Steric and Electronic Control of 1,3-Dipolar Cycloaddition Reactions in Carbon Nanotube Nanoreactors

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ABSTRACT The use of single-walled carbon nanotubes as effective nanoreactors for preparative bimolecular reactions has been demonstrated for the first time. We show that the extreme spatial confinement of guest reactant molecules inside host carbon nanotubes increases the regioselectivity for the 1,4-triazole in thermally-initiated azide-alkyne cycloaddition reactions. Through comparison of the internal dimensions of the nanotube and the steric bulk of the reactants, we demonstrate that the formation of the more linear 1,4-regioisomer can be enhanced by up to 55% depending on the extent of spatial restrictions imposed within the nanoreactors. Furthermore, through systematic variation of the substituents in the *para*-position of the alkyne reactants, we reveal the unexpected influence of the electronic properties of the reactants on the regioselectivity

of reactions within nanoreactors, which act to either oppose or promote the preferential formation of the 1,4-regioisomer induced by steric effects, reflecting the unique ability of carbon nanotubes to stabilise the dipole moment of confined reactants. Thus, we show that the observed regioselectivity of azide-alkyne cycloaddition reactions confined within carbon nanotube nanoreactors reflects a subtle interplay between both steric and electronic factors.

INTRODUCTION

The confinement of guest molecules inside host nanoscale containers offers an effective methodology for controlling the properties of the guest and thus the pathway and outcome of confined chemical reactions.[1] Inspired by the remarkable efficiency exhibited by enzymatic systems in nature, significant efforts of the synthetic chemistry community over the past two decades have focussed on developing a range of artificial nanoreactors, including cavitands,[2-4] calixarenes,[5,6] concurbiturils,[7,8] cyclodextrins,[9,10] zeolites[11,12] and supramolecular co-ordination cages,[13,14] to host chemical reactions and thus exploit the effects of extreme spatial confinement at the nanoscale on the yields and distribution of products. However, these custom-built structures often involve complex design and multi-step syntheses, typically relying upon specific host-guest interactions to facilitate high levels of encapsulation of the reactant molecules into the respective nanoscale volumes and are, therefore, generally only suitable for a limited range of reactions. Moreover, the thermal and chemical stability of the host nanoreactor limits the range of reaction conditions available for examination. In contrast, carbon nanotubes utilise ubiquitous van der Waals forces[15] to drive the encapsulation of the widest range of guest molecules into the host internal channel while offering superior thermal,[16] mechanical[17] and chemical stability.[18] Coupled

with the ability to precisely tune the diameter of carbon nanotubes through control of synthesis procedures[19] and thus provide the optimum level of confinement for a given chemical reaction, these factors suggest that carbon nanotubes potentially represent the most versatile nanoscale container for chemical reactions.[20]

Carbon nanotubes have been extensively studied as hosts for a broad range of catalytic chemical transformations whereby confinement within carbon nanotubes has been shown to influence the activity, selectivity and recyclability of molecular and nanoparticle catalysts;[21-23] yet, the direct effect of extreme nanoscale confinement in carbon nanotubes on non-catalytic chemical reactions remains relatively underexplored. The reported formation of unusual oligomers and polymers,[24-26] graphene[27-29] and inorganic nanoribbons,[30] nanotubes[31,32] and molecular nanodiamonds[33] inside carbon nanotubes clearly demonstrates the potential of narrow nanotubes to act as nanoscale reaction vessels, in these instances controlling the formation of one-dimensional macromolecular products inaccessible by other means. However, the resulting strong interactions between the host nanotube and the formed guest nanostructures prohibits the extraction and subsequent bulk characterisation of the afforded products, essential in preparative synthesis (the so-called product inhibition effect).

To the best of our knowledge and despite an increasing number of excellent theoretical contributions,[34-39] the only reported preparative, non-catalysed, organic chemical reaction performed experimentally within narrow carbon nanotubes is the aromatic halogenation reaction,[40] where it was observed that extreme spatial confinement in narrow single-walled carbon nanotubes (SWNT) directed the site selective electrophilic attack of the incarcerated aromatic guest reactant

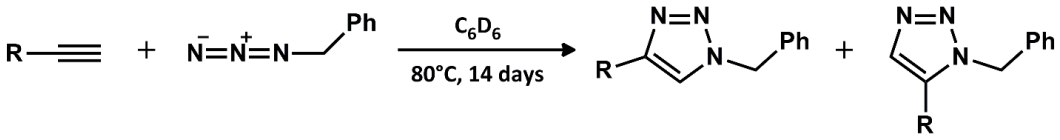
and resulted in an enhancement in the formation of the more linear *para*-regioisomer from 68 to 97%. In this study, we explore the effect of nanoscale confinement in SWNT on the formation of the products of 1,3-dipolar cycloaddition reactions, a class of bimolecular reactions with two reactants typically of commensurate size and complexity. Through careful and systematic variation of the internal dimensions of the host nanotube and the steric and electronic properties of the guest reactant molecules, we demonstrate the enhanced formation of 1,4-triazoles in the confined cycloaddition of azides to alkynes, the magnitude of which depends on both the geometric matching of the specific transition state with the inner diameter of the host nanotube and the electron-withdrawing or -donating nature of the encapsulated reactant.

RESULTS AND DISCUSSION

The confined cycloaddition reaction in SWNT

The 1,3-dipolar cycloaddition of azides to alkynes in solution under thermal initiation and in the absence of a metal catalyst are expected to produce a mixture of both 1,4- and 1,5-substituted triazoles.[41] Indeed, our control experiments exploring the reactions of benzyl azide (**2**) with various terminal alkynes (**1a-h**) afforded a mixture of both the 1,4- and 1,5-substituted triazoles (**3** and **4** respectively), with the selectivity for the 1,4-triazole ranging from 8 to 62% (**Table 1** and **S1**, Supporting Information).

