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A Cyclodextrin Molecular Reactor for the Regioselective Synthesis of 1,5-disubstituted-1,2,3-triazoles

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6^A-Deoxy-6^A-propynamido-β-cyclodextrin reacts with 4-*tert*-butylphenyl azide in aqueous solution, to form the 5-(aminocarbonyl)-substituted triazole in preference to the 4-(aminocarbonyl)-substituted analogue, in a ratio of 25:1. The cyclodextrin moiety templates the reaction through the formation of a host-guest complex of the dipole with the dipolarophile, controlling the regioselectivity of cycloaddition. In a control reaction under similar conditions, with propiolamide instead of the cyclodextrin derivative, 5- and 4-(aminocarbonyl)-1-(4-*tert*-butylphenyl)-1,2,3-triazole were formed in a ratio of 1:4. As well as reversing the regioselectivity, the cyclodextrin substituent increases the rate of cycloaddition, by at least two orders of magnitude for the reaction to give the 5-substituted cycloadduct. Even the rate of formation of the 4-substituted cycloadduct is increased by a factor of two. Less marked effects are observed with phenyl azide and 4-*tert*-butylbenzyl azide as dipoles.

Keywords: Molecular reactors; Triazoles; Cyclodextrins; Regio selectivity; Cycloadditions; Templates

INTRODUCTION

Exploiting host-guest chemistry to manipulate the outcomes of chemical transformations allows for the viable synthesis of materials that would otherwise be difficult to prepare. Porphyrins [1–3], cucurbiturils [4,5] and cyclodextrins [6–14] are among the molecular scaffolds that have been used for this purpose. In this approach, the host molecules function as molecular reactors [6,7], in that they are used as reaction vessels, but at the molecular level, to assemble the reagents and control the geometry of chemical processes.

The unique physical properties of cyclodextrins (Fig. 1) enable these species to function as hosts for a wide range of organic molecular guests in aqueous solution [9]. Through such complexation, the regioselectivity of aromatic halogenations [10,11] and carboxylation of phenols [12], and the stereoselectivity of epoxidations [13], are among the chemical processes that have been affected. By attaching the dipolarophiles to a cyclodextrin, the regioselectivity of cycloadditions between nitrile oxides and alkynes and alkenes, to generate isoxazoles and 2-isoxazolines, respectively, has also been reversed (Scheme 1) [14]. In these reactions, the host's annulus serves to govern the alignment of the bound dipole with the dipolarophile.

1,2,3-Triazoles are useful synthons in synthetic organic chemistry. They are accessible through 1,3-dipolar cycloadditions of azides with alkynes (Scheme 2) [15]. Recently, methods to improve the efficiency and regioselectivity of these cycloadditions have been investigated due to the usual lack of regiocontrol and vigorous reaction conditions that are normally required [16,17]. Sharpless and coworkers [16] reported the regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles from azides and terminal alkynes through Cu(I)-catalyzed ligation in aqueous media at room temperature. This "click chemistry" [18] has received a lot of attention and numerous applications of the method have been described [19–21]. Recently, Wang *et al.* [17] reported a similarly regioselective process which does not require a Cu(I) catalyst. By simply heating an azide and terminal alkyne using water as the solvent, preferential formation of the 1,4-disubstituted

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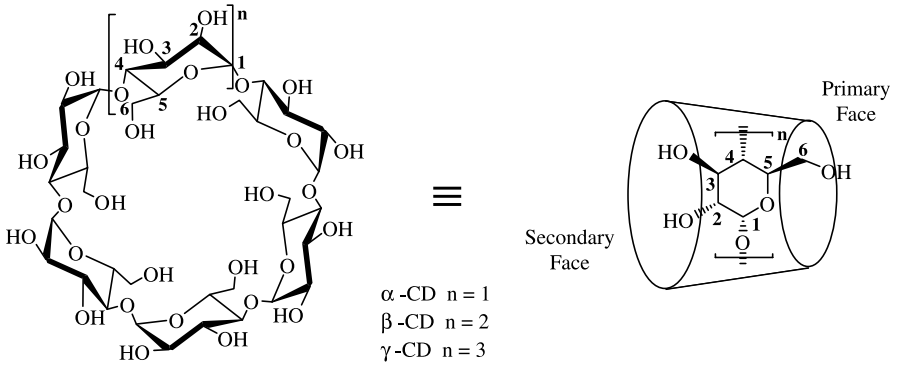
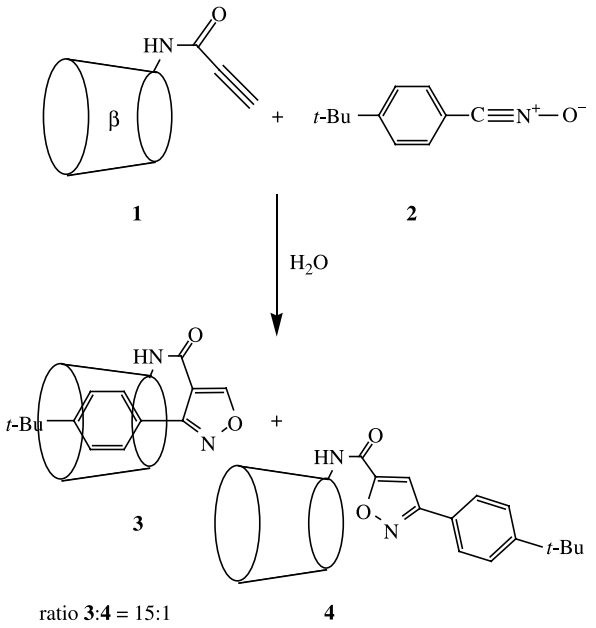


FIGURE 1 Schematic illustration of α-, β- and γ-cyclodextrin which, for simplicity, are often represented as truncated cones. The narrow end of the cone represents the face incorporating the primary hydroxyl groups and the wider end represents the face incorporating the secondary hydroxyl groups.

cycloadduct was observed. We now show that by tethering the dipolarophile to a cyclodextrin in the form of the amide **1**, the regioselectivity can be reversed and 1,5-disubstituted-1,2,3-triazoles are formed in preference to the 1,4-disubstituted analogues. In addition we report the effect of the complexation to accelerate such cycloadditions, even in the case of the reaction to give the regioisomer less favored by the cyclodextrin.

