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Attractive interactions between heteroallenes and the cucurbituril portal

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Abstract

This study reports on the remarkable attractive interaction between organic azides and the portal carbonyls of cucurbiturils. Five homologous bis- α,ω -azidoethylammonium alkanes were prepared, where the number of methylene groups between the ammonium groups ranges from 4 to 8. Their interactions with cucurbit[6]uril were studied by NMR, IR and X-ray crystallography, and by computational methods. Remarkably, while the distance between the portal plane and most atoms at the guest end groups increase progressively with the molecular size, the β -nitrogen atoms maintain a constant distance from the portal plane in all homologs, pointing at a strong attractive interaction between the azide group and the portal. Both crystallography and NMR support a specific electrostatic interaction between the carbonyl and the azide β -nitrogen, which stabilizes the canonical resonance form with positive charge on the β -nitrogen and negative charge on the γ -nitrogen. Quantum computational analyses strongly support electrostatics, in the form of orthogonal dipole-dipole interaction, as the main driver for this attraction. The alternative mechanism of $n \rightarrow \pi^*$ orbital delocalization does not seem to play a significant role in this interaction. The computational studies also indicate that the interaction is not limited to azides, but generalizes to other isoelectronic heteroallene functions, such as isocyanate and isothiocyanate.

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Notes

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Full details of instrumentation and general methods, experimental procedures; detailed NMR spectroscopic characterization of all guests and their complexes, and quantum mechanical calculations, including Figures S1–S19 and Tables S1–S3 (PDF)

X-ray crystallographic analysis data for **2@1** (CIF)

X-ray crystallographic analysis data for **3@1** (CIF)

X-ray crystallographic analysis data for **4@1** (CIF)

X-ray crystallographic analysis data for **5@1** (CIF)

X-ray crystallographic analysis data for **6@1** (CIF)

Coordinates of geometrically optimized **5@1** (CIF)

Coordinates of geometrically optimized **11@1** (CIF)

Coordinates of geometrically optimized **12@1** (CIF)

Coordinates of geometrically optimized **13@1** (CIF)

This essentially unexploited attractive interaction could be more broadly utilized as a tool not only in relation to cucurbituril chemistry, but also for the design of novel supramolecular architectures.

Graphical Abstract

Keywords

Cucurbiturils; Azide; Heteroallene; Host-guest chemistry; Orthogonal dipole-dipole interaction

INTRODUCTION

Molecular recognition and noncovalent interactions govern a wide range of chemical events,¹ including crystal growth,² supramolecular chemistry,³ self-assembly,⁴ catalysis⁵ and almost every biochemical process,⁶ including protein–ligand binding, protein–protein interactions, and DNA base-pairing. Noncovalent interactions encompass multiple binding mechanisms,⁷ such as hydrophobic,⁸ charge-charge, charge–dipole and dipole–dipole interactions, hydrogen-bonding,⁹ and delocalization of electrons into antibonding orbitals.¹⁰

For the cucurbituril host molecules, which have rich supramolecular chemistry,¹¹ binding of guest molecules is thought to be dominated by three fundamental mechanisms:¹² (a) charge–dipole interactions between a strong dipole of the host’s carbonyl-fringed portal and the positive charge of a guest; (b) hydrogen bonding between the portal carbonyls and a guest’s donor moieties; and (c) hydrophobic interactions within the cucurbituril cavity, which is formed by the concave faces of the glycoluril subunits and their methylene bridges. Identification of new binding mechanisms accessible to the cucurbiturils would further enrich the uses of this important family of hosts.

While investigating the structural and dynamic properties of bistable rotaxanes made of *N,N'*-bis-alkyl-*p*-xylylene diammonium salts and cucurbit[6]uril, **1**, we noticed a remarkable crystallographic feature in one of the complexes.¹³ The azide moiety of the guest *N,N'*-bis-(2-azidoethyl)-*p*-xylylene diammonium dichloride forms close contacts with the oxygen atoms of the host, and the azidoethyl group adopts an energetically unfavorable gauche conformation (Figure 1). These observations suggested an interesting stabilizing attraction between the azide group and the carbonyls. We realized that this unrecognized attractive interaction could provide a yet unexploited tool in supramolecular chemistry and therefore should be further explored.

Here we report on the discovery of a remarkable attractive interaction between organic azides and the portal carbonyls of cucurbiturils, and characterize this interaction by X-ray crystallography, NMR and IR spectroscopy, and quantum chemical calculations. The results indicate that the attractive heteroallene-carbonyl interaction is a general phenomenon that can be exploited for supramolecular applications in the cucurbituril family and other systems.