Table 1. The 1,3-dipolar cycloaddition of alkynes (**1a-h**) to benzyl azide (**2**).



R groups:

a) *phenyl* ***c)*** *1,1'-biphenyl* ***e)*** *4-nitrophenyl* ***g)*** *4-methoxyphenyl*

b) *cyclohexyl* ***d)*** *p-terphenyl* ***f)*** *4-bromophenyl* ***h)*** *4-aminophenyl*

Entry	Alkyne R group	L_{FG} / nm [a]	d_{NT} / nm [b]	No SWNT [c]	Confined within SWNT [d]	
				$S_{1,4}$ / % [e]	$S_{1,4}$ / % [f]	$\Delta S_{1,4}$ / % [f]
1	phenyl (**1a**)	0.6	1.0	44	47	+3
2			1.3		51	+7
3			2.0		50	+6
4	cyclohexyl (**1b**)	0.6	1.3	58	60	+2
5	1,1'-biphenyl (**1c**)	1.1	1.3	8	63	+55
6			2.0		46	+38
7	*p*-terphenyl (**1d**)	1.5	2.0	11	36	+25
8	4-nitrophenyl (**1e**)	0.8	1.3	62	80	+18
9	4-bromophenyl (**1f**)	0.8	1.3	51	66	+15
10	4-methoxyphenyl (**1g**)	0.8	1.3	42	49	+7
11	4-aminophenyl (**1h**)	0.7	1.3	40	40	0

[a] The steric bulk of the alkyne functional group is defined as the distance from the centre of the carbon atom to which the functional group is bonded, to the centre of the outermost atom, including the van der Waals radius (L_{FG}). [b] The mean carbon nanotube (d_{NT}) was determined by statistical analysis of multiple transmission electron micrographs (**S1.2**, Supporting Information). [c] Experimental conditions: benzyl azide (0.113 mmol), alkyne (0.113 mmol), d_6-benzene (1.6 mL), 80˚C, 14 days (**S1.3**, Supporting Information). [d] Experimental conditions: (benzyl azide)@SWNT (0.045 mmol), alkyne (0.045 mmol), d_6-benzene (1.6 mL), 80˚C, 14 days (**S1.4**, Supporting Information). [e] The regioselectivity for the 1,4-triazole ($S_{1,4}$) in the absence of SWNT was determined by ^{1}H NMR spectroscopy analysis of the reaction mixtures. [f] The regioselectivity for the 1,4-triazole ($S_{1,4}$) for the reactions confined within SWNT was determined by ^{1}H NMR spectroscopy analysis of the reaction mixtures after total extraction into solution. The conversion ranges from 4-80% depending on the nature of the substrate and location of the reaction.

Furthermore, previous experimental[42] and theoretical[43] studies have demonstrated the enhanced formation of the 1,4-triazole in thermally-initiated azide-alkyne cycloaddition reactions due to spatial confinement in self-assembled cavitand capsules, a consequence of both steric factors and stabilisation of the transition state leading to the preferential formation of the more linear 1,4-regioisomer in the confined reaction. As SWNT have cylindrical cavities analogous to cavitands, a similar effect was expected in carbon nanotubes. Indeed, our calculations indicate that the 1,4-triazole afforded from the confined reaction of phenylacetylene and benzyl azide inside (14,0)-SWNT is 6 kcal/mol more stable inside nanotubes relative to the corresponding 1,5-regioisomer (**Figure 1** and **S1.5**, Supporting Information). This reaction, therefore, represents an ideal experimental probe to study the effect of extreme spatial confinement in carbon nanotube nanoreactors on the regioselectivity of a preparative chemical transformation.

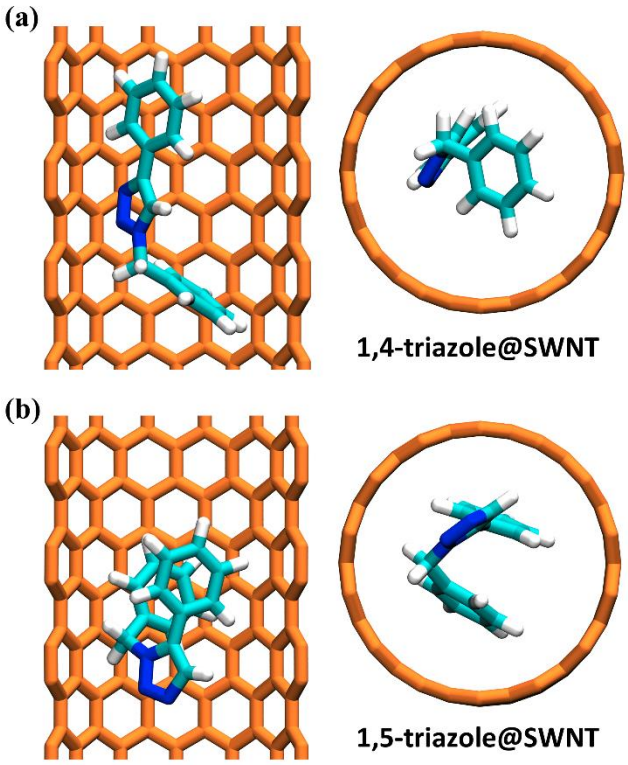


Figure 1. Optimised geometries for the (a) 1,4- and (b) 1,5-triazoles inside (14,0)-SWNT. Calculations indicate the 1,4-regioisomer is 6 kcal/mol more stable inside (14,0)-SWNT relative to the corresponding 1,5-regioisomer.