RESULTS AND DISCUSSION

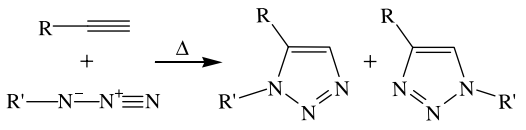
The azides used in this study were 4-*tert*-butylphenyl azide (**5a**), phenyl azide (**5b**) and 4-*tert*-butylbenzyl azide (**5c**), as benzene derivatives are known to form thermodynamically stable inclusion complexes with cyclodextrins [22,23]. 4-*tert*-Butylphenyl azide (**5a**) was expected to show the greatest effect of complexation as it is rigid and the hydrophobic moiety of this compound is known to bind particularly strongly to β-cyclodextrin [24]. The azides **5a** and **5b** were synthesized from the corresponding amines, by first forming the diazonium salts in situ through treatment with sodium nitrite, followed by reaction of the salts with sodium azide [25]. 4-*tert*-Butylbenzyl azide (**5c**) was prepared through the treatment of the analogous bromide with sodium azide [26]. The cyclodextrin-substituted dipolarophile, 6^A-deoxy-6^A-propyn amido-β-cyclodextrin (**1**), was prepared through treatment of 6^A-amino-6^A-deoxy-β-cyclodextrin with 4-nitrophenyl propynoate.



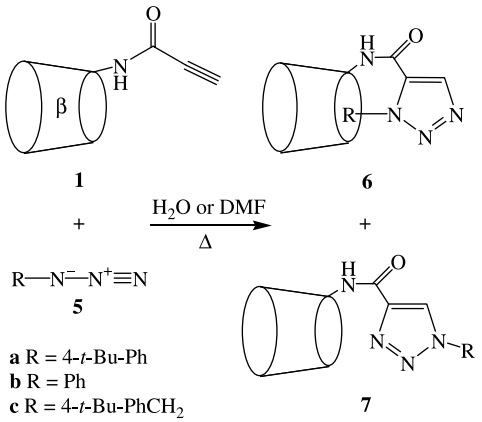
SCHEME 1 Treatment of the dipolarophile **1** with the nitrile oxide **2** in aqueous solution affords the 4-substituted isoxazole **3** and the 5-substituted isomer **4**, in a ratio of 15:1. In the absence of a cyclodextrin but under otherwise identical conditions, propiolamide (**8**) reacts with the nitrile oxide **2** to give the corresponding 4- and 5-substituted isoxazoles in a ratio of 1:4.

The reactions between the azides **5a–c** and the cyclodextrin **1** (Scheme 3) were performed in aqueous solution, anticipating that this would facilitate formation of the dipole-dipolarophile host–guest complexes. The reaction of the cyclodextrin **1** with 4-*tert*-butylphenyl azide (**5a**) was also carried out in DMF. This solvent is known to disrupt the binding of a hydrophobic guest inside a cyclodextrin annulus, and its effect on the distribution of the products was therefore of interest.

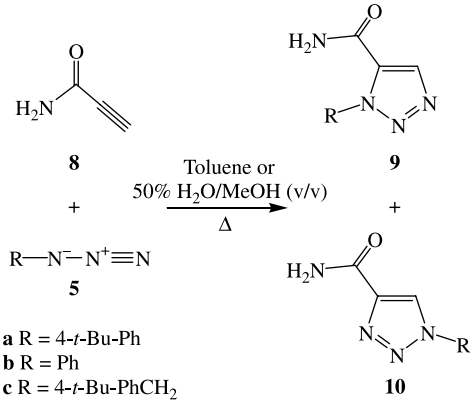
The ratios of the cycloadducts **6a–c** and **7a–c** formed in these reactions were determined by analysis of the crude product mixtures using ^{1}H NMR spectroscopy. The chemical shifts of the triazole ring protons were used to distinguish the



SCHEME 2 1,3-Dipolar cycloadditions of terminal alkynes and azides afford isomeric mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles.



SCHEME 3 Formation of the triazoles **6a–c** and **7a–c** on treatment of the azides **5a–c** with the dipolarophile **1**.



SCHEME 4 Formation of the triazoles **9a–c** and **10a–c** on treatment of the azides **5a–c** with the dipolarophile **8**.

regioisomers **6a–c** and **7a–c**. The H_4 proton of each of the 1,5-disubstituted triazoles **6a–c** resonates upfield of the resonance of the H_5 proton of the corresponding 1,4-disubstituted isomer **7a–c** [17,27,28]. For example, in d_6-DMSO, those protons of the triazoles **6a** and **7a** have chemical shifts of δ8.20 and 9.24 ppm, respectively. The regioisomers **6a–c** and **7a–c** are also distinguishable based on the chemical shifts of their phenyl group protons. These are shifted upfield for the 1,5-disubstituted triazoles **6a–c** as a result of their phenyl groups being included inside the cyclodextrin cavity. Those of the 1,5-disubstituted triazole **6a** resonate at δ7.40 and 7.55 ppm, upfield of the corresponding resonances of the 1,4-disubstituted triazole **7a**, at δ7.63 and 7.88 ppm. The ratios of the regioisomers **6a–c** and **7a–c** are shown in Table I. The 1,5-disubstituted triazoles **6a–c** were each isolated and fully characterized. Authentic samples of the 1,4-disubstituted triazoles **7a–c** were synthesized using the regiospecific copper(I)-catalyzed cycloaddition process [16].

