A powerful aqueous solvent effect in an intramolecular Diels–Alder cyclisation

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Significant promotion of both unactivated and activated carbocyclic Diels–Alder cyclisations across the furan ring system is observed on changing from an organic to an aqueous solvent system.

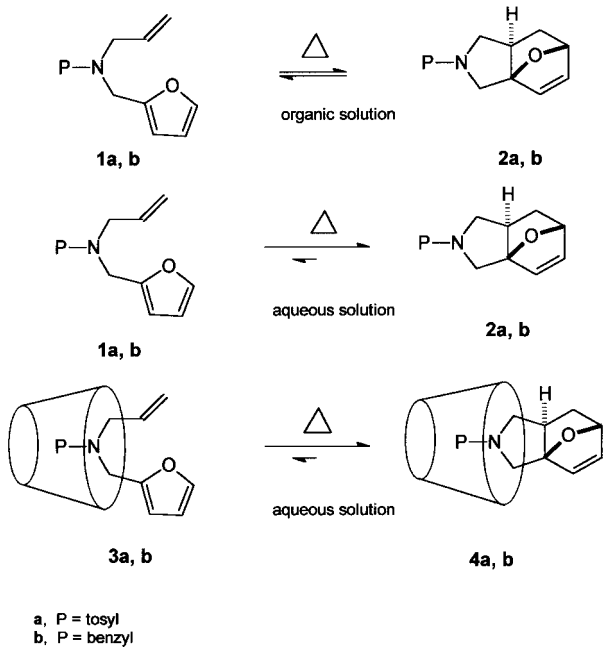
Keywords: β-cyclodextrin, Diels–Alder reaction, solvent effect, steric buttressing

Previously, our group has studied[1] the intramolecular Diels–Alder (IMDA) reaction, **1** to **2**, (Scheme 1) as part of our wider interest in the promotion of cyclisation reactions using steric buttressing.[2] We have since returned to this cyclisation as a result of our interest in developing a chiral, steric buttressing methodology. The advantages of this system are firstly the ease of entry into the acyclic precursors and secondly the fact that the cyclisation outlined in Scheme 1 creates three new chiral centres in the cyclic product **2a,b**.

We decided to investigate the β-cyclodextrin-promoted cyclisation of compounds **1a** and **1b**. In order to promote host–guest binding between the macrocycle and the aromatic portion of **1a** and **1b**, these cyclisations were carried out in aqueous solution. Previous studies by Breslow[3] and Sternbach[4] have shown that β-cyclodextrin promotes Diels–Alder reactions in aqueous solution, but with limited chiral selectivity. Studies from our group[1] concerning the cyclisation of **1a** have shown that, on heating in an organic solvent, it attains an equilibrium favouring the cyclic form (see Table 1, entry I). In the case of **1b** cyclisation is disfavoured (Table 1, entry IV). Therefore, we were also interested in determining the extent to which any hydrophobic effect[5] promoted the Diels–Alder cyclisation of **1a** and **1b**.[6]

The IMDA reactions summarised in Scheme 1 were effected in dilute aqueous solution (*ca* 0.01 M) in the presence and absence of β-cyclodextrin. Because of solubility problems in the absence of the β-cyclodextrin, the control cyclisations of **1a** and **1b** (Table 1, entries II and VI), needed to gauge more accurately the potential solvent and solute effects, could not be carried out in pure water so were carried out in 10 % v/v aqueous DMSO, to ensure complete homogeneity. The results of these studies are summarised in Table 1.

A definite solvent effect is observed on changing from an organic, to an aqueous solvent system in the cyclisation of both **1a** and **1b**. Promotion of the cyclisation is evidenced by



Scheme 1

the alteration in the position of equilibrium to heavily favour the cyclic form, and the time required for the cyclisation to reach the equilibrium. This effect is clearly seen in entry I compared to II for the reactions involving the tosyl derivative **1a**, and in entries IV and VI for the benzyl derivative **1b**; in both cases simply changing from an organic to an aqueous system has drastically altered the degree of cyclisation.