Our preliminary investigations, whereby one of the reactants was selectively confined in the internal channel of SWNT (d_{NT} = 1.3±0.1 nm) using the liquid-phase filling and fractional distillation procedure (**Figure 2**) developed in our previous study,[40] followed by the addition of the second reactant in solution, confirmed the validity of our hypothesis (**S1.4**, Supporting Information).

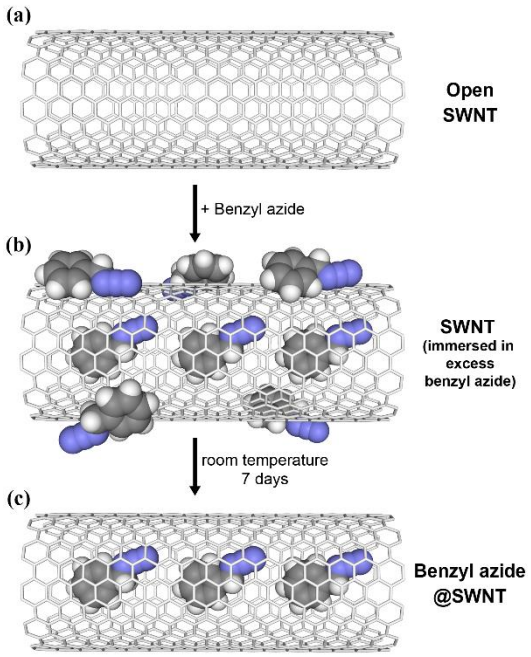


Figure 2. Schematic representation of the liquid-phase encapsulation and fractional distillation procedure used to remove excess external molecules resulting (benzyl azide)@SWNT. As the azide-alkyne cycloaddition is known to occur in the absence of nanotubes, this procedure ensures that the reaction locus is exclusively defined as the hollow interior of SWNT and thus allows us to probe the influence of spatial restrictions on the selectivity of the reaction.

Using ^{1}H NMR spectroscopy analysis of the reaction mixtures extracted from SWNT nanoreactors into solution, we observed that confinement in carbon nanotubes improves the selectivity for the 1,4-regioisomer ($S_{1,4}$) in the reaction of phenylacetylene (**1a**) with benzyl azide (**2**) by 7% (entry 2, **Table 1**). It is interesting to note that encapsulation of either the azide or alkyne reactant prior to initiation of the reaction results in similar changes in the observed regioselectivity (**S1.4**, Supporting Information), reflecting the comparable physical properties (e.g. melting point, boiling point, vapour pressure) of these two reactants. However, the efficacy of encapsulation for the range of organic reactants explored in this study is highly variable and therefore, for ease of methodology and comparison, all subsequent reactions were carried out by prior encapsulation of benzyl azide. Whilst not as dramatic as the regioselectivity changes observed inside SWNT nanoreactors for the

aromatic halogenation reactions observed in our previous study,[40] it is important to note that the SWNT used in these initial experiments possess a mean internal diameter of 1.3 nm, which, based on consideration of the geometry of the most stable conformations of the 1,4- and 1,5-triazoles formed from the cycloaddition of benzyl azide (**2**) to phenylacetylene (**1a**), does not represent the optimum nanoscale reaction environment to promote the formation of the more linear 1,4-regioisomer, i.e. through exclusion of the 1,5-regioisomer (**Figure 3**).

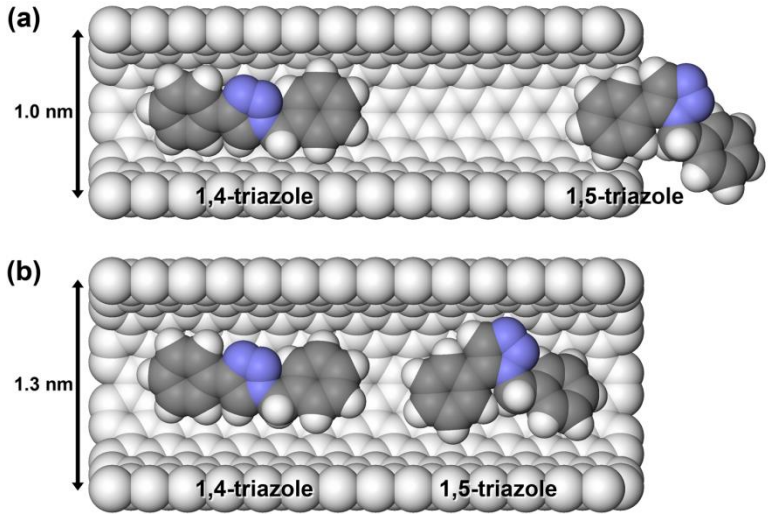


Figure 3. Three-dimensional representation of the geometry of the 1,4- and 1,5-triazole regioisomers formed from the reaction of phenylacetylene (**1a**) and benzyl azide (**2**) confined within carbon nanotubes with diameters of (a) 1.0 and (b) 1.3 nm. The narrower SWNT (a) does not allow the formation of the 1,5-triazole in its most stable conformation, so a larger change in $S_{1,4}$ is expected compared to the wider SWNT (b), where both products can fit within the SWNT cavity in their most stable conformations. However, as this is inconsistent with our experimental observations and suggests that product geometry is not the crucial consideration for this confined reaction.