Control reactions were performed with propiol amide (**8**) to determine the ratio of cycloadducts formed in the absence of a cyclodextrin. The amide **8** was prepared through reaction of methyl propiolate with ammonia. The cycloadditions were carried out by treatment of propiolamide (**8**) with each of the azides **5a–c** in toluene at reflux (Scheme 4). It was not possible to obtain homogeneous solutions using water as the solvent for these reactions, for more direct comparison with the reactions of the dipolarophile **1**, due to the low solubility of the azides **5a–c** when no cyclodextrin was present. However, the reaction of the azide **5a** with propiolamide (**8**) was also studied in 50% aqueous methanol at reflux. The crude product mixtures were analyzed using ^{1}H NMR spectroscopy to determine the ratios of the cycloadducts **9a–c** and **10a–c** (Table I). Each of the 1,5- and 1,4-disubstitued triazoles **9a**,**b** and **10a–c** was isolated by chromatography and fully characterized. A low intensity resonance at δ7.6 ppm in the spectrum in $CDCl_3$ of the product of the reaction of the azide **5c** with propiolamide (**8**) was assigned to the triazole **9c** but it was not practical to isolate this material.

The results in Table I clearly demonstrate the impact of the cyclodextrin moiety of the amide **1** on the cycloadditions with the azides **5a–c**. The proportions of the 1,5-disubstituted regioisomers **6a–c** are increased relative to the amounts of the analogous products **9a–c** formed from propiolamide (**8**). In water, 4-*tert*-butylphenyl azide (**5a**) reacts with the cyclodextrin **1** in the most selective manner, with the 1,5-disubstituted triazole **6a** accounting for more than 95% of the cycloadduct mixture. By comparison, with propiolamide (**8**) and in the absence of the cyclodextrin moiety, the 1,4-disubstituted triazole **10a** instead predominates, comprising 75 and 80%

TABLE I Ratios of the regioisomeric cycloadducts **6a–c** and **7a–c**, and **9a–c** and **10a–c** formed through reaction of the azides **5a–c** with 6^A-deoxy-6^A-propynamido-β-cyclodextrin (**1**) and propiolamide (**8**), respectively.

Dipolarophile	Azide	Solvent	Ratio of regioisomers
1	**5a**	H_2O	**6a**:**7a**, 25:1
1	**5a**	DMF	**6a**:**7a**, 1:1
1	**5b**	H_2O	**6b**:**7b**, 1.5:1
1	**5c**	H_2O	**6c**:**7c**, 1:1.3
8	**5a**	Toluene	**9a**:**10a**, 1:3
8	**5a**	50% H_2O/MeOH	**9a**:**10a**, 1:4
8	**5b**	Toluene	**9b**:**10b**, 1:2
8	**5c**	Toluene	**9c**:**10c**, $<$1:70

of the product mixture from reactions carried out in toluene and 50% aqueous methanol, respectively. DMF substantially reduces the effect of the cyclodextrin group to template the reaction to give the 1,5-disubstituted triazole **6a**, presumably by disrupting the complex between the dipole **5a** and the dipolarophile **1** (Fig. 2).

With the azide **5b**, the difference in regioselectivity observed in reactions of propiolamide (**8**) and the cyclodextrin **1** is much less pronounced, with the triazoles **6b** and **7b** being formed in the ratio 1.5:1, whereas the cycloadducts **9b** and **10b** derived from propiolamide (**8**) are produced in the ratio 1:2. This is most probably due to the complex of the azide **5b** with the cyclodextrin **1** being of much lower thermodynamic stability than those of the *tert*-butyl derivatives **5a** and **5c**. The influence of the cyclodextrin substituent on the reactions of 4-*tert*-butylbenzyl azide (**5c**) is again substantial, increasing the proportion of formation of the 1,5-disubstituted triazole **6c** relative to that of the unsubstituted analogue **9c** by a factor of at least thirty.

As already illustrated above (Fig. 2), the effect of the cyclodextrin **1** on the regioselectivity of reactions of the azides **5a–c** is attributable to the alignment of the dipoles **5a–c** with the dipolarophile **1** in their host–guest complexes. The complexation also accelerates cycloaddition. To quantify this rate increase, the initial stages of the reactions of 4-*tert*-butylphenyl azide (**5a**) (2.5 mM) with the cyclodextrin derivative **1** (5.0 mM) in D_2O and with propiolamide (**8**) (5.0 mM) in 50% D_2O/CD_3OD were monitored at 40°C using ^1H NMR spectroscopy. Under these conditions, the pseudo-first order rate constants for formation of the cycloadducts **6a**, **7a**, **9a** and **10a**, were found to be $4 \times 10^{-4}\,min^{-1}$, $1.6 \times 10^{-5}\,min^{-1}$, $<1.5 \times 10^{-6}\,min^{-1}$ and $<6.5 \times 10^{-6}\,min^{-1}$, respectively. Thus the cyclodextrin moiety of the amide **1** increases by more than two orders of magnitude the rate of formation of the 1,5-disubstituted triazole **6a** relative to that of the analogous regioisomer **9a** formed from propiolamide (**8**). Even the rate of formation of the 1,4-disubstituted triazole **7a** is more than twice as fast as that of the analogue lacking the cyclodextrin **10a**.