β-Cyclodextrin acted on **1a** and **b**, via complexes **3a, b**, to catalyse cyclisations to **4a**, **b** (entries III and V). In the case

Table 1 Conditions used for the cyclisation studies on **1a**, **1b** and **5**

Entry	Substrate	Solvent[a]	Conditions[b]	Open:Cyclic [c]	Product/Yield[d]
I	1a	Toluene	110°C, 21 h	20:80	**2a**/ –
II	1a	10 % DMSO/water	108°C, 3 h	<1:99	**2a**/ 62%
III	1a	Water	100°C, 2.5 h, β-CD	<1:99	**4a**/34%; **2a**/28%
IV	1b	Xylenes	135°C, 60 h	98:2	**2b**/ –
V	1b	Water	100°C, 8 h, β-CD	<5:95	**4b**/27%; **2b**/46%
VI	1b	10% DMSO/water	100°C, 8h	60:40	**2b**/ – [e]
VII	5	10% DMSO/water	80°C, 2 h	<1:99	**6**/ – [f]

[a]Deuterated water and DMSO used.
[b]Followed by ^{1}H NMR; times refer to >95% conversion.
[c]Equilibrium values (from ^{1}H NMR) after heating for 3 x cited conversion times, except for entries IV and VI.
[d]Isolated yield of purified product, see Experimental.
[e]Unstable, reverting to starting material on attempted isolation.
[f] See ref 10.

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of **1a**, cyclisation was effected faster, whilst, for the benzyl derivative **1b** a greater degree of cyclisation was also observed.

Isolation of the 1:1 host-guest β-cyclodextrin complexes was achieved by cooling the product solutions to 5°C and allowing the complexes, **4a** or **4b** to crystallise as white solid trihydrates (suggested by microanalysis). Cyclic products **2a** or **2b** were extracted from the cooled (to r.t.) reaction solutions of **4a** and **4b** using dichloromethane. In the case of **2a** the oil initially isolated could be crystallised from warm ethanol, with no retro-Diels–Alder product observed. For **2b** the oil initially isolated was passed through a plug of silica (to remove residual β-cyclodextrin). Analysis by ^{1}H NMR showed that although, in this instance, the purification procedure was carried out in a prompt fashion at room temperature, reversion to acyclic compound **1b** had already occurred (ratio **1b:2b** 30:70).

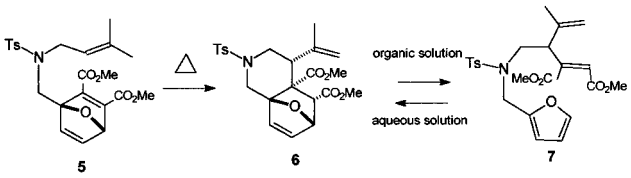
Both Sternbach[7] and Jung[8] have observed a solvent effect on IMDA reactions on changing to a polar solvent system, in both cases also using a furan diene.[9] However, in both studies either substitution on the connecting molecular framework or strong dipoles within the molecule resulted in greater potential for solvent–solute interactions. The absence of strong dipoles in either **1a** or **1b**, precludes extensive direct solvent–solute interactions. Furthermore, we observed only limited chiral selectivity in the β-cyclodextrin promoted cyclisation, amounting to only a few percent enantiomeric excess, our results being in agreement with the earlier studies of Breslow and Sternbach on this matter. Finally, ring constraints already dictate that the cyclisation is selective for the *exo* product and no variation in selectivity was observed in this regard.

In previous work we have reported that the ene-product **6** formed under mild conditions from **5** undergoes a spontaneous retro-Diels–Alder reaction to form **7**, the intermediate **6** being observed transiently (Scheme 2).[10] Heating the product **7**, an activated dienophile, in aqueous DMSO also favours the cyclic product **6** (Table 1, entry VII). On attempted isolation from the aqueous solution the cyclic product **6** again shows reversion to the open isomer **7**.

Cyclisation studies

Reactions were followed by NMR spectroscopy using deuterated solvents. ^{1}H NMR Spectra were recorded on either a Bruker AM 300 MHz or a Bruker DPX 500 MHz spectrometer. Chemical shifts are quoted in ppm and coupling constants are in Hz. For spectra run in chloroform, δ values are quoted relative to tetramethylsilane (δ = 0.00 ppm) and for spectra run in deuterium oxide, δ values are quoted relative to HDO (δ = 4.78 ppm). Alongside the monitored reactions, preparative scale reactions were also carried out using non-deuterated solvents. FT–IR spectra were recorded on a Perkin-Elmer 2000 spectrometer. Silica gel refers to Merck silica gel (60μm). Organic extracts were dried over anhydrous sodium sulfate.