Indeed, such an effect should theoretically be most prevalent inside narrow SWNT of mean internal diameter 1.0 nm; however, only a 3% increase in $S_{1,4}$ was observed in the reaction confined in this narrower SWNT container relative to the control reaction in bulk solution (entry 1, **Table 1**). Moreover, the corresponding reaction conducted in a wider SWNT of a mean internal diameter

of 2.0 nm – a reaction volume considerably larger than the dimensions of both regioisomers, where no spatial restriction is expected – showed a 6% increase in $S_{1,4}$ compared to control reactions in the absence of nanotubes (entry 3, **Table 1**). Although these observations support the anticipated phenomenon that nanoscale confinement within SWNT results in an increase in the selectivity for the 1,4-triazole, the magnitude of this observed effect cannot be rationalised simply by consideration of the size and shape of the products alone as was noted in our previous studies of the aromatic halogenation reaction.[40] It seems logical that the minimum volume required for a reaction to occur depends most crucially on the critical dimension of the largest species along the reaction pathway. In many simple reactions, such as aromatic halogenation, the critical dimension may not vary significantly throughout the reaction profile and as such, consideration of the product geometry alone will suffice. However, for bimolecular reactions such as cycloaddition, which involve considerable geometric rearrangements while traversing the reaction coordinate, consideration of the geometry of the transition state, rather than the products, is more critical when attempting to control the extent of confinement and thus the reaction selectivity in confined preparative reactions.

The effect of sterics on the confined cycloaddition reaction in SWNT

Harnessing specific non-covalent interactions in host-guest nanoscale architectures represents a powerful approach to manipulate the reactivity of confined molecules. Therefore, and to gain specific insight into the importance of the aromaticity of reactants on the mechanisms of organic chemical reactions confined within carbon nanotubes, the reactions of benzyl azide (**2**) with cyclohexylacetylene (**1b**), the aliphatic analogue of phenylacetylene (**1a**), confined within SWNT of 1.3 nm diameter were appraised. As expected, a less pronounced effect of confinement was

found, with only a 2% increase in $S_{1,4}$ in nanoreactors observed (entry 4, **Table 1**). This indicates that the extent of non-covalent interactions between the incoming reactant and the π-framework of the SWNT interior can be used to modulate the diffusion of the reactant into the SWNT inner cavity and thus the propensity for cycloaddition reactions to occur within SWNT nanoreactors. As such, greater host-guest interactions result in greater changes in the reaction pathway and *vice versa*. However, the flexibility of the reactants may also play a critical role in determining the regioselectivity of the reaction. Although comparable in size, the increased flexibility of the cyclohexyl ring may reduce the steric effect of confinement within SWNT, allowing conformational rearrangements to facilitate energetically favourable transition states for both regioisomers. Consequently, it appears evident that both the electronic nature and steric properties of reactants influence reactions in SWNT nanoreactors.

To further probe this effect of reactant steric bulk, a series of alkyne reactants possessing varying degrees of steric encumbrance were selected. To maintain a constant Tolman cone angle[44] and thus study the influence of extreme spatial confinement without complication from steric effects in the vicinity of the reaction centre, reactants were carefully chosen to vary only in their substitution at the position on the aromatic ring *para* to the alkyne. The regioselectivity of the reactions of each of the appraised alkynes with benzyl azide within SWNT of varying diameters was compared to the reaction in solution (entries 5-7, **Table 1**). In general, it was found that increasing the steric bulk of the alkyne reactant within the same diameter nanotube produced considerably larger increases in 1,4-selectivity ($\Delta S_{1,4}$), up to a 55% shift (entry 5, **Table 1**). As the steric bulk is increased within a SWNT of a given diameter, the transition state and products experience a greater degree of spatial confinement which results in a more pronounced increase in selectivity for the

1,4-triazole (*e.g.* 1,1'-biphenyl *cf.* phenyl). Conversely, when the reaction species are smaller in relation to the SWNT cavity and thus experience less extreme spatial confinement, there is a less pronounced change in selectivity as a consequence of confinement. In this way, by varying the steric bulk of reactant functional groups, the extent of confinement can be tuned to achieve optimum confinement and thus greater control over reaction selectivity. It must be acknowledged that, by increasing the steric bulk of the alkyne, the aromaticity has also been increased and thus, the non-covalent interaction of the alkyne with the SWNT will undoubtedly be enhanced, further facilitating the confined reaction. However, the influence of these two variables is not easily deconvoluted.

The effect of electronics on the confined cycloaddition reaction in SWNT

Frontier molecular orbital theory indicates that cycloaddition reactions are sensitive to both steric and electronic factors. Substituents of varying electronic properties can influence both kinetics, by shifting the frontier molecular orbital energy levels, and regioselectivity, by inducing an asymmetric distribution of the frontier molecular orbital density across the atoms involved in the reaction. Carbon nanotubes, due to their electron withdrawing properties, have been shown to exhibit interesting effects when species are in intimate contact with either the internal or external surface of the nanotube.[45-47] For these reasons, the electronic influence of the host SWNT on the selectivity of 1,3-dipolar cycloaddition within SWNT was investigated by further variation of the alkyne substituent. In the absence of carbon nanotubes, the appraised cycloaddition reactions (entries 8-11, **Table 1**) exhibit a clear, yet subtle trend in regioselectivity related to the alkyne electronic properties, whereby electron-withdrawing substituents increase the selectivity for the 1,4-triazole (**Figure 4a,** black line).