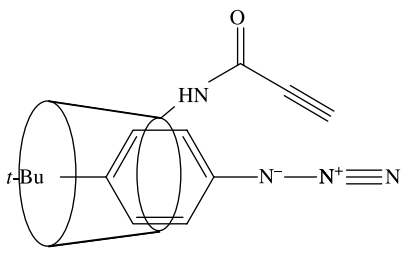


FIGURE 2 Schematic representation of the host-guest complex that forms between the cyclodextrin **1** and the azide **5a**, to control the regioselectivity and accelerate the cycloaddition between these species.

CONCLUSION

It is therefore apparent that the cyclodextrin derivative **1** serves as a molecular reactor for the regioselective synthesis of 1,5-disubstituted-1,2,3-triazoles. While stereo- and regio-control of chemical reactions is often achieved by selectively blocking access to the other isomers and slowing reaction rates as a consequence, in the case of the reactions of the amide **1** with the azide **5a**, the cyclodextrin substituent accelerates the cycloaddition to give each of the regioisomers **6a** and **7a**, only more so in the former case. Consequently the cyclodextrin is a template for both processes, but a better one for the reaction to give the 1,5-disubstituted regioisomer **6a**.

EXPERIMENTAL

General

NMR spectra were recorded on either a Varian Gemini 300 spectrometer operating at 300 MHz (^1H) or 75 MHz (^{13}C), or a Varian Inova 500 spectrometer operating at 500 MHz (^1H) or 125 MHz (^{13}C). Electron impact mass spectra (EI) were recorded on a Micromass VG AutoSpec mass spectrometer, operating with an ionization potential of 70 eV and a source potential of 8 KV. Low-resolution electrospray ionization mass spectra (ESI) were recorded on a Micromass VG Quattro II triple quadrupole mass spectrometer and high-resolution data were recorded on a Bruker Apex 4.7T FTICR-MS mass spectrometer. Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum One spectrophotometer. Elemental analyses were performed by the Australian National University Microanalytical Service. Melting points (mp) were determined on a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected. Column chromatography was carried out on Merck silica gel 60 (40–6.3 μm) with analytical grade solvents, driven by a positive pressure of nitrogen. High-performance liquid chromatography (HPLC) was carried out using a Waters Alliance Separation Module 2690 with a Waters 996 photodiode array detector. Column 1 refers to use of an Alltech Apollo C_{18} 5μ, 4.6 × 250 mm column and column 2 to the use of a Phenomenex Luna C_{18} 5μ, 10 × 250 mm column. The retention times of the 1,5-disubstituted triazoles **6a–c** are stated relative to that of 6^A-deoxy-6^A-propynamido-β-cyclodextrin (**1**) (t_R), when eluting with acetonitrile/water (10% v/v) with a flow rate of $1\,cm^3\,min^{-1}$. β-Cyclodextrin was obtained from Nihon Shokuhin Kako Co., Japan, in 99.1% purity. It was recrystallized from water and dried under vacuum over P_2O_5 to constant weight before use to

prepare 6^A-amino-6^A-deoxy-β-cyclodextrin [29]. Water was deionized and then purified with a Milli-Q™ reagent system to ensure a resistivity of $<15\,M\Omega\,cm^{-1}$. Bio-Rex 70 resin was obtained from Bio-Rad Laboratories, Inc, CA and Diaion HP-20 resin was purchased from Supelco®, PA. All other chemicals were purchased from Sigma–Aldrich Chemical Company and were used as received.

General Procedure for Preparation of the Azides 5a and 5b

Aqueous sodium nitrite (2 M, 1.05 mol. equiv.) was added dropwise to rapidly stirred mixtures of the appropriate amines (1.0 g) in AcOH (9 mL) and concentrated H_2SO_4 (4 mL) maintained at 0–5°C. After 10 min, an aqueous solution of urea (2 M, 1.05 mol. equiv.) was added to each of the reaction mixtures to consume the excess sodium nitrite. A solution of sodium azide in water (2.5 M, 1.1 mol. equiv.) was then added and the mixtures were stirred for a further 3 h at 0–5°C, before they were poured into ice-cold water and basified with 50% aqueous sodium hydroxide. The mixtures were extracted with EtOAc (3 × 50 mL), and the combined extracts from each mixture were washed with water (2 × 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography of the residues on silica gel, eluting with EtOAc/hexanes (2–5% v/v), gave the title compounds **5a** and **5b** as light yellow oils.

4-tert-Butylphenyl Azide (5a)

(0.72 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, $J = 8.9$ Hz, 2H), 6.97 (d, $J = 8.9$ Hz, 2H), 1.31 (s, 9H); IR (neat): 2089, 2123 cm^{-1}; *m/z* (EI): 175 ($M^{+\cdot}$, 7%), 160 (13), 134 (27), 133 (61), 57 (100); *m/z* (EI): calcd for $C_{10}H_{13}N_3$ ($M^{+\cdot}$), 175.1109; found, 175.1111.

Phenyl Azide (5b)

(0.71 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 2H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.04 (d, $J = 8.1$ Hz, 2H); IR (neat): 2079, 2129 cm^{-1} (lit. [25] 2100 cm^{-1}).