8-p-Toluenesulfonyl-8-aza-1,4-epoxybicyclo[4.3.0]non-2-ene **2a**: *Method A* (See Table 1, Entry II): A solution of *N*-(toluenesulfonyl)-*N*-(allyl)-2-furfurylamine[1] **1a** (0.34 g, 1.2 mmol) in 9:1 water/DMSO (39 cm^3) was heated under reflux for 6 h. The solution was then diluted with water (100 cm^3) and washed with DCM (3 × 75 cm^3). Bulk solvent was then removed from the combined organic fractions and the yellow residue remaining redissolved in DCM (25 cm^3) and washed with water (3 × 25 cm^3), dried, filtered and the solvent removed *in vacuo* to give a yellow oil. This was crystallised from warm ethanol to afford the title sulfonamide as a white solid (0.21 g, 62 %). *Method B* (See Table 1, Entry III): To a warm solution of β-cyclodextrin (2.36 g, 2.1 mmol) in water (173 cm^3) was added *N*-(toluenesulfonyl)-*N*-(allyl)-2-furfurylamine **1a** (0.61 g, 2.1 mmol) in DMSO (2.5 cm^3) and the resulting solution heated under a gentle reflux. After 3 h the solution was cooled to room temperature and washed with DCM (3 × 40 cm^3), dried, filtered and solvent removed under reduced pressure to afford a yellow oil. Crystallisation from warm ethanol gave the title sulfonamide as a white solid (0.17 g, 28 %), m.p. 115–116°C; ν_{max} (thin film/DCM)/cm^{-1}: 2949, 2875, 1599, 1342, 1163; δ_H (500 MHz; $CDCl_3$) 1.35 (1 H, dd, *J* 7.5, 11.7), 1.62–1.65 (1 H, m), 1.06–2.08 (1 H, m), 2.42 (3 H, s), 2.68 (1 H, t, *J* 9.7), 3.51 (1 H, d, *J* 12.1), 3.89 (1 H, t, *J* 8.4), 1 H, d, *J* 12.1), 4.93 (1 H, d, *J* 4.4), 6.30-6.34 (2 H, m), 7.31 (2 H, d, *J* 8.1), 7.70 (2 H, d, *J* 8.1); (Found: C, 61.6; H, 5.9; N, 4.8. $C_{15}H_{17}NSO_3$ requires C, 61.8; H, 5.9; N, 4.8 %).



Scheme 2

8-Benzyl-8-aza-1,4-epoxybicyclo[4.3.0]non-2-ene **2b**: To a warm solution of β-cyclodextrin (5.48 g, 4.8 mmol) in water (402 cm^3) was added *N*-(benzyl)-*N*-(allyl)-2-furfurylamine[1] **1b** (1.10 g, 4.8 mmol) in d_6-DMSO (2 cm^3) and the resulting solution heated under reflux for 21 h. After this time the reaction mixture was allowed to cool to room temperature and washed with DCM (4 × 75 cm^3), followed by reduction, under reduced pressure, of the volume of the combined organic extracts by half. The organic fraction was then washed with water (3 × 50 cm^3), dried, filtered and evaporated to dryness *in vacuo*. Filtering through a pad of silica, eluting with DCM, gave a yellow oil (0.51 g, 46 %); ν_{max}(thin film/DCM)/cm^{-1}: 3029, 2867, 1638; δ_H (300 MHz; $CDCl_3$) 1.27 (1 H, dd, *J* 7.4, 11.5), 1.70 (1 H, ddd, *J* 3.4, 4.3, 11.5), 2.03 (1 H, dddd, *J* 3.4, 7.0, 7.4, 10.3), 2.20 (1 H, dd, *J* 8.4, 10.3), 2.68 (1 H, d, *J* 11.8), 3.17 (1 H, dd, *J* 6.9, 8.4), 3.54 (1 H, d, *J* 11.8), 3.76 (2 H, s, N–CH_2), 5.00 (1 H, dd, *J* 1.6 and 4.4), 6.26 (1 H, dd, *J* 1.6, 5.8), 6.40 (1 H, d, *J* 5.8), 7.21–7.40 (5 H, m, Ar).