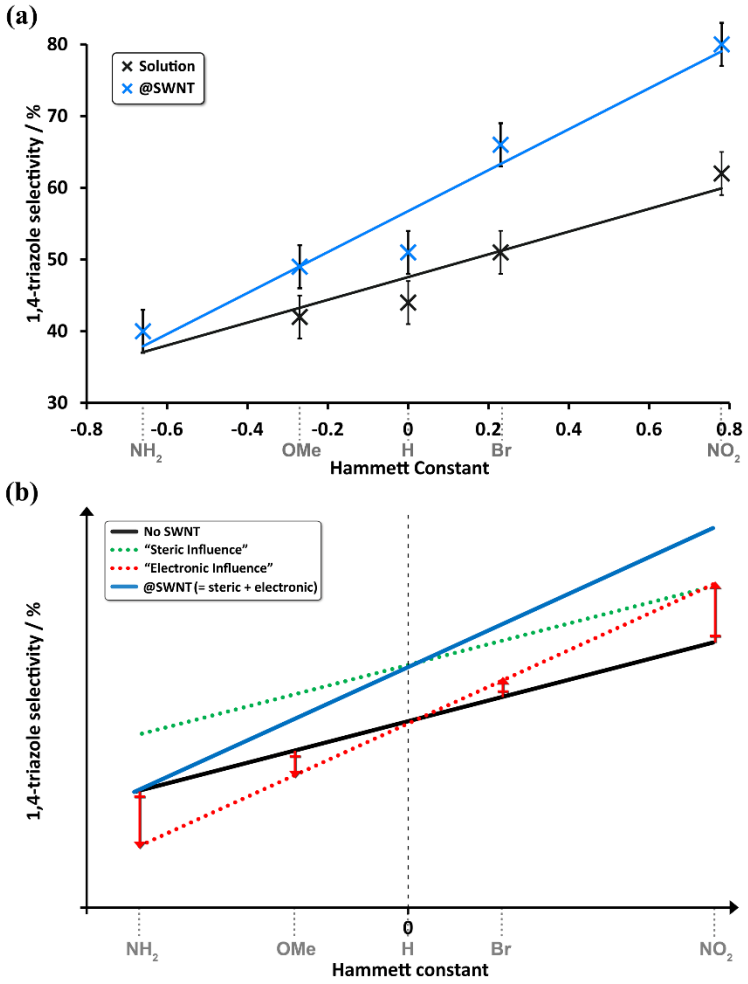


Figure 4. (a) Plot of selectivity for the 1,4-triazole against the Hammett constant for each alkyne aromatic *para*-substituent in the 1,3-dipolar cycloaddition of benzyl azide to a range of alkynes both in solution (black) and confined within a SWNT (blue) of 1.3 nm diameter. A clear correlation shows that an increase in alkyne electron-withdrawing nature (more positive Hammett constant) results in a greater 1,4-selectivity. Crucially, this trend is amplified by confinement within SWNT. Error bars show the ±3% error in ^{1}H NMR measurements. (b) Schematic representation of the postulated combination of steric and electronic confinement effect in relation to the observed experimental trends. Solid lines denote experimental trends, dotted lines represent the postulated hypothetical deconvolution. It is proposed that a subtle influence of steric confinement acts to increase selectivity for the 1,4-triazole to a similar degree for each of the appraised alkynes (green). In combination, the electronic effect of confinement within carbon nanotubes (red) acts to alter regioselectivity in different directions, depending on the electron-withdrawing or donating nature of the alkyne substituent, and to varying degrees, depending on the alkyne dipole moment. The combination of these two influences accounts for the observed trend in regioselectivity in confinement (blue) as a function of alkyne electronic properties.

Electron withdrawing groups tend to increase the relative molecular orbital coefficients on the terminal alkyne carbon atom, which introduces a slightly more favoured orbital overlap with the azide benzylic nitrogen, thus stabilising the transition state leading to the 1,4-triazole. As *para*-substituents can influence the regioselectivity by subtle distortion of molecular orbitals, the external influence of a carbon nanotube host on the confined molecular orbitals has the potential to offer additional influence through a similar mechanism. Interestingly, confinement within SWNT increased the 1,4-triazole selectivity in all but one case, up to an 18% shift in the most extreme instance. Furthermore, the trend in unconfined regioselectivity as a function of alkyne electron-withdrawing nature appears to be amplified by confinement within SWNT (**Figure 4a**, blue line). The greatest enhancement in $S_{1,4}$ upon confinement was observed for the alkyne with the most electron-withdrawing *para*-substituent (18% increase for 4-nitrophenylacetylene). It is important to note that the overall steric bulk of each of the appraised functional groups is similar (L_{FG}, **Table 1**) and any slight variation cannot account for the observed correlation. The varying influence of the host SWNT in these reactions therefore suggests that electronic effects (**Figure 4b**, red dashed line) induced by the nanotube can partially contribute to the observed increases in selectivity for the 1,4-triazole in confinement in combination with the known steric effects (**Figure 4b**, green dashed line).

The Hammett constant used to describe each functional group gives a measure of the dipole moment of the alkyne, providing both direction and magnitude. It is this dipole moment which dictates the electron density on the alkyne bond and thus, indirectly, the selectivity of the reaction. The high polarisability of carbon nanotubes allows stabilisation of guest species with high charge-

separation (*i.e.* high dipole moment) which effectively increases the dipole moment.[34] The high dipole moment of the guest molecule induces this response from the polarisable host carbon nanotube and therefore the magnitude of this stabilisation varies depending on the magnitude of the intrinsic dipole moment of the molecule. In this way, encapsulated molecules with a high dipole moment will exhibit an even greater dipole moment due to confinement, whereas guest molecules with a lower dipole moment will be influenced to a lesser extent (**Figure 5**).