4-tert-Butylbenzyl Azide (5c)

4-*tert*-Butylbenzyl bromide (0.57 g, 2.5 mmol) was added to a solution of sodium azide in DMSO (0.5 M, 5.5 mL) and the mixture was stirred at 50°C for 24 h. The reaction was then quenched with water (15.5 mL) and the mixture was stirred until it had cooled to room temperature, before it was extracted with ether (3 × 15 mL). The combined extracts were washed with water (2 × 25 mL) and brine (1 × 25 mL), and then they were dried ($MgSO_4$) and concentrated under reduced pressure, to afford the title compound **5c** as a colorless oil (0.44 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 4.31 (s, 2H), 1.30 (s, 9H); IR (neat): 2098 cm^{-1}; *m/z* (EI): 189 ($M^{+\cdot}$, 50%), 174 (53), 147 (100), 146 (60), 91 (63); *m/z* (EI): calcd for $C_{11}H_{15}N_3$ ($M^{+\cdot}$), 189.1266; found, 189.1267.

4-Nitrophenyl Propynoate

Propiolic acid (0.70 g, 10 mmol) was added to a stirred solution of 4-nitrophenol (1.39 g, 10 mmol) in freshly distilled ethyl acetate (10 mL), suspended in an ice bath under a nitrogen atmosphere. 1,3-Dicyclohexylcarbodimide (2.06 g, 10 mmol) was added and a white precipitate formed. The ice bath was removed after 10 min and the reaction mixture was stirred at ambient temperature for a further 22 h, before it was filtered and the filter cake was washed with ethyl acetate (6 × 5 mL). The filtrate and washings were combined and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/hexanes (3:1 v/v), to give the title compound as a colorless solid (1.43 g, 75%): mp 136–137°C (lit. [30] mp 137 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, $J = 7.0$ Hz, 2H), 7.36 (d, $J = 7.0$ Hz, 2H), 3.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 149.6, 145.7, 125.3, 122.2, 78.1, 73.4; *m/z* (EI): 191 ($M^{+\cdot}$, 28%), 174 (20), 53 (100).

6^A-Deoxy-6^A-propynamido-β-cyclodextrin (1)

6^A-Amino-6^A-deoxy-β-cyclodextrin (1.0 g, 0.88 mmol), 4-nitrophenyl propynoate (0.18 g, 0.93 mmol) and triethylamine (93 mg, 0.92 mmol) were dissolved in dry DMF (5 mL) under a nitrogen atmosphere and the resultant yellow solution was stirred at ambient temperature for 5 h. The volume of the mixture was then reduced by approximately 50% under reduced pressure, before ethanol (100 mL) and ether (50 mL) were added. The yellow precipitate that formed was collected by centrifugation (4000 rpm, 5 min). This material was dissolved in a 10% aqueous ammonia solution (5 mL) and acetone (200 mL) was added, to give a light yellow precipitate that was collected by centrifugation (4000 rpm, 5 min) and washed with acetone (100 mL). The dissolution/precipitation process was repeated twice, and the remaining solid was dissolved in water (150 mL). The solution was passed through a column of Bio-Rex 70 ion-exchange resin (H^+ form) to remove any unreacted 6^A-amino-6^A-deoxy-β-cyclodextrin, before it was concentrated under reduced pressure. The residue was chromatographed on Diaion HP-20 resin, eluting with CH_3OH/H_2O (0–15% v/v). The eluant was concentrated under reduced pressure to remove methanol and then freeze-dried, to give the title compound **1** as a colorless solid (0.33 g, 32%): ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.61 (m, 1H), 5.80–5.70

(m, 14H), 4.91–4.85 (m, 7H), 4.52–4.42 (m, 6H), 4.11 (s, 1H), 3.66–3.38 (m, 42H); m/z (ESI): 1208 ($M + Na^+$). This material was found to be identical to an authentic sample that had been prepared by treatment of 6^A-amino-6^A-deoxy-β-cyclodextrin with propiolyl chloride [14].

General Procedure for Reactions of the Cyclodextrin 1 with the Azides 5a–c in Water

Solutions of 6^A-deoxy-6^A-propynamido-β-cyclodextrin (**1**) (45 mg, 38 μmol) and one of the azides **5a–c** (0.12 mmol, dissolved in 0.1 mL ethanol) in H_2O (3 mL) were stirred at 95 °C, for 24 h (**6c**) or 48 h (**6a** and **6b**). Small aliquots were then removed and concentrated under reduced pressure. The residues were analyzed using ^1H NMR spectroscopy to determine the ratios of formation of the cycloadducts **6a–c** and **7a–c**. For the reactions of the azides **5a** and **5b**, the remainders of the product mixtures were diluted with aqueous ethanol (20% v/v, 20 mL), washed with ethyl acetate (2 × 20 mL) and concentrated under reduced pressure to give the crude products. With the azide **5c**, the crude product was obtained by concentrating the reaction mixture under reduced pressure.

5-(N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-aminocarbonyl)-1-(4-tert-butylphenyl)-1,2,3-triazole (6a)

The title compound **6a** was present in the crude reaction product as a 25:1 mixture with the regioisomer **7a**. It was isolated by chromatography of the mixture on Diaion HP-20 resin, eluting with methanol/water (0–25% v/v), and obtained as a colorless solid (28 mg, 54%). A sample for elemental analysis was obtained using HPLC (column 2), eluting with acetonitrile/water (15% v/v): ^1H NMR (500 MHz, d_6-DMSO): δ 8.40 (m, 1H), 8.20 (s, 1H), 7.55 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 5.90–5.71 (m, 14H), 4.92 (m, 1H), 4.86–4.82 (m, 6H), 4.57–4.45 (m, 6H), 3.68–3.33 (m, 42H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 158.0, 152.2, 133.8, 133.0, 125.8, 124.1, 102.1, 101.6, 83.9, 81.5, 73.0–72.1, 70.4, 59.9, 34.6, 31.2; m/z (ESI): 1383 ($M + Na^+$, 60%), 1361 ($M + H^+$, 80), 703 ($M + 2Na^{2+}$, 100); m/z (ESI): calcd for $C_{55}H_{85}N_4O_{35}$ ($M + H^+$), 1361.4994; found, 1361.4997. Anal. Calcd for $C_{55}H_{84}N_4O_{35}\cdot 11H_2O$: C, 42.33; H, 6.85; N, 3.59%. Found: C, 42.51; H, 6.69; N, 3.55%. HPLC (column 1) $t_R = 1.5$.

