfer sequence with trifluoroacetic acid-triethylsilane.[13] Reduction of **3** was accomplished, however, with lithium aluminum hydride (2.5 equiv) in dry THF. Following destruction of the

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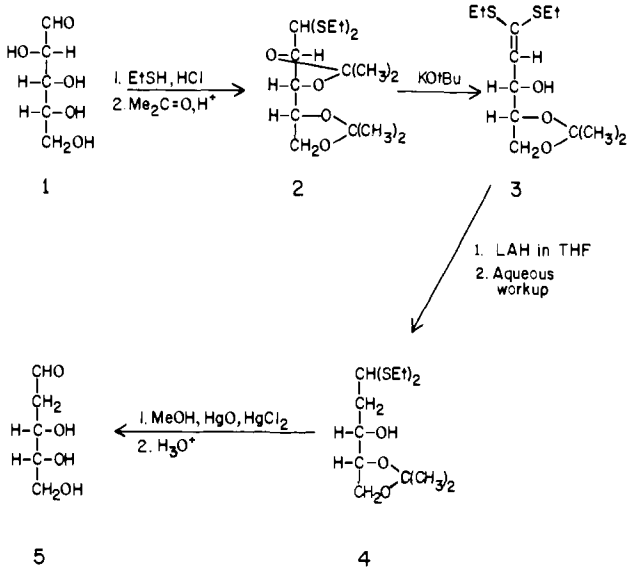
Table I. Proton Noise Decoupled ^{13}C NMR Spectra (δ, 25.1 MHz) of Ketene Dithioacetals **3** and **6** and Reduction Products **4** and **7**

Compd	C-1	C-2	C-3,4	C-5	Isopropylidene C	Isopropylidene CH_3[a]	Ethyl CH_2[a]	Ethyl CH_3
3	134.90	133.18	69.24, 77.71	64.94	108.98	(26.65, 27.13)	(24.88, 26.00)	13.56, 14.67
4	48.39	39.32	70.05, 78.82	65.97	109.55	25.37, 26.71	23.75, 24.46	14.51
2(*S*)-Deuterio-**4**	48.15	38.99 (t, J = 19 Hz)	69.74, 78.83	66.01	109.47	25.34, 26.68	23.51, 24.38	14.51
1-Deuterio-**4**	48.10 (t, J = 22 Hz)	39.23	69.61, 78.73	65.95	109.32	25.30, 26.65	23.36, 24.32	14.52
1,2(*S*)-Dideuterio-**4**	48.25 (t, J = 22 Hz)	39.05 (t, J = 19 Hz)	69.63, 78.77	66.00	109.41	25.31, 26.64	23.37, 24.32	14.49
6	135.95	133.34	70.68, 79.05	65.84	109.84	(27.06, 27.62)	(25.43, 26.71)	13.93, 15.05
7	47.83	40.28	69.60, 79.00	66.02	109.55	25.35, 26.61	23.95, 24.35	14.58
2(*R*)-Deuterio-**7**	47.75	39.95 (t, J = 20 Hz)	69.55, 78.88	65.98	109.51	25.30, 26.57	23.99, 24.37	14.51
1-Deuterio-**7**	47.52 (t, J = 20 Hz)	40.12	69.53, 78.97	65.95	109.45	25.32, 26.55	23.85, 24.29	14.53
1,2(*R*)-Dideuterio-**7**	47.46 (t, J = 20 Hz)	39.81 (t, J = 20 Hz)	69.53, 78.93	65.99	109.52	25.32, 26.58	23.89, 24.29	14.53

[a] The isopropylidene CH_3 and ethyl CH_2 resonances have not been assigned for compounds **3** and **6** and are shown in parentheses. These resonances have been assigned for compounds **4** and **7** and their deuterated derivatives based on a correlation with the spectrum of 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose dimethyl acetal (see Experimental Section).

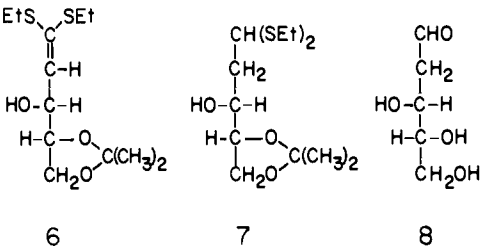
Scheme I. Synthesis of 2-Deoxy-D-*erythro*-pentose from D-Arabinose



excess $LiAlH_4$ and workup in the usual way,[14] pure 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (**4**) was isolated in 80% yield.

Removal of the protecting groups of **4** to give the free 2-deoxyaldose (**5**) was accomplished most conveniently, and in the highest yield (62% overall), by a two-step procedure involving conversion of the diethyl dithioacetal to the dimethyl acetal followed by mild aqueous acid hydrolysis (0.01 N trifluoracetic acid, 18 h at 4 °C). Attempted hydrolysis of the dithioacetal by S-methylation and base treatment,[15] or with chloramine-T,[16] gave poor yields. Final purification of **5**, and all other 2-deoxyaldoses prepared herein, was accomplished by gel filtration over a 2.5 × 98 cm column of Bio-Gel P-2 in water. Fractions were assayed by the thiobarbituric acid procedure,[17] a specific colorimetric test for 2-deoxyaldoses, and, in all cases, the major positive peak was found to be the expected 2-deoxyaldose.