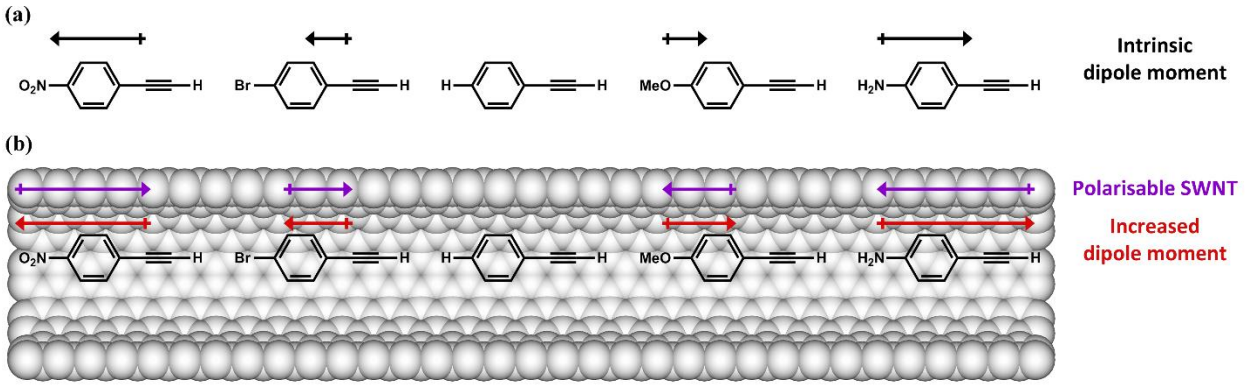


Figure 5. Schematic representation of the dipole moments for the appraised alkynes both (a) in solution, and (b) confined within a SWNT. The highly polarisable host carbon nanotube stabilises the polar species, effectively increasing the guest alkyne dipole moment (red) in comparison to the same alkyne in bulk solution (black). In this way, the extent to which the carbon nanotube influences the electronic properties of the confined molecule, and thus the regioselectivity of the reaction, depends on the initial dipole moment (*i.e.* extent to which the *para*-substituent is electron-withdrawing or -donating).

In the case of an electron-deficient alkyne (*e.g.* 4-nitrophenylacetylene), an increase to the dipole moment due to confinement within SWNT will further reduce electron density on the alkyne, thus promoting the formation of the 1,4-triazole to a greater extent. Whereas a less electron-deficient alkyne with a lower dipole moment (*e.g.* 4-bromophenylacetylene) will experience a less pronounced increase in dipole moment upon confinement, and thus will exhibit a smaller increase in selectivity for the 1,4-triazole by comparison. Conversely, for alkynes with electron-donating

substituents, exhibiting a dipole moment in the opposite direction, an increase in dipole moment due to confinement will further *increase* the electron density on the alkyne, thus, reducing selectivity for the 1,4-triazole. Therefore, in this way, confinement within carbon nanotubes effectively amplifies the underlying substituent electronic effects, resulting in an increase to the gradient of the trend demonstrated (**Figure 4a**).

Within this dipole-dependent postulation, it might be expected that the reaction of 4-aminophenylacetylene within carbon nanotubes would afford a lower $S_{1,4}$ value than that of the bulk solution. However, in addition to the postulated *electronic* effect, the subtle effect of *steric* confinement will act to increase the selectivity for the 1,4-triazole equally for each of the appraised alkynes. The observed effect of confinement on selectivity is likely to reflect a balance between both steric and electronic effects. Therefore, the net zero change in selectivity upon confinement for the reaction of 4-aminophenylacetylene may be a result of competition between electronic effects, acting to subtly reduce $S_{1,4}$, and steric effects, acting to subtly increase $S_{1,4}$ (**Figure 4b**). However, it is important to note that the maximum change in $S_{1,4}$ observed as a consequence of electronic effects (up to 18%) remains much smaller than that observed when the extent of steric confinement is optimised (up to 55%). The conclusion that, even within narrow carbon nanotubes, steric effects are typically dominant over electronic effects is supported by the solution phase studies of Huisgen.[48]

The selective retention of products from the confined cycloaddition reaction in SWNT

When analysing the effect of confinement on the selectivity of cycloaddition reactions, it is of utmost importance that the product mixture analysed is a true representation of the confined

reaction. Typical reaction work up procedures must include the removal of solid nanotube from suspension in order to allow solution-phase analysis of the product mixture. However, previous studies into reactions confined within molecular nanoreactors have highlighted the potential problems of product inhibition, whereby the product molecule can become irreversibly bound within the host cavity and are thus difficult to remove.[42] In order to circumvent this practical limitation, previous studies have utilised *in situ* analysis of the confined product mixture, made possible by the solubility of molecular nanoreactors. However, the extremely limited solubility of carbon nanotubes, coupled with the restricted sensitivity of solid state NMR spectroscopy and complications arising from interactions of SWNT with the magnetic field, necessitates the solution-phase analysis of product mixtures after the removal of all SWNT solid. It is, therefore, imperative that all organic material (*i.e.* reactant and product) is removed from the nanotube prior to analysis in order to be confident that spectroscopy measurements accurately represent the outcome of the confined reaction.

To quantitatively extract the triazole products in this case, the carbon nanotube solid required consecutive washing, up to three times, with sonication in a small amount of organic solvent. It was shown that additional washing of the nanotube beyond this did not extract any additional organic products within the detection limits of NMR spectroscopy and sensitivity of thin layer chromatography. Furthermore, energy dispersive X-ray (EDX) analysis of the SWNT remaining after this procedure showed no remaining encapsulated products within the limits of detection (**Figure 6**).