5-(N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-aminocarbonyl)-1-phenyl-1,2,3-triazole (6b)

The title compound **6b** was present in the crude reaction product as a 1.5:1 mixture with the regioisomer **7b**. It was isolated by HPLC (column 2), eluting with acetonitrile/water (13% v/v), and obtained as a colorless solid (6 mg, 12%): ^1H NMR (500 MHz, d_6-DMSO): δ 8.76 (m, 1H), 8.28 (s, 1H), 7.52 (m, 5H), 5.86–5.69 (m, 14H), 4.90–4.85 (m, 7H), 4.53 (m, 5H), 4.39 (m, 1H), 3.90–3.25 (m, 42H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 157.6, 136.6, 134.1, 132.5, 129.3, 129.0, 124.9, 102.3–101.7, 83.9, 81.6, 81.3, 73.0, 72.4–72.0, 69.7, 59.8; m/z (ESI): 1327 ($M + Na^+$, 67%), 1305 ($M + H^+$, 100), 675 ($M + 2Na^{2+}$, 79); m/z (ESI): calcd for $C_{51}H_{77}N_4O_{35}$ ($M + H^+$), 1305.4368; found, 1305.4434. Anal. Calcd for $C_{51}H_{76}N_4O_{35}\cdot 9H_2O$: C, 41.75; H, 6.46; N, 3.82%. Found: C, 41.88; H, 6.30; N, 3.62%. HPLC (column 1) $t_R = 2.3$.

5-(N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-aminocarbonyl)-1-(4-tert-butylbenzyl)-1,2,3-triazole (6c)

The title compound **6c** was present in the crude reaction product as a 1:1.3 mixture with the regioisomer **7c**. It was isolated by HPLC (column 2), eluting with acetonitrile/water (15% v/v), and obtained as an off-white solid (14 mg, 27%): ^1H NMR (500 MHz, d_6-DMSO): δ 8.21 (s, 1H), 8.07 (m, 1H), 7.19 (d, $J = 7.8$ Hz, 2H), 6.93 (d, $J = 7.8$ Hz, 2H), 6.02–5.64 (m, 16H), 4.93–4.46 (m, 7H), 4.61–4.42 (m, 5H), 4.32 (m, 1H), 4.12 (m, 1H), 3.99 (m, 1H), 3.91 (m, 1H), 3.78–3.00 (m, 36H), 2.86 (m, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 157.1, 150.3, 133.8, 132.2, 130.5, 127.7, 124.6, 102.5, 102.2–101.8, 84.1, 81.6–81.1, 73.1–71.3, 59.7–59.4, 58.8, 52.8, 34.3, 31.4; m/z (ESI): 1397 ($M + Na^+$, 36%), 1375 ($M + H^+$, 75), 710 ($M + 2Na^{2+}$, 100); m/z (ESI): calcd for $C_{56}H_{87}N_4O_{35}$ ($M + H^+$), 1375.5151; found, 1375.5173. Anal. Calcd for $C_{56}H_{86}N_4O_{35}\cdot 6H_2O$: C, 45.34; H, 6.67; N, 3.78%. Found: C, 45.31; H, 6.42; N, 3.71%. HPLC (column 1) $t_R = 1.3$.

General Procedure for Preparation of the Triazoles 7a–c

Aqueous sodium ascorbate (0.1 M, 17 μL, 1.7 μmol) and aqueous copper (II) sulfate pentahydrate (0.03 M, 6 μL, 0.18 μmol) were added to solutions containing 6^A-deoxy-6^A-propynamido-β-cyclodextrin (**1**) (20 mg, 17 μmol) and one of the azides **5a–c** (22 μmol in 0.1 mL ethanol) in H_2O (1 mL). The reaction mixtures were stirred for 20 h at ambient temperature and in each case a white precipitate formed. Acetone (30 mL) was added and the precipitates were collected by centrifugation (4000 rpm, 5 min) to give the crude products.

4-(N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-aminocarbonyl)-1-(4-tert-butylphenyl)-1,2,3-triazole (7a)

The crude product was recrystallized from water to give the title compound **7a** as a colorless solid (16 mg,

70%): ^{1}H NMR (500 MHz, d_6-DMSO): δ 9.24 (s, 1H), 8.23 (m, 1H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.63 (d, $J = 8.3$ Hz, 2H), 5.92–5.61 (m, 14H), 4.98–4.77 (m, 7H), 4.59–4.30 (m, 6H), 3.95–3.00 (m, 42H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 159.5, 151.8, 143.5, 134.0, 126.8, 126.6, 119.9, 102.1, 81.6, 73.0–72.0, 69.9, 59.8, 34.6, 31.1; m/z (ESI): 1383 ($M + Na^+$, 23%), 1361 ($M + H^+$, 4), 227 (100); m/z (ESI): calcd for $C_{55}H_{85}N_4O_{35}$ ($M + H^+$), 1361.4994; found, 1361.4990. Anal. Calcd for $C_{55}H_{84}N_4O_{35}\cdot 9H_2O$: C, 43.34; H, 6.74; N, 3.68%. Found: C, 43.42; H, 6.72; N, 3.56%.