The synthesis of 2-deoxy-D-*threo*-pentose (**8**) was accomplished in a similar manner from D-xylose, which was converted to its 2,3:4,5-di-*O*-isopropylidene diethyl dithioacetal in 65–75% yield.[10,18] Treatment of the latter with *tert*-BuOK, followed by reduction of the intermediate ketene dithioacetal (**6**) with $LiAlH_4$ as before, gave 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (**7**) in 84% yield. Removal



of the protecting groups under the same conditions described above for the erythro isomer (**4**), and purification by gel filtration, gave 2-deoxy-D-*threo*-pentose (**8**) in 63% yield.

Deuterium Labeling Studies

To establish the mechanism of the lithium aluminum hydride reduction of the ketene dithioacetal intermediates, combinations of $LiAlH_4$ or $LiAlD_4$ reductions and H_2O or D_2O workups were performed. The positions of deuterium labeling were determined from the ^{13}C NMR spectra of the reduction products (**4** and **7**) and the final 2-deoxyaldoses (**5** and **8**). In the spectrum of **4** (Table I), C-1 and C-2 have chemical shifts of δ 48.39 and 39.32, respectively, as established by off-resonance decoupling, and by comparison with the spectra of **2** and **3**. When the reduction of **3** was accomplished with $LiAlD_4$, followed by H_2O workup, the 2-deuterio derivative of **4** was formed, i.e., the C-1 resonance at δ 48.15 remained a singlet in the fully hydrogen-decoupled spectrum, but the C-2 resonance at 38.99 was observed as a triplet (J = 19 Hz). If, however, the reduction was accomplished with $LiAlH_4$, followed by the addition of excess D_2O prior to workup, the ^{13}C NMR spectrum of the product contained a very weak triplet (J = 22 Hz) at δ 48.10 (C-1) and a singlet at 39.23 (C-2) demonstrating that the 1-deuterio had been formed. Finally, when the reduction of **3** was accomplished with $LiAlD_4$, followed by the addition of excess D_2O prior to workup, the ^{13}C NMR spectrum of the product contained triplets at both δ 48.25 (J = 22 Hz) and 39.05 (J = 19 Hz), demonstrating that the expected 1,2-dideuterio derivative of **4** had been formed.

Identical results were obtained from deuterium labeling experiments with **7**, derived from D-xylose (Table I), i.e., H-1

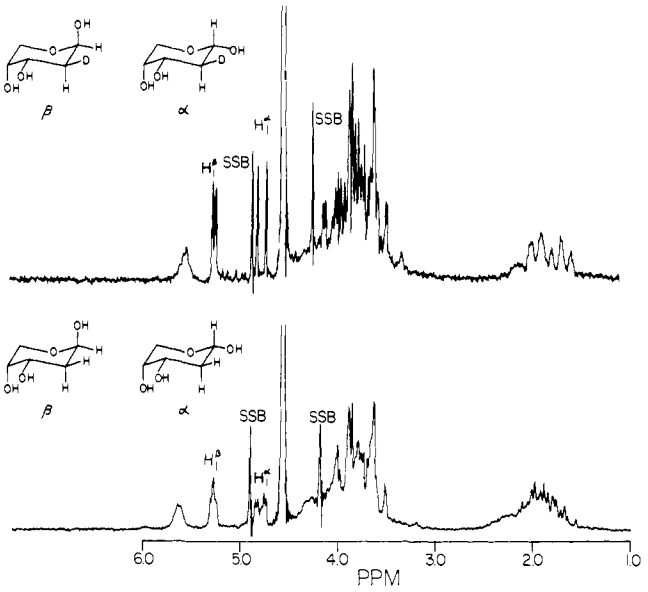


Figure 1. The 100-MHz proton magnetic resonance spectra of 2-deoxy-D-*erythro*-pentose (**5**) (lower spectrum) and 2-deoxy-2(*S*)-deuterio-D-*erythro*-pentose (**9**) (upper spectrum) in D_2O at 27 °C with sodium 3-trimethylsilyl-2,2,3,3-tetradeuteriopropionate external standard (coaxial capillary). The signal at δ 5.6 corresponds to the H-1 resonance of a furanose form.

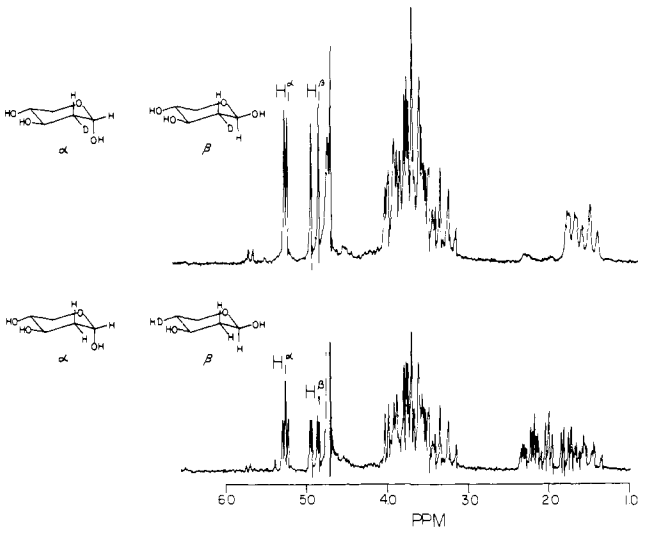
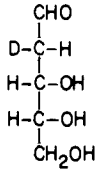


Figure 2. The 100-MHz proton magnetic resonance spectra of 2-deoxy-D-*threo*-pentose (**8**) (lower spectrum) and 2-deoxy-2(*R*)-deuterio-D-*threo*-pentose (**10**) (upper spectrum) in D_2O at 27 °C with sodium 3-trimethylsilyl-2,2,3,3-tetradeuteriopropionate external standard (coaxial capillary).

in the reduction product was derived from water added on workup and H-2 was derived from lithium aluminum hydride. The positions of deuterium labeling were confirmed by the ^{13}C NMR spectra of the free sugars (**5** and **8**) and their deuterated derivatives. The C-1 and C-2 resonances of 2-deoxyaldoses are well separated from the other ^{13}C resonances, and are readily observed. The C-2 resonances of all 2-deuterio derivatives were observed as triplets (J = 20 Hz), demonstrating coupling to one deuterium atom, and the C-1 resonances of all 1-deuterio derivatives were not observed, owing in part to acquisition parameters and loss of sensitivity. All other resonances in the spectra of deuterated derivatives, however, were identical with those found in the spectra of the parent sugars (**5** and **8**).