RESULTS AND DISCUSSION

Synthesis

In order to characterize the attractive interaction between organic azides and the CB[6] portals, we synthesized a series of guest molecules with two azidoethylamine end groups, the *N,N'*-(2-azidoethyl)- α,ω -alkanediamines **2–6**, using a general four-step procedure (Scheme 1, see supporting information for details). Reaction of bromoethylamine hydrobromide, **7**, with sodium azide in water produced 2-azidoethylamine **8**. Protection of the latter with Boc anhydride afforded **9**, which underwent *N*-alkylation with the appropriate α,ω -dibromoalkane to produce compounds **10a–e**. Finally, removal of the Boc protecting groups with ethanolic HCl afforded the guest molecules, **2–6**, in the form of their dihydrochloric salt in overall yields of 20–30%.

NMR studies

The stoichiometry of the inclusion complexes was determined by ^1H NMR. Each of the protonated guest molecules, **2–6**, was dissolved in D_2O -DCl at pH 5, then mixed with solid **1** (1 equiv) and the mixture was kept at room temperature for 16 h. Formation of 1:1 inclusion complexes was evident from their ^1H NMR spectra, which exhibited significant changes in the chemical shifts of the guest molecules in comparison with their spectra in the absence of **1** (Scheme 2 and Supporting Information). Consistent with previous observations,^{13,14} all protons of the guest molecule residing in the host interior exhibited significant upfield shifts, which increased with the depth of burial in the binding cavity. For example, a comparison between free **5** and its complex **5@1**, revealed that the upfield shifts of the oligomethylene chain were shifted by 0.02, 0.52, 0.88 and 0.98 ppm, beginning with the α -methylene attached to the ammonium groups and moving inward. The induced shift presumably reflects the cumulative influence of the 12 urea units in **1**, each of which presents a face to the interior of the cavity. Thus, the upfield chemical shifts upon complexation are characteristic, and indicate that the interior of cucurbituril comprises a proton-shielding region relative to the aqueous medium employed for solvating the host species.¹⁴

Interestingly, the upfield shift of the α -methylene protons, which reside at the portals, decreases with increased chain length: $\delta = 0.78, 0.25, 0.07, 0.02$ and 0.00 ppm for C4, C5, C6, C7 and C8, respectively. This trend indicates that with chains of increasing length, the α -methylene group is pushed further out of the cavity. We have previously reported that all guest protons that reside outside the cavity in the vicinity of the portal undergo deshielding, probably due to the strong anisotropic effect exerted by the combined dipole of the carbonyl groups at the portal.¹³ Thus, in the case of the octamethylene chain of **6**, the

lack of any shift exhibited by the α -methylene protons indicates that the shielding and deshielding effects completely offset one another.

The observation that the α -methylene group resides at the portal, regardless of the length of the guest's oligomethylene chain, may be understood in terms of induced fit,¹⁵ as further supported by our crystallographic data (*vide infra*). For example, while the penta-methylene chain exhibits an all-anti conformation, the hexa-methylene chain adopts a slightly folded conformation that allows it to retain favorable interactions with the host.¹⁶ This phenomenon has been reported for alkyltrimethylammonium salts hosted by cucurbiturils,¹⁷ as well as for other host-guest complexes.¹⁸

The chemical shifts of the azidoethyl groups, which always reside outside the cavity, represent another informative conformational probe (Scheme 2 and Figure 2). As can be concluded from the crystallographic data (*vide infra*), guest **3**, which contains a pentamethylene chain, forms the shortest contact between the β -nitrogen atom of the azide and the host carbonyl (Figure 2B). This effect may explain the induced chemical shift differences shown in Figure 2A: electrostatic interactions between the carbonyl and the azide tend to stabilize one canonical resonance form of the azide (B in Scheme 3) and destabilize resonance form C (Scheme 3). This would make the α -nitrogen more electron-deficient, leading to enhanced deshielding effect of the adjacent carbon atoms.

IR study

To further probe the host-guest interactions, we compared the solid state IR bands of the free guests with those of their host-guest complexes, focusing on the absorptions of the urea and azide groups (2050–2150 and 1700–1750 cm^{-1} , respectively). Both bands can report on the local electrostatic environment. For example, the azide stretching vibration band of β -azidoalanine at 2000–2200 cm^{-1} is strongly red-shifted (14 cm^{-1}) in the hydrophobic environment of DMSO relative to water.¹⁹

As evident from Figure 3A, the ureido carbonyl vibration frequency becomes increasingly red-shifted (6–16 cm^{-1}) on going from free CB[6] to complexes with guests of increasing size. This trend indicates that the exposure of the host carbonyl groups to the surrounding aqueous environment is progressively attenuated by the hydrophobic parts of the guest molecules, which replace more water molecules. The trends found for the azido stretching frequencies are more complex. In general, increased intermolecular interactions upon binding would weaken the internal N-N bonds, manifested by red shifts.