8-p-Toluenesulfonyl-8-aza-1,4-epoxybicyclo[4.3.0]non-2-ene β-*cyclodextrin complex* **4a**: To a well-stirred solution of β-cyclodextrin (0.42 g, 0.4 mmol) in water (30.6 cm^3) was added *N*-(allyl)-*N*-(4-toluenesulfonyl)-2-furfurylamine[1] **1a** (0.11 g, 0.4 mmol) in methanol (0.6 cm^3). The resulting solution was heated under reflux for 4 h then allowed to cool to 5°C overnight. A precipitate formed which was collected by filtration and recrystallised from water to afford the 1:1 complex **4a** as a white powder (0.18 g, 34 %), m.p. >240°C; $[\alpha]_D^{25.9}$ + 126.5 (c = 3.4 × 10^{-3}, l = 1, water); ν_{max}(thin film/Nujol)/cm^{-1}: 3331, 2924, 1639, 1600, 1327, 1152, 1020; δ_H(500 MHz; D_2O) 1.49–1.57 (2 H, m), 1.97–2.03 (1 H, m), 1.50 (3 H, s), 2.64–2.72 (1 H, m), 4.41 (1 H, dd, *J* 2.8, 11.6), 3.59–3.92 (65 H, m), 5.01 (1 H, d, *J* 3.1), 5.06 (7 H, d, *J* 3.5), 6.34 (1 H, dd, *J* 3.1, 8.0), 6.52 (1 H, d, *J* 8.0), 7.48 (2 H, d, *J* 8.1), 7.64 (2 H, d, *J* 8.1); (Found: C, 46.1; H, 6.7; N, 0.7. $C_{57}H_{87}NSO_{38}.3H_2O$ requires C, 46.25; H, 6.3; N, 0.95 %).

8-Benzyl-8-aza-1,4-epoxybicyclo[4.3.0]non-2-ene β-*cyclodextrin complex* **4b**: To a well-stirred solution of β-cyclodextrin (1.05 g, 0.9 mmol) in water (77 cm^3) at reflux was added *N*-(benzyl)-*N*-(allyl)-2-furfurylamine[1] **(1b)** (0.21 g, 0.9 mmol) in DMSO (2.5 cm^3). The resulting solution was heated under reflux for 8 h, then cooled to room temperature before storing at 5°C overnight. A precipitate formed and this was collected by filtration and then recrystallised from water to afford the 1:1 complex **4b** as a white power (0.34 g, 27 %), m.p. > 225°C; $[\alpha]_D^{25.5}$ + 123.8 (c = 2.1 × 10^{-3}, l = 1, water); ν_{max}(Nujol)/cm^{-1}: 3313, 2923, 1639, 1102; δ_H(500 MHz; D_2O) 1.44 (1 H, dd, *J* 7.6, 11.6), 1.70–1.73 (1 H, m), 2.01–2.03 (1 H, m), 2.18–2.24 (1 H, m), 2.78 (1 H, dd, *J* 6.7, 12.6), 3.16 (1 H, t, *J* 7.0), 3.51–3.95 (66 H, m), 5.07 (7 H, d, *J* 3.6), 5.09 (1 H, d, *J* 4.1), 6.42 (1 H, d, *J* 5.9), 6.50 (1 H, dd, *J* 4.1, 5.9), 7.37–7.43 (5 H, m); (Found: C, 48.2; H, 6.7; N, 0.7. $C_{57}H_{87}NO_{36}.3H_2O$ requires C, 48.3; H, 6.6; N, 1.0 %).

Cyclisation of compound **7** *to* **6**: The precursor furan **7**[10] (20 mg) was dissolved in deuterated DMSO (0.2 cm^3) and then made up to 2 cm^3 with D_2O and the solution used in reactions monitored by ^{1}H NMR at 500 MHz and 80°C. Cyclisation was complete after 2 h . The product **6** showed δ_H (500 MHz, 10% DMSO in D_2O) 1.62 (3H, s, *Me*), 2.44 (3H, s, Ar*Me*), 3.00 (1 H, m, C*H*), 3.3–3.5 (3 H, m, NCH_2, C*H*), 3.66 (6 H, s, 2 x CO_2*Me*), 4.37, 4.38 (2H, ABq, *J* 12, NCH_2), 4.79 (1 H, s, *H*C=C), 4.92 (1 H, s, *H*CO), 6.03 (1 H, s, *H*C=C), 6.18 (1 H, s, *H*C=C), 6.32 (1 H, s, *H*C=C), 7.37 (2 H, d, *J* 7.9, Ar), 7.66 (2 H, d, *J* 7.9, Ar). [For full characterisation of **6** and **7** see ref 10.]

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