Stereochemistry of Hydride Transfer. The stereochemistry of hydride transfer was determined from a comparison of the ^1H NMR spectra of **5** and **8** and their 2-deuterio and 1,2-dideuterio derivatives. In the spectrum of **5** (Figure 1, lower spectrum), as previously reported,[19] the H-1 resonance of the α-pyranose form in the $^1C_4$ conformation occurs at δ 4.78 as a doublet of doublets ($J_{H\text{-}1a,2a}$ = 8.7 Hz, $J_{H\text{-}1a,2e}$ = 2.8 Hz). The H-1 resonance of the β-pyranose form is observed downfield at δ 5.27, as an apparent triplet, with $J_{H\text{-}1e,2e} \simeq J_{H\text{-}1e,2a}$ = 3.2 Hz. In the spectrum of the 2-deuterio derivative of **5** (Figure 1, upper spectrum), the H-1 resonance of the α-pyranose form is observed at δ 4.78 as a doublet with a large coupling constant (J = 8.7 Hz), demonstrating that H-2 is axial. The H-1 resonance of the β-pyranose form (δ 5.27) was also a doublet (J = 3.2 Hz), but, since the coupling constants between H-1 and H-2a,2e are approximately equal, the J value for H-1 in the β-pyranose form cannot be used to deduce the stereochemistry of deuterium substitution at C-2. The H-2 resonances of the α- and β-pyranose forms of the 2-deuterio derivative of **5** also reveal the stereochemistry at C-2. The H-2 resonance of the α-pyranose form (δ 1.71) is an apparent triplet (J = 10 Hz) due to trans-diaxial coupling with H-1 and H-3. The H-2 resonance of the β-pyranose form (δ 1.97), however, is a broad doublet due to trans-diaxial coupling with H-3 (J = 11 Hz), and a smaller, unresolved coupling with H-1. These assignments were confirmed in the spectrum of the 1,2-dideuterio derivative of **5**. The H-2 resonances of both the α- and β-pyranose forms were both doublets (J = 11 Hz) due to trans-diaxial coupling with H-3. The H-2 resonances of both the 2-deuterio and 1,2-dideuterio derivatives of **5** were line broadened, presumably owing to geminal deuterium coupling.

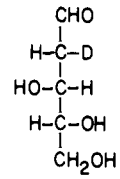
These studies demonstrate unequivocally that 2-deoxy-2(*S*)-deuterio-D-*erythro*-pentose (**9**) was formed exclusively



9

via reduction of **3** with $LiAlD_4$. The chemical shifts and J values reported herein for **9** are, with one exception,[20] in agreement with those previously reported for the same compound prepared from glucose by a much lengthier synthesis.[21]

The stereochemistry of hydride transfer for the reduction of the *threo*-ketene dithioacetal (**6**) was similarly established from the ^1H NMR spectra of **8** and its 2-deuterio and 1,2-dideuterio derivatives. In the spectrum of **8** (Figure 2, lower spectrum) H-1 of the β-pyranose form in the $^4C_1$ conformation[22] is observed at δ 4.91, as a doublet of doublets, with $J_{H\text{-}1a,2a}$ = 9.1 Hz and $J_{H\text{-}1a,2e}$ = 2.2 Hz. The H-1 resonance of the α-pyranose form in the $^4C_1$ conformation[22] is observed at δ 5.27, as an apparent triplet ($J_{H\text{-}1e,2e} = J_{H\text{-}1e,2a}$ = 3.6 Hz). In the spectrum of the 2-deuterio derivative of **8** (Figure 2, upper spectrum), H-1 of the β-pyranose form (δ 4.92) is a doublet with J = 9.2 Hz, demonstrating that H-2 is axial and the H-2 resonance at δ 1.51 is a triplet (J = 10 Hz). The H-1 resonance of the α-pyranose form (δ 5.28) is a doublet (J = 3.2 Hz) and the H-2 resonance of that form (δ 1.74) is a doublet of doublets (J = 9.2 and 3.0 Hz). In the 1,2-dideuterio derivative of **8** the H-2 resonances of both the α- and β-pyranose forms (δ 1.76 and 1.54, respectively) are doublets with J = 9.5 and 10 Hz, respectively, reflecting trans-diaxial coupling with H-3. These results therefore demonstrate conclusively that 2-deoxy-2(*R*)-deuterio-D-*threo*-pentose (**10**) was the sole product formed via reduction of **6** with $LiAlD_4$.