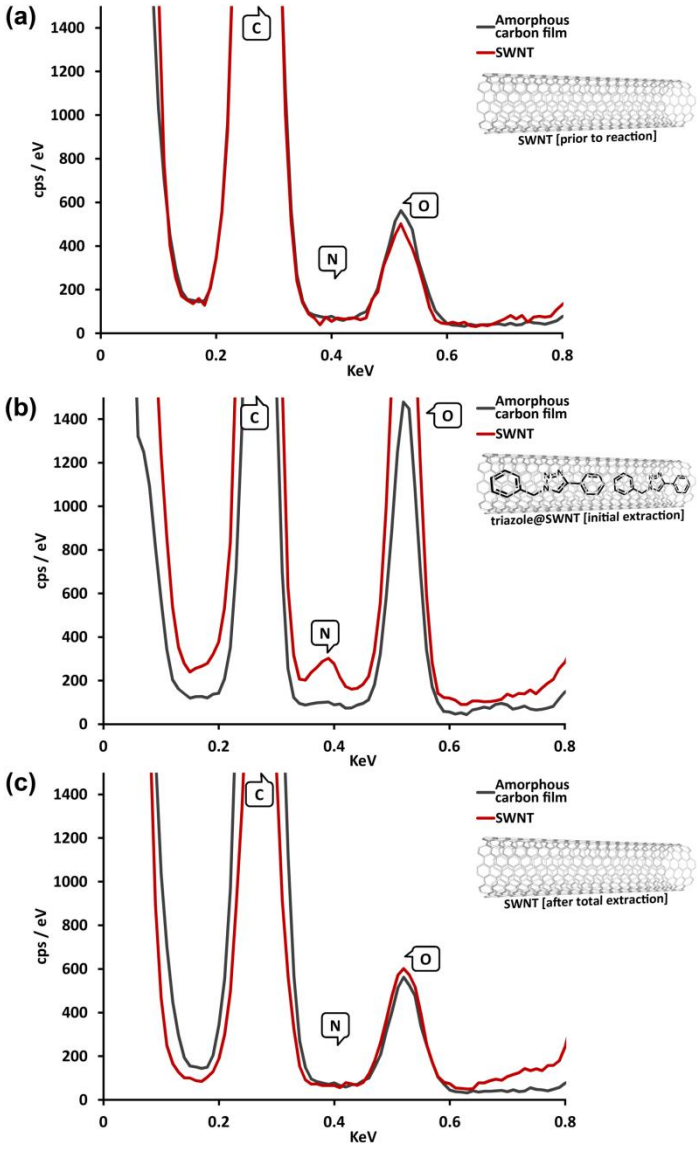


Figure 6. Energy dispersive X-ray spectra of SWNT (d_{NT} = 1.3 nm). (a) Prior to the addition of any organic molecules, no nitrogen is detected, as expected. (b) Immediately subsequent to the initial extraction procedure, a clear peak at 0.4 KeV is observed corresponding to the nitrogen atoms of either benzyl azide reactant or triazole products. (c) Subsequent to the complete extraction procedure, no nitrogen is detected, demonstrating the full extraction of organic molecules within the limits of detection by EDX spectroscopy. In each case, the spectrum of a SWNT bundle (red) is compared to the spectrum of the amorphous carbon background (black), the difference in which indicates the signal observed due to the SWNT sample.

The complete extraction of products was found to be particularly important when studying the selectivity of confined cycloaddition reactions because the measured distribution of products in

the extracted solution varied when comparing product mixtures from consecutive extraction stages (**Table 2**).

Table 2. Selectivity for the 1,4-triazole ($S_{1,4}$) after initial ($^{i}S_{1,4}$) and total ($^{T}S_{1,4}$) product extraction, consistently showing deceptively high values for $\Delta S_{1,4}$ in the initial extraction, potentially due to a selective retention of the 1,5-triazole by the nanotube.

Entry	Alkyne R group	d_{NT} / nm	No SWNT	Initial extraction		Total extraction	
			$S_{1,4}$ / %	$^{i}S_{1,4}$ / %	$\Delta S_{1,4}$ / %	$^{T}S_{1,4}$ / %	$\Delta S_{1,4}$ / %
1	phenyl (**1a**)	1.0	44	45	+1	47	+3
2		1.3		72	+28	51	+7
3		2.0		45	+1	50	+6
4	cyclohexyl (**1b**)	1.3	58	60	+2	60	+2
5	1,1'-biphenyl (**1c**)	1.3	8	63	+55	63	+55
6		2.0		76	+68	46	+38
7	*p*-terphenyl (**1d**)	2.0	11	34	+23	36	+25
8	4-nitrophenyl (**1e**)	1.3	62	85	+23	80	+18
9	4-bromophenyl (**1f**)	1.3	51	82	+31	66	+15
10	4-methoxyphenyl (**1g**)	1.3	42	61	+19	49	+7
11	4-aminophenyl (**1h**)	1.3	40	39	+1	40	0

It was shown that the apparent 1,4-triazole selectivity values for the initial extraction aliquots were, in many cases, positively skewed when compared to the overall product mixtures after complete extraction. In almost all cases, the selectivity for the 1,4-triazole is greater in the initial extraction, indicating that the 1,5-triazole is preferentially held within the internal cavity due to stronger interactions with the host nanotube (relative to the 1,4-regioisomer). This leads to a reduced rate of diffusion of the 1,5-triazole into the bulk solution, a consequence of the greater energy required to extract (E_{EXT}) the 1,5-regioisomer from the nanotube cavity (**Figure 7**), and deceptively high values for 1,4-triazole selectivity in the initial extract, although it is important to note that these tend to decrease slightly after total extraction.