The mixed effects shown in Figure 3B suggest that the azide groups in the free guest molecules (blue) are involved in inter- or intramolecular attractive interactions, which could be weaker or stronger than the azide-carbonyl interactions in the bound complexes (red). Indeed, gas-phase MM2 dynamics calculations (Figure S13) indicate that the free guest molecules feature intramolecular ion-dipole interactions between an azide group and a distant ammonium group, which is augmented by a dipole-dipole attractive interaction of two azides in an antiparallel orientation. Although gas-phase calculations may not fully represent the situation in the solid, the strong tendencies of the free guest molecules to participate in inter- and intramolecular attractive interactions are self-evident. The loss of

these interactions upon binding to **1** may not be fully compensated by the attractive host-guest interactions at the level of a single azide group.

X-ray crystal structures

The crystallographic studies provide valuable structural information concerning specific interactions within the host-guest complexes. Single crystals of **2@1**, **3@1**, **4@1**, **5@1** and **6@1** suitable for X-ray analysis were obtained from acidic (pH=6) aqueous solution by vapor diffusion. Crystallographic and refinement data of all structures are provided in Supporting Information (Table S1).

Our structures (Figure 4) may be compared with the reported complexes of **1** hosting α,ω -alkanediammonium guests.¹⁵ Interestingly, all complexes exhibit centrosymmetric structures, except for **5@1**. In both families of complexes the oligomethylene chain connecting the two ammonium groups adopts the same conformation within the CB[6] interior. The shorter guests adopt an extended conformation inside the cavity, while the longer ones adopt bent conformations. The distance between the ammonium groups varies from 6.18 Å in **2@1** to 10.14 Å in **6@1**. Since the distance between the two portal planes, which accommodate the carbonyl oxygen atoms, is 6.1±0.1 Å, the oligomethylene chain in **2@1** adopts a fully extended conformation, whereas the longer chains exhibit partially folded conformations.

The intramolecular distances between two ammonium nitrogen atoms in the fully extended conformation of free **3**, **4**, **5** and **6** are 7.51, 8.81, 10.0 and 11.33 Å, respectively.²⁰ These distances shrink to 7.36, 7.80, 8.61 and 10.14 Å in their corresponding complexes (Figure 5A). These folded conformations award the guest molecules with maximal charge-dipole interactions between the ammonium groups and the portals, along with favorable hydrophobic interactions between the oligomethylene chain and the interior of **1**. In addition, the longer chains also show multiple alternative conformations and occasional missing atoms (Figure 4). These chains thus appear to be partly disordered and so presumably pay a lower penalty in configurational entropy on binding than the shorter chains.²¹

Since this study aims at understanding the nature of the specific interactions between the host portals and the azide groups of the guest, their relative orientation is of particular interest. All structures reveal two consistent features. First, the azide group itself preserves a nearly linear geometry, as reflected by the consistent bond angles, N-N-N (172±1°). Second, all azide groups maintain short contacts with two carbonyl oxygen atoms through their central β - and terminal γ -nitrogen atoms (Figures 5B, 6 and 7).

The significantly short inter-atomic distances between the positively polarized nitrogen atoms of the azido groups and the negatively polarized carbonyl oxygen atoms approach the sum of the effective van der Waals radii of these atoms (~3.07 Å, Figure S14).²² Remarkably, while the distance between the portal plane and most atoms at the guest end groups increase progressively with the molecular size, the β -nitrogen atoms maintain a constant distance from the portal plane in all homologs (Figure 5B), pointing at a strong attractive interaction between the azide group and the portal.

Such distances require a gauche conformation of the azidoethyl chain, which is reflected by the N-C-C-N dihedral angle in all bound guest molecules, ranging between 64° and 71°. ²³ This binding mode is modulated by the size of the guest. With the smaller guests, **2**, **3** and **4**, the host carbonyl groups interact mainly with the β - and γ -nitrogen atoms of the azide. In the non-symmetrical complex **5@1**, however, one of the two azides is pushed further away from the portal. In this mode the γ -nitrogen is further removed from the carbonyl oxygen, while hydrogen bonds are formed between the methylene group on the α -nitrogen and the carbonyls (Figure 4d). This trend is more pronounced with the symmetrical complex **6@1** where both azide groups are pushed away from the portal.

