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Formation of oligotriazoles catalysed by cucurbituril

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The catalytic activity of cucurbituril in 1,3-dipolar cycloadditions has been applied to the synthesis of oligotriazoles.

The supramolecular chemistry of cucurbituril is unique amongst cavitands due to its multiple modes of molecular recognition.[1,2] Cucurbituril binds strongly alkali and alkali earth metal cations and ammonium ions.[1–3] It encapsulates aliphatic[4–7] and aromatic molecules[3,8,9] most of which are substituted with mono- or di-ammonium ions required for strong binding. Probably its most remarkable feature is the ability to catalyse 1,3-dipolar cycloadditions, between suitably substituted aliphatic azides and terminal alkynes in a regioselective fashion.[1,10,11] Mock *et al.*[10] were the first to study the catalytic mechanism of this reaction and after detailed investigations[11] concluded that rate acceleration to the triazole product is a consequence of release of strain present in the ternary complex involving cucurbituril, an alkyne and an azide. More recently a very similar catalytic process was designed by Sanders *et al.*[12] through the elegant and careful construction of cyclic metalloporphyrin trimers which were shown to catalyse a Diels–Alder reaction with regiostereochemical control inside their cavities.

Not unexpectedly Mock *et al.* went on to explore cucurbituril as a catalyst for the polyaddition reaction between dialkyne and diazide monomers but without success.[1] Product inhibition was claimed to be the reason for the very low catalytic activity of cucurbituril since only a mixture of mono- and di-triazoles had formed.

Since then polymers involving cucurbituril have been synthesised but in all cases cucurbituril has been part of a directed polyrotaxane synthesis making use of preformed pseudorotaxane monomers.[6,13,14] As a catalyst for polymer synthesis cucurbituril has only been revisited once by Steinke *et al.*[15] who used the cavitand in stoichiometric amounts (thereby avoiding product inhibition) which resulted in the successful synthesis of mainchain polyrotaxanes.

After our initial attempts to prepare cucurbituril-catalysed polytriazoles with azidoethyl and propargyl disubstituted hexanediamines had been unsuccessful[15] we decided to repeat Mock's original experiments[10,11] aiming at improving our monomer design in the process (Fig. 1).

Bis(propargyl)amine HCl (**1**) was synthesised by reacting BOC protected propargylamine with propargyl bromide followed by treatment with HCl. Bis(2-aziodethyl)amine HCl (**2**) was accessed through bis(chloroethyl)amine HCl and cucurbituril (**3**) was obtained using the protocol by Kim *et al.*[16] Reactions were carried out in 0.2 M Na_2SO_4 in D_2O or DCl in D_2O (20% wt) using equimolar ratios of monomers (**1**) and (**2**) and concentrations of cucurbituril ranging from 2 to 0.1 equivalents. Reaction conditions are summarised in Table 1. The rotaxinated oligotriazole backbone (**4**) was separated from cucurbituril afterwards to obtain free oligotriazole (**5**) by extracting the basified aqueous solution with chloroform (Table 1).

Analysis of the ^{1}H NMR spectra of reactions **PT1** to **PT5** focused on the ratio of the integration of the newly formed triazole ring protons to cucurbituril protons (Table 1). **PT5** is the 'blank' experiment and it was found that no triazole rings are formed in the absence of cucurbituril under otherwise identical reaction conditions. For reactions **PT1** to **PT4** however triazole formation was observed. If more than one triazole ring is formed for every cucurbituril macrocycle (**3**) present ([triazole]/[**3**] > 1; Table 1) it means that on average cucurbituril has taken part in more than one catalysed 1,3-dipolar cycloaddition indicative of catalytic turnover. This is the case for reactions **PT3-B** and **PT4-A** in which subequimolar amounts of cucurbituril to monomer have been used and after 336 h at rt the maximum number of triazole rings had been formed. Subsequent heating of the samples at 80 °C for 96 h induces further triazole formation. In these cases the cycloaddition reaction is most