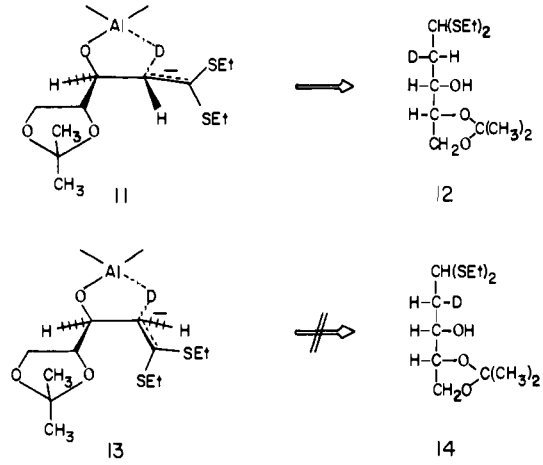


10

Mechanism of the Reduction. To determine whether the free C-3 hydroxyl group of **3** and **6** is required for reduction of the ketene dithioacetal, the 3-*O*-methyl ether of **3** was prepared. Attempted reduction of this derivative with $LiAlH_4$ failed. Because of the obligatory requirement for the free C-3 hydroxyl group, the reduction of **3** is envisioned to proceed via directed hydride transfer (Scheme II) through an alkoxyaluminum hydride salt (**11** or **13**). It is apparent, however, that the reduction actually proceeds via the intermediate with the s-trans configuration about C-2–C-3 (**11**) to give, on workup, the product with the observed *S* stereochemistry at C-2 (**12**). The failure to form product with *R* stereochemistry at C-2 (**14**) is attributed to steric crowding in the transition state with the s-cis configuration about the C-2–C-3 bond (**13**).

This mechanism also accounts for the *R* stereochemistry observed at C-2 for hydride transfer in the reduction of the threo isomer (**6**), as hydride transfer proceeds as expected, through the lower energy transition state with the s-trans configuration about the C-2–C-3 bond.

Scheme II. Transition State Representations for the Reduction of 3 by Lithium Aluminum Hydride



Experimental Section

General. With the exception of aqueous hydrolyses, all syntheses were carried out under an atmosphere of dry nitrogen. Elemental analyses were obtained on samples purified by high performance liquid chromatography by elution on Porasil A in $CHCl_3$. High resolution mass spectra were recorded on an AEI MS-30 mass spectrometer. Optical rotations were measured at the sodium D line on a Perkin-Elmer Model 241 polarimeter on samples obtained as syrups after chromatography on silica gel.

NMR Spectra. ^1H spectra were recorded at 27 °C and ^{13}C spectra were recorded at 34 °C on a Varian XL-100-15 NMR spectrometer. Spectra recorded with $CDCl_3$ as solvent are referenced to internal tetramethylsilane, and those recorded with D_2O as solvent are referenced to sodium 3-trimethylsilyl-2,2,3,3-tetradeuteriopropionate, contained in an internal capillary as a solution in D_2O. Coupling constants in ^{13}C spectra are recorded ±1 Hz, and in ^1H spectra, ±0.5 Hz. ^{13}C spectra were recorded with proton noise decoupling, but off-resonance decoupling was performed to identify methyl, methylene, methine, and quaternary carbon atoms.

2,3:4,5-Di-*O*-isopropylidene-D-arabinose Diethyl Dithioacetal (2). D-Arabinose diethyl dithioacetal (10.0 g, 39.1 mmol) was converted to its 2,3:4,5-di-*O*-isopropylidene derivative (**2**, 9.85 g, 75%) as previously described:[8,9] $[\alpha]^{23}_D$ +83.3° (*c* 1.4, CH_3OH) (lit.[9] +83°); ^1H NMR ($CDCl_3$) δ 1.15–1.44 (complex, 18 H, ethyl CH_3, isopropylidene CH_3), 2.69 (q, *J* = 8 Hz, 4 H, ethyl CH_2), 3.81–4.31 (complex, 6 H, H-1,2,3,4,5); ^{13}C NMR ($CDCl_3$) δ 14.48 (ethyl CH_3), 24.51, 24.99, 25.30, 26.69, 27.08, 27.37 (ethyl CH_2, isopropylidene CH_3), 52.44 (C-1), 67.84 (C-5), 77.29, 79.27, 85.21 (C-2,3,4), 109.66, 110.03, (isopropylidene C); M^+, *m/e* 336.1436 ($C_{15}H_{28}O_4S_2$ requires 336.1428). Anal. C, H, S.

2-Deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose Diethyl Dithioacetal (3). To a solution of 1.50 g (13.37 mmol) of *tert*-BuOK in 75 mL of freshly distilled THF and 25 mL of dry Me_2SO at 23 °C was added dropwise over 15 min a solution of **2** (3.00 g, 8.93 mmol) in 30 mL of THF. After stirring for 1 h at 23 °C, the reaction mixture was poured over 400 g of ice. The aqueous layer was extracted three times with 150-mL portions of $CHCl_3$, and the combined $CHCl_3$ extracts were washed with cold water, dried over anhydrous Na_2SO_4, and evaporated under vacuum, to give 2.04 g (7.34 mmol, 82%) of **3** as a yellow oil. Removal of colored contaminants was accomplished by elution of the product in EtOAc–hexane (1:4 v/v) through a silica gel column (2.5 × 30 cm), giving 1.65 g (5.94 mmol, 67%) of pure **3**: $[\alpha]^{23}_D$ +49.2° (*c* 0.9, $CHCl_3$); ^1H NMR (C_6D_6) δ 1.10 (t, *J* = 6 Hz, 6 H, ethyl CH_3), 1.29, 1.44 (two s, 6 H, isopropylidene CH_3), 2.40–2.92 (complex, 5 H, OH, ethyl CH_2), 3.76–4.22 (complex, 3 H, H-4,5), 4.97 (dd, *J* = 4 and 8 Hz, 1 H, H-3), 6.08 (d, *J* = 8 Hz, 1 H, H-2); M^+, *m/e* 278.1016 ($C_{12}H_{22}O_3S_2$ requires 278.1010). Anal. C, H, S.