The attractive interaction between the carbonyl oxygens and azide nitrogens may be characterized by the distance ($d_{N...O}$) between the two heteroatoms and the angle (θ) between the $d_{N...O}$ vector and the carbonyl bond (Figure 6). The distance $d_{N...O}$ is of particular interest because it can shed light on the issue of binding mechanism, pointing at the relative importance of either $n \rightarrow \pi^*$ interaction, ²⁴ which involves substantial orbital overlap (*vide infra*), or the orthogonal dipolar option, which is less sensitive to distance. ²⁵

A scatterplot of θ versus $d_{N...O}$ for these complexes (Figure 7A) shows that the shortest interactions between the carbonyl oxygen and the two distal nitrogens of the azide involve the β -nitrogen rather than the γ -nitrogen. Interestingly, for the short β -nitrogen interactions, the angle θ is narrowly distributed around 140° (Figure 7A), and θ diminishes approximately linearly with increasing $d_{N...O}$.

In order to set these results in context, we searched the Cambridge Structural Database (CSD) ²⁶ for short contacts ($< 3.9 \text{ \AA}$) and found 45 structures exhibiting 84 interactions between a carbonyl oxygen and the azide β -nitrogen. The distribution of geometries for the intermolecular cases (Figure 7B, red circles) encompasses the geometries found in our host-guest complexes (Figure 7A, red circles), typically falling within 140° $\pm$ 20° at a distance of 2.8–3.3 Å. The distribution of angles for the intramolecular interactions (Figure 7B, red circles with dark margin) is shifted and narrowed relative to the intermolecular cases. Expectedly, tighter geometric constraints in the intramolecular setting would limit the binding geometry.

We used ITC measurements to evaluate the net contribution of the azide-carbonyl attraction to the overall binding interaction between **1** and an azidoalkyl group. The binding properties of guest molecules **2**, **3** and **4** were compared with those of their truncated analogs, 1,4-diaminobutane (**2'**), 1,5-diaminopentane (**3'**) and 1,6-diaminohexane (**4'**), all in the form of dihydrochloride salts. With all six cases the binding stoichiometry was found to be approximately 1:1. The ITC experiments were duplicated on two different ITC instruments, and the ΔH values were found to be fully reproducible (Table S2 and Figures S15–S17). Nevertheless, since the ITC sigmoidal curves were too steep to elucidate binding constants with errors smaller than 10%, they should be considered on a qualitative basis (see supporting information).

Computational analysis

The interactions between the host, **1**, and the azide moiety of guest **5** were further analyzed by quantum-mechanical (QM) electronic structure calculations. We examined the attractive forces between the azide group of the guest and the carbonyl group of the host, and compared these with the corresponding interactions of three geometrically similar groups, isocyanate, isothiocyanate, and propadiene. Like azide, isocyanate and isothiocyanate are heteroallenes, and thus might form similarly attractive interactions with the host. In contrast, propadiene is a nonpolar allene, and thus may not establish such favorable interactions. The character of these various interactions was further analyzed in terms of potential contributions from dispersion forces, electrostatic interactions, and $n \rightarrow \pi^*$ delocalization.²⁴

The crystal structure of **5@1** was modified, using the Maestro software²⁷ to generate models of complete host-guest complexes for the isocyanate, isothiocyanate and propadiene guests (**11**, **12**, **13**, respectively, Scheme 4). Each host-guest complex, **5@1**, **11@1**, **12@1** and **13@1**, was then geometrically optimized using the semi-empirical PM6-DH+²⁸ method with the COSMO²⁹ implicit solvation model (see also SI). Higher-level quantum calculations, used to assess interaction energies, etc., were then carried out on fragments of these optimized systems, where the host was represented by methylenediurea, **14**, and the guests by the small molecules **15–18**, Scheme 4, without further changes in geometry. The azides at the two host portals adopt somewhat different geometries in the crystal structure of **5@1**; the optimized host-guest structures retain these differences, and we report computations for both geometries. Separate geometry optimizations, with PM6-DH+ and COSMO, were also carried out for each of the guest fragments in isolation, in order to look for possible geometric changes on binding to the host.