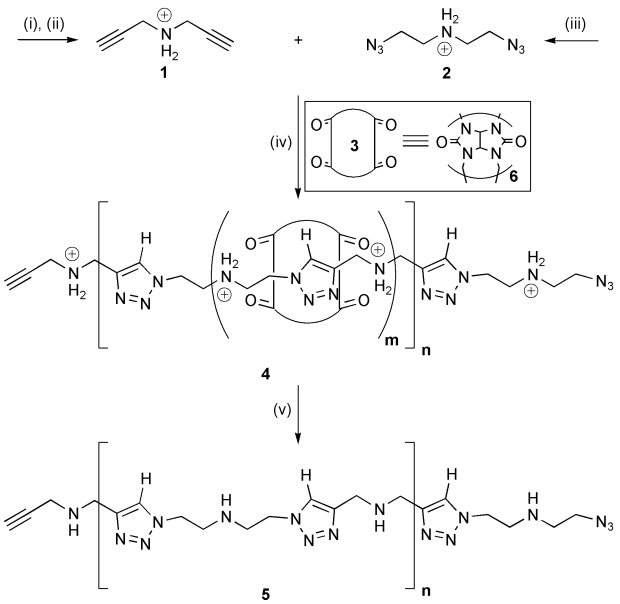

Fig. 1 Synthesis of oligotriazole pseudooligorotaxanes **4** and free oligotriazoles **5**. (i) $CH{\equiv}CCH_2NH_2$, $(BOC)_2O$; DMAP, dioxane, 20 °C, 48 h, 92%; (ii) $CH{\equiv}CCH_2Br$, DMF, NaH, then Et_2O, HCl_g, 80%; (iii) bis(2-chloroethyl)amine HCl, NaN_3, H_2O, 6 h rt, 2 h 70 °C, 60%; (iv) 0.2 M Na_2SO_4 in D_2O (see Table 1 for details), (v) 1 M NaOH, pH 12, $CHCl_3$ extraction (see Table 1 for details).

Table 1 Reaction conditions and ^{1}H NMR data for **PT1–PT5**

Compound	Molar equiv. [**1**]	[**2**]	[**3**]	Time/temp. (h/°C)	[Triazole]/[3]
PT1-A[a]	1	1	2	168/25	0.4
PT2	1	1	2	168/25	0.7
PT3-A	1	1	0.5	168/25	2.0
PT3-B	1	1	0.5	336/25	2.1
PT4-A	1	1	0.1	168/25	1.4
PT5	1	1	0	336/25	0.0

[a] All reactions were carried out in 0.2 M Na_2SO_4 in D_2O apart from **PT1** where DCl–D_2O (20% wt) was used instead.

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Table 2 FAB MS data for **PT1** and **PT3**

PT3-B	MW (theo.)	MW (det.)	**PT1**	MW (theo.)	MW (det.)	**PT1** extr.	MW (theo.)	MW (det.)
$[\mathbf{1}]_2[\mathbf{2}]_2$	640.6	644.1	[**1**] + [**3**] − Cl	1090.2	1087.7	[**1**][**2**]	248.3	249.1
$[\mathbf{1}]_3[\mathbf{2}]_2 + 2H_2O - N_2$	772.7	771.8	$[\mathbf{1}]_2[\mathbf{2}] + [\mathbf{3}] + H_2O$	1463.4	1463.2	$[\mathbf{1}]_2[\mathbf{2}]_2$	496.6	497.3
$[\mathbf{1}]_3[\mathbf{2}]_3 + 2H_2O - N_2$	962.9	964.4	$[\mathbf{1}][\mathbf{2}]_2 + [\mathbf{3}] - Cl$	1490.5	1491.2	$[\mathbf{1}]_3[\mathbf{2}]_3$	744.9	744.5
$[\mathbf{1}][\mathbf{2}] + [\mathbf{3}] + 2H_2O$	1352.3	1350.2	$[\mathbf{1}]_3[\mathbf{2}]_3 + [\mathbf{3}]\ 3H_2O$	2010.9	2014.3	$[\mathbf{1}]_4[\mathbf{2}]_3$	838.0	835.8
$[\mathbf{1}]_5[\mathbf{2}]_4 - Cl$	1375.3	1374.4	$[\mathbf{1}]_5[\mathbf{2}]_4 + [\mathbf{3}] + H_2O - N_2$	2397.2	2395.5			

[**1**] and [**2**] = monomers, [**3**] = cucurbituril (Fig. 1), det. = detected, extr. = extracted.

