Application of DMSO Acidities to the Wittig Reaction with 6-Deoxy-6-formyl-β-cyclodextrin

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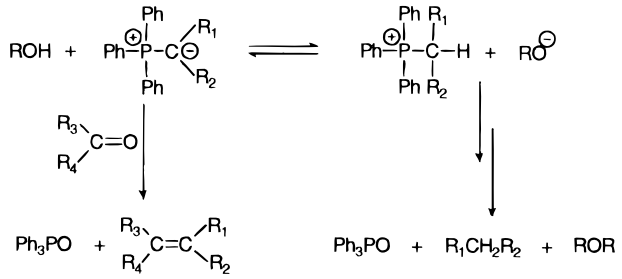
Methods for the construction of C-sugars are important in carbohydrate chemistry. The Wittig reaction[1] is a versatile route into such compounds; however, it is rarely applied with unprotected carbohydrates. We are interested in the construction of photoactive β-cyclodextrins (β-CDs). Recently, we discovered that an ether-linked dicyanoanthracene-β-CD undergoes ether migration under mildly basic conditions and thus sought out a more resilient tether such as a C−C double bond. Herein we determine the conditions amenable for the Wittig reaction with unprotected β-cyclodextrin derivatives and report the olefination of 6-deoxy-6-formyl-β-CD with a dicyanoanthracene derivative.

The implementation of the Wittig reaction in carbohydrate synthesis usually requires the prior protection of the alcohol groups. Masking the acidic hydroxyls allows even nonstabilized ylides such as methylenetriphenylphosphorane to be used.[2] Stabilized ylides containing an ester or sulfone group have been used with partially protected[3] or even unprotected carbohydrates.[4] A Michael cyclization often occurs after the Wittig reaction which can be suppressed with $Cu(OAc)_2$.[4] With unprotected carbohydrates the success of the reaction depends on the ylide acting as a nucleophile with a carbonyl center rather than as a Brønsted base with a hydroxyl group (Scheme 1). The latter process can result in decomposition of the ylide by cleavage of the P−C bond.[5] The acid-base reaction is an equilibrium between a soft (ylide) and a hard (alkoxide) base and is therefore subject to experimental manipulation.

Solvent effects can be used to alter the strength of the bases. Hard bases are greatly stabilized by H-bonding solvents, whereas soft bases are not very affected by H-bonding. Changing the solvent from water to a polar, aprotic medium such as DMSO or DMF will increase the base strength of the alkoxide but will hardly affect the ylide. For example, the pK_a of CH_3OH is 15.5 in water, but it increases to 29.0 in DMSO.[6] Thus, a solvent like DMSO is ideal for conducting the Wittig reaction since it effectively weakens the basicity of the ylide relative to that of the alkoxide.

The triphenylphosphonium group greatly stabilizes an adjacent carbanion due to the polarizability of phosphorus.[7] For example, the pK_a of $Ph_3P^+CH_3$ is only 22 in DMSO, whereas the pK_a of CH_4 is over 50. Substitution with additional anion stabilizing groups makes the corresponding ylide a weak base. The pK_a of Ph_3P^+-CH_2COOEt, the conjugate acid of the ester ylide cited above, is 8.50.

Scheme 1



Results and Discussion

Since the acid−base properties of the ylide and the carbohydrate affect the success of the Wittig reaction, the pK_a's of β-CD, **1** and **2**, in DMSO were determined. The overlapping indicator method of Bordwell[8] was employed, and the results are presented in Table 1. At least two different indicators were used for each pK_a determination: one with a lower pK_a and one with a higher pK_a than the determined pK_a. The results show that β-CD is a weaker acid in DMSO than in water (pK_a = 12.1).[9] On the other hand, it is still a much stronger acid in DMSO than is methanol. This intermediate effect can be ascribed to the intramolecular H-bonding stabilization of the C2-alkoxide by the C3-OH of the adjacent glucose unit.[10] The triphenylphosphonium group makes **2** a stronger acid than **1**. The increase in acid strength in going from **1** to **2** is not as dramatic as in going from CH_4 to $Ph_3P^+CH_3$ because the ylide from **2** is already stabilized by resonance with an electron-withdrawing aryl group.[11] Since **2** is a significantly stronger acid than β-CD, the reaction of the ylide from **2** with 6-deoxy-6-formyl-β-CD (**3**) should be favorable. In fact, any ylide precursor with a pK_a significantly less than 17.6 should provide a viable reagent for reaction with **3**.