4-(N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-aminocarbonyl)-1-phenyl-1,2,3-triazole (7b)

The crude product was recrystallized from water to give the title compound **7b** as an off-white solid (19 mg, 86%): ^{1}H NMR (500 MHz, d_6-DMSO): δ 9.26 (s, 1H), 8.27 (m, 1H), 7.98 (d, $J = 7.5$ Hz, 2H), 7.64 (t, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 7.5$ Hz, 1H), 5.88–5.69 (m, 14H), 4.97–4.79 (m, 7H), 4.57–4.53 (m, 3H), 4.47 (t, $J = 6.0$ Hz, 1H), 4.42 (t, $J = 6.0$ Hz, 1H), 4.35 (t, $J = 6.0$ Hz, 1H), 3.95–3.20 (m, 42H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 159.5, 143.6, 136.3, 130.0, 129.2, 124.5, 120.4, 102.1, 101.5, 84.3, 81.5, 73.1–71.8, 60.0–59.5; m/z (ESI): 1327 ($M + Na^+$, 70%), 1305 ($M + H^+$, 38), 675 ($M + 2Na^{2+}$, 100); m/z (ESI): calcd for $C_{51}H_{77}N_4O_{35}$ ($M + H^+$), 1305.4368; found, 1305.4309. Anal. Calcd for $C_{51}H_{76}N_4O_{35}\cdot 7H_2O$: C, 42.80; H, 6.34; N, 3.91%. Found C, 42.71; H, 6.12; N, 3.69%.

4-(N-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-aminocarbonyl)-1-(4-tert-butylbenzyl)-1,2,3-triazole (7c)

The crude product was chromatographed on a Waters Sep-Pak® cartridge, eluting with water/methanol (0–30% v/v), to give the title compound **7c** as a colorless solid (10 mg, 43%): ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.62 (s, 1H), 8.10 (m, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 5.95–5.62 (m, 14H), 5.60 (s, 2H), 4.95–4.80 (m, 7H), 4.58–4.30 (m, 6H), 3.88–3.15 (m, 42H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 159.6, 150.7, 142.8, 132.7, 127.7, 126.4, 125.6, 102.0, 84.1, 81.4, 73.0–71.9, 69.5, 59.8, 52.8, 34.3, 31.0; m/z (ESI): 1397 ($M + Na^+$, 75%), 1375 ($M + H^+$, 17), 710 ($M + 2Na^{2+}$, 100); m/z (ESI): calcd for $C_{56}H_{86}N_4O_{35}Na$ ($M + Na^+$), 1397.4970; found, 1397.4939. Anal. Calcd for $C_{56}H_{86}N_4O_{35}\cdot 9H_2O$: C, 43.75; H, 6.82; N, 3.64%. Found: C, 43.93; H, 6.73; N, 3.62%.

Reaction of the Cyclodextrin 1 with the Azide 5a in DMF

A solution of 6^A-deoxy-6^A-propynamido-β-cyclodextrin (**1**) (45 mg, 38 μmol) and the azide **5a** (21 mg, 0.12 mmol) in DMF (3 mL) was stirred at 95 °C for 20 h. A small aliquot was then removed and concentrated under reduced pressure. The residue was analyzed using ^{1}H NMR spectroscopy to determine the ratio of formation of the cycloadducts **6a** and **7a**.

Propiolamide (8)

Methyl propiolate (1.00 g, 11.9 mmol) was added dropwise to liquid ammonia (100 mL) cooled to −78°C (dry ice/acetone) and the mixture was stirred at that temperature for 24 h, before the cooling bath was removed and the ammonia was allowed to evaporate under a stream of dry nitrogen. The residue was taken up in EtOAc (150 mL) and the solution was washed with water (3 × 100 mL). The aqueous washings were combined and extracted with EtOAc (3 × 150 mL). The combined organic solutions were washed with brine (1 × 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue, eluting with hexanes/EtOAc (3:2 v/v), followed by recrystallization from Et_2O/hexanes, afforded the title compound **8** as colorless needles (0.24 g, 29%): mp 60–61°C (lit. [31] mp 61–62°C); ^{1}H NMR (300 MHz, CD_3OD): δ 3.62 (s, 1H); m/z (EI): 69 ($M^{+\cdot}$, 43%), 53 (53), 41 (41), 28 (100).

General Procedure for Reactions of Propiolamide (8) with the Azides 5a–c in Toluene

Solutions of propiolamide (**8**) (40 mg, 58 mmol) and one of the azides **5a–c** (0.58 mmol) in freshly distilled toluene (5 mL) were heated at reflux for 20 h, then they were concentrated under reduced pressure. Small aliquots of the residues were analyzed using ^{1}H NMR spectroscopy to measure the ratios of formation of the cycloadducts **9a–c** and **10a–c**. The remainders of the product mixtures were chromatographed on silica gel, eluting with CH_3OH/CH_2Cl_2 (0–3%, v/v), to give the triazoles **9a**,**b** and **10a–c**, as colorless solids after recrystallization from CH_2Cl_2/hexanes. None of the triazole **9c** was isolated, but a resonance at δ7.6 ppm in the spectrum in $CDCl_3$ of the product of the reaction of the azide **5c** was assigned to this material, on which basis the ratio of formation of the triazoles **9c** and **10c** is conservatively estimated to be $<1{:}70$.

5-(Aminocarbonyl)-1-(4-tert-butylphenyl)-1,2,3-triazole (9a)

The title compound **9a** was produced in a 1:3 mixture with the regioisomer **10a** and isolated as described above (19 mg, 13%): mp 159–161°C; ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.28 (bs, 1H), 8.24 (s, 1H), 7.84 (bs, 1H), 7.55 (d, $J = 7.5$ Hz, 2H), 7.42 (d,

$J = 7.5$ Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 158.8, 152.0, 134.3, 134.2, 132.5, 125.7, 124.6, 34.6, 31.0; m/z (EI): 244 ($M^{+\cdot}$, 32%), 201 (100), 160 (27), 134 (48). Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93%. Found: C, 63.81; H, 6.62; N, 22.93%.