2-Deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose Diethyl Dithioacetal (4). To a stirred mixture of $LiAlH_4$ (3.10 g, 81.7 mmol) in 250 mL of THF was added, over 20 min at 23 °C, a solution of **3** (5.64 g, 20.3 mmol) in 80 mL of THF. After stirring for 3.5 h, the reaction mixture was worked up in the usual way[14] to give 4.55 g (80%) of **4**, chromatographically pure by TLC (silica gel PF-254; EtOAc–hexane, 1:4 v/v): $[\alpha]^{23}_D$ −7.8° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 8 Hz, 6 H, ethyl CH_3), 1.35, 1.41 (two s, 6 H, isopropylidene CH_3), 1.81–2.05 (complex, 2 H, H-2), 2.45–2.81 (complex, 5 H, OH, ethyl CH_2), 3.81–4.15 (complex, 5 H, H-1,3,4,5); M^+, *m/e* 280.1175 ($C_{12}H_{24}O_3S_2$ requires 280.1166). Anal. C, H, O, S.

2-Deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*erythro*-pent-1-enose Diethyl Dithioacetal. To a solution of 2.15 g (19.2 mmol) of *tert*-BuOK in 90 mL of THF and 30 mL of Me_2SO at 23 °C was added dropwise over 15 min a solution of **2** (4.30 g, 12.8 mmol) in 20 mL of THF. After the mixture was stirred for 1 **h** at 23 °C, 7.26 g (51.1 mmol) of MeI was added and stirring was continued for 45 min. The reaction mixture was poured over ice and worked up as described for **3** to give 3.57 g (12.2 mmol) of product. Chromatography on silica gel in EtOAc–hexane (1:4 v/v) as described for **3** gave 3.05 g (82%) of pure 2-deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*erythro*-pent-1-enose diethyl dithioacetal: $[\alpha]^{23}_D$ +17.6° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23, 1.26 (two t, *J* = 8 Hz, 6 H, ethyl CH_3), 1.31, 1.38 (two s, 6 H, isopropylidene CH_3), 2.60–2.88 (complex, 4 H, ethyl CH_2), 3.26 (s, 3 H, OCH_3), 3.62–4.18 (complex, 3 H, H-4,5), 4.26–4.48 (m, 1 H, H-3), 5.58 (d, *J* = 8 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 14.13, 15.24 (ethyl CH_3), 25.36, 26.47, 26.98, 27.50 (ethyl CH_2, isopropylidene CH_3), 56.66 (OCH_3), 66.76 (C-5), 77.66, 79.28 (C-3,4), 109.69 (isopropylidene C), 133.50 (C-2), 137.39 (C-1); $M^+ - CH_3OH$, *m/e* 260.0876 ($C_{12}H_{20}O_2S_2$ requires 260.0904). Anal. ($C_{13}H_{24}O_3S_2$) C, H, O, S.

2-Deoxy-2(*S*)-deuterio-4,5-*O*-isopropylidene-D-*erythro*-pentose Diethyl Dithioacetal (12). Reduction of **3** (2.00 g, 7.19 mmol) with $LiAlD_4$, followed by workup as described above and chromatography on silica gel (2.5 × 30 cm) in EtOAc–hexane (1:4 v/v), gave 1.50 g (74%) of 2(*S*)-deuterio-**4**: $[\alpha]^{23}_D$ −7.3° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (t, *J* = 7 Hz, 6 H, ethyl CH_3), 1.29, 1.35 (two s, 6 H, isopropylidene CH_3), 1.90 (d, *J* = 10 Hz, H-2), 2.41–2.73 (complex, 4 H, ethyl CH_2), 3.20 (br s, 1 H, OH), 3.75–4.07 (complex, 5 H, H-1,3,4,5); M^+, *m/e* 281.1232 ($C_{12}H_{23}O_3DS_2$ requires 281.1229).

2-Deoxy-1-deuterio-4,5-*O*-isopropylidene-D-*erythro*-pentose Diethyl Dithioacetal. Reduction of **3** (2.00 g, 7.19 mmol) was accomplished with $LiAlH_4$ (0.68 g, 17.9 mmol) as described above, and excess hydride was decomposed by the addition of a paste made from 15 g of Na_2SO_4 and 10 mL of D_2O. After 18 h at 23 °C, the reaction mixture was filtered and the solids were washed with THF. The combined THF extracts were dried over anhydrous Na_2SO_4 and evaporated under vacuum. Purification was accomplished by elution over a silica gel column (2.5 × 30 cm) in EtOAc–hexane (1:4 v/v) to

give 1.64 g (81%) of 1-deuterio-**4**: $[\alpha]^{23}_D$ −8.1° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7 Hz, 6 H, ethyl CH_3), 1.33, 1.41 (two s, 6 H, isopropylidene CH_3), 1.93 (complex, 2 H, H-2), 2.50–2.84 (complex, 4 H, ethyl CH_2), 3.30 (br s, 1 H, OH), 3.83–4.10 (complex, 4 H, H-3,4,5); M^+, *m/e* 281.1256 ($C_{12}H_{23}O_3DS_2$ requires 281.1229).