The Wittig reaction between 6-deoxy-6-formyl-β-CD and the ylide derived from **2** proceeds smoothly (Scheme 2). Since **3** forms a hydrate,[12] it is dehydrated by azeotropic distillation with benzene (in DMSO) prior to reaction with the ylide. The ylide is generated separately in DMSO by using KO-*t*-Bu, which is also the optimal base for the pK_a determinations. The condensation between the ylide and **3** requires heating at benzene reflux for only several hours judging by the disappearance of the intense green color of the ylide. A crude product is obtained after one precipitation from acetone

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(1) For a recent review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 863−927.
(2) For example: Wnuk, S. F.; Robins, M. J. *Can. J. Chem.* **1991**, *69*, 334−338. Hicks, D. R.; Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* **1976**, 869−870.
(3) Barnes, N. J.; Davidson, A. H.; Hughes, L. R.; Procter, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1292−1294. Just, G.; Ramjeesingh, M.; Liak, T. J. *Can. J. Chem.* **1976**, *54*, 2940−2947.
(4) Horton, D.; Koh, D. *Carbohydr. Res.* **1993,** *250*, 231−247.
(5) Johnson, A. W. In *Ylides and Imines of Phosphorus* Wiley: New York, 1993; pp 132−133.
(6) Olmstead, W. N.; Margolin, Z. Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295−3299 and references therein.
(7) Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968−972.
(8) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006−7014.
(9) Van Etten, R. L.; Clowes, G. A.; Sebastian, J. F.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3253−3262.
(10) Gillet, B.; Nicole, D. J.; Delpuech, J.-J. *Tetrahedron Lett.* **1982**, 65−68.
(11) Zhang, X.-M.; Fry, A. L.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 4101−4106.
(12) Yoon, J. Y.; Hong, S. H.; Martin, K. A.; Czarnik, A. W. *J. Org. Chem.* **1995**, *60*, 2792−2795.

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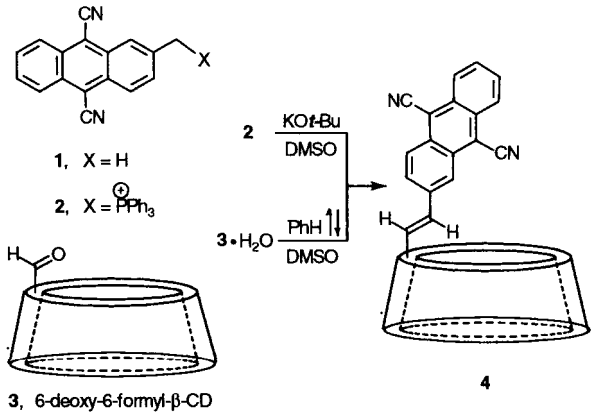
Table 1. pK_a's of β-CD, 1 and 2, in DMSO

compound	indicator	indicator pK_a	determined pK_a
β-CD	*a*	18.9	17.8
β-CD	*b*	16.95	17.6
β-CD	*c*	16.2	17.4
			av 17.6
1	*d*	18.6	18.1
1	*e*	17.2	17.9
			av 18.0
2	*f*	10.8	11.0
2	*g*	11.0	10.8
			av 10.9

[a] 4-Chloro-2-nitroaniline. [b] 2-Indanone. [c] Fluorenone oxime. [d] Imidazole. [e] Nitromethane. [f] *p*-Nitrophenol. [g] Benzoic acid.

Scheme 2



which is contaminated only with unreacted cyclodextrin derivatives. HPLC analysis by the method of standard addition indicates a 21% yield. This product is of sufficient quality to be purified directly by preparative HPLC giving an overall isolated yield of 10%. Spectral data are consistent with the product structure. The ^{1}H NMR resonances of the protons of the new double bond are most relevant. Interestingly, they are nearly coincident in DMSO and DMSO/D_2O even at elevated temperatures. Fortunately, they are distinct in CD_3CN/D_2O where they show a coupling constant of J = 16.4 Hz indicative of the expected trans-orientation. We are currently exploring the Wittig reaction as a route to other cyclodextrin derivatives.

Experimental Section

General Methods. β-Cyclodextrin-6-tosylate was prepared by treatment of aqueous β-CD with 3 equiv of NaOH followed by reaction with TsCl in CH_3CN.[13] The crude product was purified by three successive recrystallizations from water and converted to the 6-aldehyde by heating in DMSO (dried over CaH_2 and distilled *in vacuo*) to 135 °C for 2 h with 2,4,6-trimethylpyridine (distilled).[12] The aldehyde was precipitated from acetone and used without further purification. Preparative high performance liquid chromatography was performed on a Waters 244 system equipped with a UV absorption detector (254 nm), using a Whatman Magnum 20 ODS-3 column and a linear H_2O/CH_3CN gradient (25−45% aqueous CH_3CN over 30 min) at 18 mL/min. Analytical HPLC was performed on a Waters 600E system equipped with a variable wavelength absorption detector set at 254 nm, using a Whatman ODS-3 column and a linear H_2O/CH_3CN gradient (20−40% aqueous CH_3CN over 40 min) at 1.0 mL/min. Acidity measurements were conducted in DMSO (dried and distilled as above) under Ar. Dimsyl solutions were made with KH for the β-CD acidity determinations, whereas solutions of KO-*t*-Bu in DMSO were used with **1** and **2**. A basic DMSO solution in a septum-topped UV/vis cuvette was titrated with a DMSO solution of a colored indicator (In) or unknown (**1**, **2**) until a mixture of acid and conjugate base was produced ($[InH] + [In^-]$ = ca. 10^{-4} M). This mixture was then titrated with a colorless acid (ca.10^{-2} M in DMSO). Possible homohydrogen[14] bonding effects with β-CD were not considered.