5-(Aminocarbonyl)-1-phenyl-1,2,3-triazole (9b)

The title compound **9b** was produced in a 1:2 mixture with the regioisomer **10b** and isolated as described above (30 mg, 28%): mp 141–145°C; ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.30 (bs, 1H), 8.29 (s, 1H), 7.86 (bs, 1H), 7.59–7.51 (m, 5H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 158.6, 136.6, 134.8, 132.6, 129.4, 129.0, 125.1; m/z (EI): 188 ($M^{+\cdot}$, 23%), 144 (49), 132 (30), 77 (100). Anal. Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.28; N, 29.77%. Found: C, 57.19; H, 4.37; N, 29.86%.

4-(Aminocarbonyl)-1-(4-tert-butylphenyl)-1,2,3-triazole (10a)

The title compound **10a** was produced in a 3:1 mixture with the regioisomer **9a** and isolated as described above (73 mg, 52%): mp 261–262°C; ^{1}H NMR (500 MHz, d_6DMSO): δ 9.21 (s, 1H), 8.00 (bs, 1H), 7.86 (d, $J = 7.5$ Hz, 2H), 7.61 (m, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 161.3, 151.8, 143.7, 134.0, 126.6, 124.7, 120.1, 34.5, 31.0; m/z (EI): 244 ($M^{+\cdot}$, 29%), 201 (100), 160 (67), 134 (56), 57 (54). Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93%. Found: C, 63.83; H, 6.50; N, 23.07%.

4-(Aminocarbonyl)-1-phenyl-1,2,3-triazole (10b)

The title compound **10b** was produced in a 2:1 mixture with the regioisomer **9b** and isolated as described above (66 mg, 61%): mp 238–241 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ 9.27 (s, 1H), 8.02 (bs, 1H), 7.98 (d, $J = 9.0$ Hz, 2H), 7.64 (m, 3H), 7.54 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 161.2, 143.8, 136.3, 129.9, 129.1, 124.8, 120.4; m/z (EI): 188 ($M^{+\cdot}$, 24%), 144 (47), 77 (100). Anal. Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.28; N, 29.77%. Found: C, 57.12; H, 4.44; N, 29.77%.

4-(Aminocarbonyl)-1-(4-tert-butylbenzyl)-1,2,3-triazole (10c)

The title compound **10c** was the only cycloadduct isolated from the reaction of the azide **5c** (57 mg, 38%): mp 219–220 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.60 (s, 1H), 7.89 (bs, 1H), 7.49 (bs, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 5.61 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 161.5, 150.8, 143.1, 132.8, 127.8, 126.6, 125.6, 52.8, 34.3, 31.1; m/z (EI): 258 ($M^{+\cdot}$, 37%), 243 (24), 229 (34), 202 (76), 173 (100), 147 (97), 132 (68), 131 (84), 117 (62), 91 (30). Anal. Calcd for $C_{13}H_{16}N_4O$: C, 65.09; H, 7.02; N, 21.69%. Found: C, 64.99; H, 6.86; N, 21.81%.

Reaction of Propiolamide (8) with the Azide 5a in 50% Aqueous Methanol

A solution of propiolamide (**8**) (1.7 mg, 25 μmol) and the azide **5a** (2.2 mg, 13 μmol) in H_2O/CH_3OH (5 mL, 50% v/v) was stirred at 95 °C for 48 h, before it was concentrated under reduced pressure. The residue was analyzed using ^{1}H NMR spectroscopy to determine the ratio of formation of the cycloadducts **9a** and **10a**.

Rates of Reaction of the Azide 5a with 6^A-Deoxy-6^A-propynamido-β-cyclodextrin (1) to give the Cycloadducts 6a and 7a

A solution of 6^A-deoxy-6^A-propynamido-β-cyclodextrin (**1**) (5 mM) and 4-*tert*-butylphenyl azide (**5a**) (2.5 mM) in D_2O containing 4% EtOH, maintained at 40°C, was monitored using ^{1}H NMR spectroscopy over a period of 21 h. Spectra were recorded every 20 min to record the ratio of the remaining azide **5a** and the product triazole **6a**. Approximately 50% of the azide **5a** had reacted after 21 h. From the initial stages of reaction and allowing for the ratio of formation of the triazoles **6a** and **7a**, the pseudo-first order rate constants for formation of the triazoles **6a** and **7a** were calculated to be 4×10^{-4} min^{-1} and 1.6×10^{-5} min^{-1}, respectively.

Rates of Reaction of the Azide 5a with Propiolamide (8) to give the Cycloadducts 9a and 10a

A solution of propiolamide (**8**) (5 mM) and 4-*tert*-butylphenyl azide (**5a**) (2.5 mM) in D_2O/CD_3OD (50% v/v), maintained at 40°C, was monitored using ^{1}H NMR spectroscopy over a period of 185 h. Spectra were recorded every 24–48 h to record the ratio of the remaining azide **5a** and the product triazole **10a**. Even after 185 h, at least 80% of the azide **5a** remained unreacted. On this basis and allowing for the ratio of formation of the azides **9a** and **10a**, the pseudo-first order rate constants for formation of the triazoles **9a** and **10a** were calculated to be $< 1.5 \times 10^{-6}$ min^{-1} and $< 6.5 \times 10^{-6}$ min^{-1}, respectively.

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