2-Deoxy-1,2(*S*)-dideuterio-4,5-*O*-isopropylidene-D-*erythro*-pentose Diethyl Dithioacetal. Reduction of **3** (2.00 g, 7.19 mmol) with $LiAlD_4$ under conditions described for 2(*S*)-deuterio-**4**, D_2O workup as described for 1-deuterio-**4**, and chromatography on silica gel as previously described gave 1,2(*S*)-dideuterio-**4** (1.49 g, 73%): $[\alpha]^{23}_D$ −9.1° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7 Hz, 6 H, ethyl CH_3), 1.34, 1.41 (two s, 6 H, isopropylidene CH_3), 1.96 (br s, 1 H, H-2), 2.48–2.82 (complex, 4 H, ethyl CH_2), 3.17 (br s, 1 H, OH), 3.80–4.08 (complex, 4 H, H-3,4,5); M^+, *m/e* 282.1272 ($C_{12}H_{22}O_3D_2S_2$ requires 282.1291).

2-Deoxy-D-*erythro*-pentose (5). To compound **4** (4.87 g, 17.4 mmol) in 50 mL of MeOH was added, with vigorous stirring, 12.2 g of yellow mercuric oxide and 12.2 g of mercuric chloride. After 7 h at 29 °C, the mixture was filtered, the precipitate was washed with MeOH, and the combined MeOH solutions were evaporated to dryness under vacuum. The residue was extracted with three 100-mL portions of $CHCl_3$, which were combined and filtered, then washed with 200 mL of 1 N KI and water, dried over anhydrous $MgSO_4$, and evaporated to dryness. The resultant pale yellow oil was applied to a silica gel column (2.5 × 30 cm), which was eluted first with 400 mL of EtOAc–hexane (1:6 v/v), then with EtOAc. Evaporation of the EtOAc eluate yielded pure 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose dimethylacetal (2.85 g, 75%): ^1H NMR ($CDCl_3$, exchanged with D_2O) δ 1.35, 1.41 (two s, 6 H, isopropylidene CH_3), 1.48–2.10 (complex, 2 H, H-2), 3.35 (s, 6 H, OCH_3), 3.54–4.16 (complex, 4 H, H-3,4,5), 4.62 (t, *J* = 6 Hz, 1 H, H-1); ^{13}C NMR ($CHCl_3$) δ 25.39 26.75 (isopropylidene CH_3), 36.06 (C-2), 52.91, 53.76 (OCH_3), 66.46 (C-5), 69.16, 78.81 (C-3,4), 103.61 (C-1), 109.48 (isopropylidene C). The dimethyl acetal (0.20 g, 0.91 mmol) was hydrolyzed for 24 h in 15 mL of 0.01 N trifluoroacetic acid at 4 °C, diluted with 2 vol of water, and evaporated under vacuum to dryness, then again diluted with water and evaporated to dryness two times to remove acid. Final purification was accomplished by gel filtration on Bio-Gel P-2 to give pure **5** (0.10 g, 82%); $[\alpha]^{23}_D$ −53.8° (*c* 0.5, H_2O) (lit.[23] −58°); ^1H NMR (equilibrated in D_2O) δ 1.5–2.5 (complex, 2 H, H-2), 3.4–4.4 (complex, 4 H, H-3,4,5), 4.78 (dd, *J* = 2.8 Hz, 8.7 Hz, H-1 α-pyranose), 5.27 (t, *J* = 3.2 Hz, H-1 β-pyranose), 5.56–5.72 (complex, H-1 α,β-furanose); ^{13}C NMR (equilibrated in D_2O) δ 36.52, 37.90, 43.85, 43.95 (C-2), 64.34, 65.45, 65.63, 67.41, 68.79, 69.30, 70.10, 70.25, 73.74, 74.01, 88.10, 88.61 (C-3,4,5), 94.47, 96.68, 100.90 (C-1).[24,25]

2-Deoxy-2(*S*)-deuterio-D-*erythro*-pentose (9). 2(*S*)-Deuterio-**5** (0.44 g) was prepared from 2(*S*)-deuterio-**4** (1.70 g, 6.05 mmol) as described above for the conversion of **4** to **5** in an overall yield of 53%: $[\alpha]^{23}_D$ −47.2° (*c* 5.3, H_2O); ^1H NMR (equilibrated in D_2O) δ 1.71 (t, *J* = 10 Hz, H-2 α-pyranose), 1.97 (br d, *J* = 11 Hz, H-2 β-pyranose), 3.3–4.2 (complex, H-3,4,5), 4.78 (d, *J* = 8.7 Hz, H-1 α-pyranose), 5.27 (d, *J* = 3.2 Hz, H-1 β-pyranose); ^{13}C NMR (equilibrated in D_2O) C-2 resonances,[26] δ 36.35 (t, *J* = 20 Hz), 37.69 (t, *J* = 20 Hz), 43.80 (t, *J* = 20 Hz).

2-Deoxy-1-deuterio-D-*erythro*-pentose. 1-Deuterio-**5** (0.72 g) was prepared from 1-deuterio-**4** (2.30 g, 8.19 mmol) as described above for the conversion of **4** to **5** in an overall yield of 65%: $[\alpha]^{23}_D$ −50.0° (*c* 5.9, H_2O); ^1H NMR (equilibrated in D_2O) δ 1.6–2.5 (complex, H-2), 3.3–4.2 (complex, H-3,4,5); ^{13}C NMR (equilibrated in D_2O) C-1 resonances not observed.[26]

2-Deoxy-1,2(*S*)-dideuterio-D-*erythro*-pentose. 1,2(S)-Dideuterio-**5** (0.36 g) was prepared from 1,2(*S*)-dideuterio-**4** (1.14 g, 4.06 mmol) as described above for the conversion of **4** to **5** in an overall yield of 65%: $[\alpha]^{23}_D$ −47.2° (*c* 2.6, H_2O); ^1H NMR (equilibrated in D_2O) δ 1.71 (d, *J* = 11 Hz, H-2 α-pyranose), 1.97 (d, *J* = 11 Hz, H-2 β-pyranose), 3.3–4.2 (complex, H-3,4,5); ^{13}C NMR (equilibrated in D_2O) C-2 resonances,[26] δ 35.49 (t, *J* = 20 Hz), 36.88 (t, *J* = 20 Hz), 42.93 (t, *J* = 20 Hz), C-1 resonances not observed.