(9,10-Dicyanoanthracenyl-2-methyl)triphenylphosphonium Bromide (2). 2-Bromomethyl-9,10-dicyanoanthracene[15] (1.81 g, 5.63 mmol) and triphenylphosphine (1.48 g, 5.63 mmol) were covered with benzene (150 mL), and the reaction was heated at reflux overnight. The reaction was cooled and the benzene was removed *in vacuo*. The residue was recrystallized from $CHCl_3$ and benzene yielding the phosphonium salt (2.40 g, 4.11 mmol, 73%). ^{1}H NMR ($CDCl_3$) δ 8.38 (m, 2 H), 8.29 (d, J = 9.0 Hz, 1 H), 8.18 (d, J = 9.0 Hz, 1 H), 7.92−7.80 (m, 12 H), 7.71−7.65 (m, 6 H), 6.03 (d, J = 14.9 Hz, 2 H) ; ^{13}C NMR ($CDCl_3$) δ 135.5, 134.7, 134.6, 132.1, 131.2, 130.9, 130.7, 130.6, 130.5, 130.3, 130.2, 130.1, 130.0, 126.4, 126.2, 126.0, 118.2, 117.1, 115.3, 115.1; ($CDCl_3$/DMSO-d_6) δ 134.4, 134.2, 133.0, 132.0, 131.0, 130.9, 130.7, 130.3, 130.2, 130.0, 128.3, 128.2, 126.2, 125.9, 125.8, 117.5 (J = 86 Hz), 114.9, 114.7, 111.2, 110.9, 30.8 (J = 47 Hz).

Anal. Calcd for $C_{35}H_{24}N_2PBr{\cdot}1H_2O$: C, 69.89; H, 4.36; N, 4.66. Found: C, 69.76; H, 4.12; N, 4.54.

6-Deoxy-6-(9,10-dicyanoanthracenyl-2-methylene)-β-cyclodextrin (4). 6-Deoxy-6-formyl-β-cyclodextrin[12] (**3**), (1.20 g, 1.06 mmol) was dissolved in DMSO (50 mL) and benzene (50 mL) under nitrogen. The reaction was heated to reflux overnight, and water was collected in a Dean-Stark trap. The Wittig reagent was prepared by adding KO-*t*-Bu (120 mg, 1.07 mmol) to a solution of **2** (590 mg, 1.01 mmol) in DMSO (16 mL) under nitrogen. This reaction was stirred for 15 min, then the mixture was added by syringe in one portion to the cooled β-cyclodextrin aldehyde solution. The condensation reaction was heated to reflux for 3 h under nitrogen. After this period benzene was removed *in vacuo*, and DMSO was removed by vacuum distillation (0.1 Torr). The residue was dissolved in a minimum volume of hot H_2O (15 mL), and the solution was added dropwise to acetone (500 mL). The solid which precipitated was collected and vacuum dried giving 1.25 g of material. HPLC analysis of this solid indicated a yield of 300 mg (0.221 mmol, 21%). Separation by HPLC (ret. time = 21.5 min with preparative HPLC, 20.6 min on analytical HPLC) of a portion (580 mg) of this solid ultimately gave **4** (72 mg, 0.053 mmol, 10%). ^{1}H NMR (CD_3CN/D_2O) δ 8.18−8.15 (m, 3 H), 8.03 (s, 1 H), 7.97 (d, J = 7.5 Hz, 1 H), 7.83−7.78 (m, 2 H), 6.98 (d, J = 16.4 Hz, 1 H), 6.80 (dd, J = 16.4 and 3.3 Hz, 1 H), and β-CD resonances; ^{13}C NMR (D_2O, 50 °C) δ 138.8, 133.0, 132.9, 132.2, 132.1, 131.8, 131.7, 131.6, 131.3, 130.7, 128.9, 128.8, 126.4, 126.1, 126.0, 123.4, 116.1, 115.8, 110.5, 109.6, 104.0, 103.9, 103.8, 103.6, 103.4, 103.3, 86.8, 86.7, 82.6, 82.5, 82.4, 82.3, 82.0, 75.3, 74.8, 74.7, 74.6, 74.5, 74.4, 74.3, 73.9, 73.8, 73.7, 73.6, 73.4, 73.2, 62.0, 61.9, 61.8, 61.6, 61.5, 61.4, 61.3; UV (H_2O) log ϵ sh 3.72 (389 nm), 3.79 (405 nm), sh 3.65 (433 nm).

Anal. Calcd for $C_{59}H_{76}N_2O_{34}{\cdot}2H_2O$: C, 50.72; H, 5.77; N, 2.00. Found: C, 50.64; H, 5.61; N, 1.86.

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(13) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kunaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860−3868.

(14) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424−1427.

(15) Hubbard, B. K.; Beilstein, L. A.; Heath, C. E.; Abelt, C. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1005−1009.