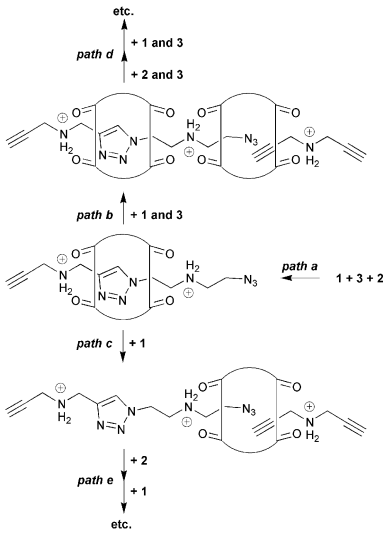

Fig. 2 Catalytic pathways of oligotriazole formation.

likely induced thermally and not a result of the presence of cucurbituril. Equimolar amounts of cucurbituril to azide and alkyne functional groups present, as for examples **PT1** and **PT2**, led to ratios of triazole to cucurbituril of less than one. This was not unexpected for **PT1** since the reaction was carried out at low pH similar to the work by Mock *et al*. (aqueous formic acid (H_2O–HCOOH (1 : 1)) and the result is consistent with their findings.[11,17] The neutral aqueous 0.2 M Na_2SO_4 medium for **PT2** was found to lead to higher conversion than the acidic reaction medium (**PT1**). We associate the increase in the formation of triazole rings (**PT2**) with the difference in pH.[18] Dissociation is accelerated at higher pH and thus leads to an increase in the observed rate of the dissociation as shown by Mock *et al*. using model compounds.[19] The further increase of the ratio of triazole to **3** when reducing the amount of **3** to subequimolar levels (**PT3** and **PT4**) could be an indication of the rate of dissociation being affected by an associative displacement mechanism (the presence of an excess of a guest accelerates dissociation of the substrate encapsulated by **3**) also experimentally verified by Mock *et al*.[19] However based on our studies on the threading behaviour of **3** onto a poly(hexamethylene imminium) backbone,[20] we expect at high concentrations of **3** path ***c*** to become neglible and path ***b*** to be dominant because of the high association constant and low rate of dissociation of the monotriazole pseudorotaxane (Fig. 2). Association of a second molecule of cucurbituril adjacent to the first through sharing of the ammonium ion of monomer fragment **2** is sterically unfavourable[20] and the correct conformation of the ternary complex required for the catalysis is not accessible.[11] At subequimolar concentrations of **3** on the other hand path ***b*** is no longer dominant and catalytic turnover becomes possible *via* path ***c***.

Table 2 shows representative MS data (FAB) for reactions **PT1** and **PT3**. In both cases we find evidence for the formation of oligotriazoles in which up to 9 monomers (**1** and **2**; **PT1**) have been joined to form an oligotriazole chain containing the same number of triazole rings. For **PT1** we have also included data showing the composition of the organic phase after extraction of the aqueous phase with chloroform, also confirming the presence of oligotriazole chains. All of the data are in full agreement with the findings of our NMR analysis demonstrating the ability of cucurbituril to exhibit catalytic turnover albeit very sluggishly. We interpret the presence of higher triazole oligomers as the result of different catalytic pathways being available simultaneously thus resulting in a distribution of oligotriazole chain lengths. Fig. 2 captures the various pathways potentially involved in the overall catalytic process.

After the formation of the first triazole ring (path ***a***) a second one is formed by either following path ***b*** (followed by ***d***) or path ***c*** (followed by ***e***). Path ***c*** and ***e*** are required for catalytic turnover whereas path ***b*** illustrates reduction (or suppression) of catalytic activity caused by steric crowding and high affinity of the catalyst for the product.

Further investigations into the role of the solvent and the stoichiometry between **3** and each monomer are currently underway to establish further mechanistic details of the catalytic process with the aim to prepare polytriazoles in this fashion.

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