2-Deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose Diethyl Dithioacetal (6). Compound **6** (9.80 g, 35.3 mmol) was prepared in 84% yield from 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (14.0 g, 41.7 mmol)[10,18] as described above for the preparation of **3**: $[\alpha]^{23}_D$ −48.5° (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7 Hz, 6 H, ethyl CH_3), 1.29, 1.44 (two s, 6 H, isopropylidene CH_3), 2.6–3.06 (complex, 5 H, ethyl CH_2, OH), 3.66–4.20 (complex, 3 H, H-4,5), 4.78 (m, 1 H, H-3), 5.92 (d, *J* = 8 Hz, 1 H, H-2); M^+, *m/e* 278.0954 ($C_{12}H_{22}O_3S_2$ requires 278.1010). Anal. C, H, S.

2-Deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose Diethyl Dithioacetal (7). Reduction of **6** (9.00 g, 32.4 mmol) with $LiAlH_4$ was accomplished as described above for the reduction of **3** to give 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (6.35 g) in 70% yield: $[\alpha]^{23}_D$ +25.6° (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 8 Hz, 6 H, ethyl CH_3), 1.36, 1.44 (two s, 6 H, isopropylidene CH_3), 1.52–2.20 (m, 2 H, H-2), 2.4–2.8 (m, 4 H, ethyl CH_2), 2.93 (d, *J* = 5 Hz, OH), 3.6–4.2 (complex, 5 H, H-1,3,4,5); M^+, *m/e* 280.1175 ($C_{12}H_{24}O_3S_2$ requires 280.1166). Anal. C, H, S.

2-Deoxy-2(*R*)-deuterio-4,5-*O*-isopropylidene-D-*threo*-pentose Diethyl Dithioacetal. Reduction of **6** (2.00 g, 7.19 mmol) with $LiAlD_4$ and aqueous workup as described for the preparation of 2(*S*)-deuterio-**4** gave 2(*R*)-deuterio-**7** (1.45 g, 72%): $[\alpha]^{23}_D$ +26.1° (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 8 Hz, 6 H, ethyl CH_3), 1.36, 1.43 (two s, 6 H, isopropylidene CH_3), 2.40–2.78 (m, 4 H, ethyl CH_2), 2.92 (d, *J* = 5 Hz, OH), 3.60–4.20 (complex, 5 H, H-1,3,4,5). M^+, *m/e* 281.1231 ($C_{12}H_{23}O_3DS_2$ requires 281.1229).

2-Deoxy-1-deuterio-4,5-*O*-isopropylidene-D-*threo*-pentose Diethyl Dithioacetal. Reduction of **6** (2.00 g, 7.19 mmol) with $LiAlH_4$ followed by D_2O workup as described above for the preparation of 1-deuterio-**4** gave 1-deuterio-**7** (1.58 g, 78%): $[\alpha]^{23}_D$ +2.7° (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 8 Hz, 6 H, ethyl CH_3), 1.36, 1.43 (two s, 6 H, isopropylidene CH_3), 1.54–2.20 (m, 2 H, H-2), 2.40–2.84 (m, 4 H, ethyl CH_2), 3.01 (br s, 1 H, OH), 3.60–4.10, complex, 4 H, H-3,4,5); M^+, *m/e* 281.1223 ($C_{12}H_{23}O_3DS_2$ requires 281.1229).

2-Deoxy-1,2(*R*)-dideuterio-4,5-*O*-isopropylidene-D-*threo*-pentose Diethyl Dithioacetal. Reduction of **6** (2.28 g, 8.20 mmol) with $LiAlD_4$ and D_2O workup as described above for the preparation of 1,2(*S*)-dideuterio-**4** gave 1,2(*R*)-dideuterio-**7** (1.76 g, 76%): $[\alpha]^{23}_D$ +27.1° (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 8 Hz, 6 H, ethyl CH_3), 1.35, 1.44 (two s, 6 H, isopropylidene CH_3), 1.68 (br s, 1 H, H-2), 2.4–2.64 (m, 4 H, ethyl CH_2), 2.92 (d, *J* = 5 Hz, OH), 3.6–4.16 (complex, 4 H, H-3,4,5); M^+, *m/e* 282.1286 ($C_{12}H_{22}O_3D_2S_2$ requires 282.1291).

2-Deoxy-D-*threo*-pentose (8). 2-Deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (**7**, 0.60 g, 2.14 mmol) was converted to **8** as described above for the preparation of **5** and the product was purified by gel filtration to give **8** (0.18 g) in 63% overall yield: $[\alpha]^{23}_D$ +2.0° (*c* 1.8, H_2O) (lit.[27] −2°); ^1H NMR (equilibrated in D_2O) δ 1.34–2.4 (complex, H-2), 3.16–4.06 (complex, H-3,4,5), 4.91 (dd, *J* = 9.1 Hz, 2.2 Hz, H-1 β-pyranose), 5.27 (t, *J* = 3.6 Hz, H-1 α-pyranose), 5.69 (weak t, *J* = 5 Hz, H-1 furanose); ^{13}C NMR (equilibrated in D_2O) δ 39.25, 41.59, 45.38 (w, C-2), 63.15 (w), 65.47, 67.82, 70.91, 72.65, 73.16, 74.27 (w), 84.25 (w, C-3,4,5), 94.60, 97.02, 100.63 (w, C-1).