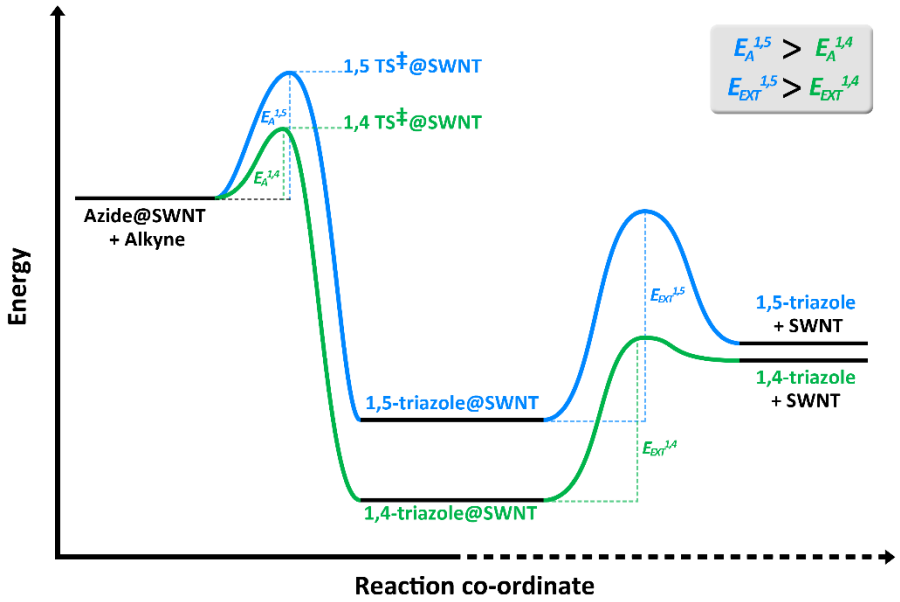


Figure 7. Schematic representation of the reaction profile (full line) for the azide-alkyne cycloaddition reaction within SWNT and subsequent product desorption from SWNT (dashed line) showing the competitive formation of both the 1,4-triazole (green) and the 1,5-triazole (blue). The activation energy (E_A) for the formation of the 1,4-triazole inside SWNT is expected to be smaller than that for the 1,5-triazole due to the combined confinement effects discussed. However, when the 1,5-triazole forms, it seemingly exhibits stronger interactions with the host SWNT and thus, the energy required to extract (E_{EXT}) the 1,5-triazole is greater than that required for the 1,4-triazole.

This complication must always be considered for reactions confined within any nanoscale host, because the additional stage of product extraction may involve an energy barrier that must be overcome. However, selective interactions between the host nanotube and isomeric products may, if strong enough, provide a novel means of *in situ* product separation, affording further control over the resulting products but not by directly influencing the reaction pathway.

CONCLUSION

The 1,3-dipolar cycloaddition of various alkynes to benzyl azide within the internal cavity of narrow carbon nanotubes has been studied, showing consistent increases in selectivity for the 1,4-triazole (up to 55%) due to extreme spatial confinement within SWNT. As hypothesised, the more linear 1,4-triazole is favoured within the SWNT cavity in almost all cases. It was shown that the extent of confinement can be tuned by varying the diameter of the SWNT host or the steric bulk of guest reactants in order to maximise the effect of confinement on selectivity. In many examples, measurable increases in 1,4-triazole selectivity were observed, despite the host nanotube cavity providing sufficient volume for both products to be encapsulated freely. This suggests that, to understand the mechanism of size or shape selectivity induced by the nanotube, the geometry of the regioisomeric transition states is the most important consideration.

A clear correlation between the electron-withdrawing nature of alkyne substituents and the increase in 1,4-triazole selectivity within SWNT suggests that the polarisability of carbon nanotubes provides an additional subtle influence on selectivity. It is postulated that the highly polarisable host SWNT stabilises the alkyne dipole moment, effectively increasing the partial charge separation. This phenomenon acts to amplify the underlying trend in regioselectivity by decreasing the alkyne electron density for electron-deficient alkynes and increasing the electron density for electron-rich alkynes. Therefore, confined cycloaddition reactions are influenced by a balance of both steric and electronic factors induced by confinement within carbon nanotube nanoreactors. However, from these results, it appears that steric effects can induce the greatest change in selectivity; the most sterically constricted reaction showing an increase in selectivity for the 1,4-triazole of 55%, compared with an 18% increase for the most electron-withdrawing.

It was found that, although the formation of the 1,5-triazole is less favoured within SWNT, once formed, this isomer can be selectively withheld from solution by stronger interactions with the SWNT cavity. This demonstrates that efficient extraction of products is critical, but this also highlights an additional potential method offering further control over product distribution if this effect could be harnessed.

Whilst the selectivity results obtained do not compare with those obtained in the copper-catalysed analogue,[49,50] this study clearly demonstrates that, in the absence of a catalyst, the intrinsic effects of the nanoreactor, such as spatial confinement and electronic interactions between the reactants and nanotube, can be harnessed to modulate molecular reactivity. Coupled with recent advances in *operando* spectroscopic analysis,[51] this strategy allows for a more intimate understanding of the physical state of the confined molecules and thus paves the way for more rational design of nanoreactors for preparative synthesis.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI:

Synthesis and characterization of trizoles and details of calculations for triazoles@SWNT (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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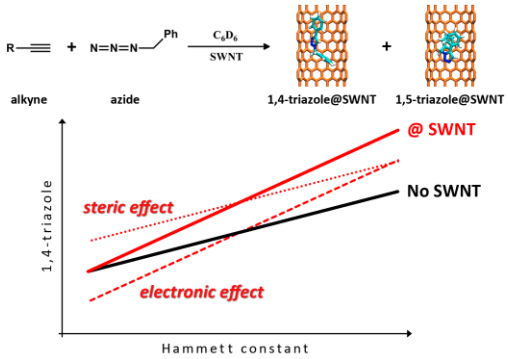
TOC graphic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