2-Deoxy-2(*R*)-deuterio-D-*threo*-pentose (10). Compound **10** (0.16 g) was prepared from 2-deoxy-2(*R*)-deuterio-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (0.63 g, 2.24 mmol) as described above for the conversion of **4** to **5** in an overall yield of 53%: $[\alpha]^{23}_D$ +0.8° (*c* 5.0, H_2O); ^1H NMR (equilibrated in D_2O) δ 1.51 (t, *J* = 10 Hz, H-2 β-pyranose), 1.74 (dd, *J* = 9.2 Hz, 3.0 Hz, H-2 α-pyranose), 3.16–4.08 (complex, H-3,4,5), 4.92 (d, *J* = 9.2 Hz, H-1 β-pyranose), 5.28 (d, *J* = 3.2 Hz, H-1 α-pyranose), 5.71 (weak d, *J* = 6 Hz, H-1 furanose); ^{13}C NMR (equilibrated in D_2O) C-2 resonances,[26] δ 39.43 (t, *J* = 20 Hz), 41.80 (t, *J* = 20 Hz).

2-Deoxy-1-deuterio-D-*threo*-pentose. 1-Deuterio-**8** (0.34 g) was prepared from 2-deoxy-1-deuterio-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (1.30 g, 4.62 mmol) as described for the conversion of **4** to **5** in an overall yield of 53%: $[\alpha]^{23}_D$ +2.4° (*c* 3.1, H_2O); ^1H NMR (equilibrated in D_2O) δ 1.30–2.40 (complex, H-2), 3.18–4.10 (complex, H-3,4,5); ^{13}C NMR (equilibrated in D_2O) C-1 resonances not observed.[26]

2-Deoxy-1,2(*R*)-dideuterio-D-*threo*-pentose. 1,2(*R*)-Dideuterio-**8** (0.35 g) was prepared from 2-deoxy-1,2(*R*)-dideuterio-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (1.23 g, 4.36 mmol) as described for the conversion of **4** to **5** in an overall yield of 59%: $[\alpha]^{23}_D$ −2.5° (*c* 6.1, H_2O); ^1H NMR (equilibrated in D_2O) δ 1.54 (d, *J* = 10 Hz, H-2 β-pyranose), 1.76 (d, *J* = 9.5 Hz, H-2 α-pyranose), 3.18–4.10 (complex, H-3,4,5); ^{13}C NMR (equilibrated in D_2O) C-2 resonances,[26] δ 38.86 (t, *J* = 20 Hz), 41.13 (t, *J* = 20 Hz), C-1 resonances not observed.

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Complexation of 4-Biphenylcarboxylate by Cyclohexaamylose. A Conductometric and ^{13}C Nuclear Magnetic Resonance Spectrometric Analysis

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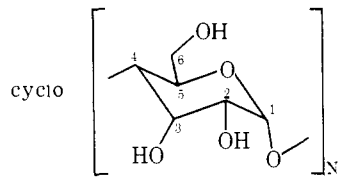
Abstract: Conductometric and ^{13}C NMR spectrometric analyses of aqueous solutions containing variable concentrations of cyclohexaamylose and lithium or sodium salts of the 4-biphenylcarboxylate anion indicate formation of a ternary complex composed of two cyclohexaamylose molecules and a single 4-biphenylcarboxylate ion. Conductometric measurements of corresponding equilibrium constants at five temperatures between 20 and 45 °C yielded values of -28 ± 2 kcal mol^{-1} and -72 ± 6 cal mol^{-1} deg^{-1} for the standard enthalpy and entropy changes, respectively, of the complexation reaction. Chemical shifts of cyclohexaamylose and 4-biphenylcarboxylate carbons in the complex are discussed in terms of a bitoroidal ternary model.

Introduction

Cyclohexaamylose, commonly named α-cyclodextrin, is a member of the homologous cycloamylose (I) series of cyclic



I

oligomers which consists of 6–12 α-1,4-linked D-glucopyranosyl residues.[1] The prefix terminology α, β, γ····cyclodextrin refers to degrees of cyclic oligomerization where $N = 6, 7, 8\cdots$, respectively. α-Cyclodextrin ($N = 6$) is known to bind molecules and ions in the interior cavity of its torus-shaped molecule. The resultant inclusion complexes have been investigated by various spectral methods and these have been reviewed.[2]

Published studies[2b] of the binding of a large number of substrates by cycloamyloses have generally assumed a 1:1 stoichiometry in the complexation reaction. However, there are some examples of two cycloamylose:one substrate stoichiometries involving methyl orange,[3,4] orange I,[5] 6-*p*-toluidinylnaphthalene 2-sulfonate (TNS),[6] *n*-heptane,[7] and cyclohexane.[7] Complexes with 3:1 stoichiometries have been suggested with palmitoyl Co-A substrate.[8]

The diversity of these systems and the relative absence of structural and thermodynamic information regarding higher complexes led us to further study the reaction of α-cyclodextrin with multifunctional substrates. We selected the 4-biphenylcarboxylate anion and investigated the interactions between its polar and nonpolar sites with the various zones of the α-cyclodextrin cavity. As shown in studies of related complexations,[9,10] structural information of this kind may be readily provided by ^{13}C NMR spectrometry. On the other hand, 4-biphenylcarboxylate is an ionic substrate, and its concentration may be conveniently monitored by conductometry at dilution levels inaccessible to ^{13}C NMR spectrometry. We therefore measured stoichiometric, thermodynamic, and structural

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