Both symmetry-adapted perturbation theory (SAPT),³⁰ implemented in the PSI4 program,³¹ and MP2,³² implemented in Gaussian D.01,³³ were used to compute interaction energies for the fragment dimers representing the host-guest interactions of interest. SAPT has been shown to accurately describe noncovalent interactions between molecules, including binding energies of large organic complexes.³⁴ We computed the total interaction energies, as well as the decomposed energy terms resulting from electrostatic (elst), exchange (exch), induction (ind), and dispersion (disp) contributions using SAPT2+3/aug-cc-pVTZ³⁵. It is worth noting that all orders of SAPT tend to overestimate attractive forces, and the performance of the SAPT approach depends strongly on the order of the SAPT expansion. However, the SAPT2+3 level used here, provides a full description of third-order interactions with accuracy that approaches the gold-standard CCSD(T)/CBS level.^{36, 37} Since current implementations of SAPT cannot include solvent effects, we also carried out similar calculations with MP2/aug-cc-pVTZ, both with and without the polarizable continuum method (PCM) implicit solvent model of water.³⁸

The nature of these host-guest interactions were further characterized by calculations by the NBO 3.0 program³⁹ as implemented in Gaussian 09 D.01. First, the electrostatic character of the heteroallene moieties of the guests was evaluated by computing atom-centered natural charges, using natural population analysis (NPA)⁴⁰, and assigning each atom a partial charge equal to its nuclear charge less the total population of its natural atomic orbitals. Second, the

possibility that $n \rightarrow \pi^*$ interactions might play a role in the azide-carbonyl attraction was evaluated with natural bond orbital (NBO) analysis, which uses second-order perturbation theory to estimate energies of donor-acceptor interactions.⁴¹

The geometrically optimized **5@1** structure has $d_{N...O}$ distances of 3.2 and 3.5 Å for the azide moieties at the two host portals, as measured between the β -position of each azide group and the closest host carbonyl oxygen atom. These distances agree well with those observed in the crystal structure (Figure 4B) and are comparable with distances measured between groups engaged in orthogonal dipole interactions.²⁵ For the end groups of the **5** analogs, isocyanate, **11**, isothiocyanate, **12**, and propadiene, **13**, the corresponding distances are slightly increased, to 3.3 and 3.6 Å for **11**, 3.4 and 3.6 Å for **12**, and 3.5 and 3.6 Å for **13**.

Interaction energies computed by various methods (Table 1) evidence significant attractive forces between the polar, heteroallene guest-representative molecules **15–17** and the host-representative molecule, **14**, and weaker attractive forces for the nonpolar propadiene-containing complexes. The comparison of SAPT energy decompositions reveals that the favorability of the azide-containing complexes is due to more than just dispersion. While MP2 on its own tends to predict more favorable interaction energies than does SAPT2+3, when the MP2 calculation is performed with the PCM solvent model, the interaction weakens. For the polar heteroallenes, this is consistent with the expectation that dipolar interactions will be weaker in a high dielectric solvent, like water.

The SAPT2+3 energy decompositions offer further insight regarding the attractive host-guest interactions. While the largest attractive component for all guests is dispersion, the electrostatic component is stronger in all heteroatom-containing functional groups than in the nonpolar propadiene analog. The induction energy component is comparably small for all guests, indicating that mutual polarizing effects only have a minor influence on the overall stabilizing energies. The exchange term, which includes exchange-induction and exchange-dispersion effects, measures repulsion, and is stronger for the propadiene than for the polar functional groups. Thus, the weaker repulsion and stronger electrostatic attraction of the three heteroallenes, account for their overall greater attraction to the host fragment, relative to that of propadiene.

The role of electrostatics is further elucidated by the natural atomic charges computed for all guest fragments in complex with methylenediurea, **14** (Table 2). The structures correspond to those used in Table 1, and two sets of charges are listed, as the fragments adopt slightly different geometries at the two portals of the host. While the methyl propadiene has partial charges less than 0.11 e at each position, the azide, isocyanate, and isothiocyanate analogs have partial charges at the α - and β -positions whose magnitudes are greater than 0.3 e . The substantial localization of positive charge at the β -position in all three heteroallenes is consistent with a favorable electrostatic interaction with the negative charge on the nearby carbonyl oxygen of the host.

We also considered whether the attractive interactions between the polar guest groups and the host carbonyl might result, at least in part, from $n \rightarrow \pi^*$ delocalizations.²⁵ These interactions are characterized by the delocalization of a lone pair (n) of a donor group,

typically a heteroatom nucleophile, into an antibonding orbital (π^*) of an acceptor group, typically a carbonyl group.⁴² In the host-guest systems, we would expect delocalization of a lone pair of the carbonyl oxygen atom donor in the host to the antibonding orbital of an acceptor in the guest functional group. We used two computational criteria to check whether $n \rightarrow \pi^*$ interactions play a role in these stabilizing heteroallene/carbonyl interactions. First, recognizing that such interactions would make the α - β - γ angle deviate from linearity,⁴³ we carried out PM6-DH+ geometry optimizations in COSMO implicit solvent for the various guests free in solution, and compared the resulting structures with the optimized host-guest geometries.

We observed no significant host-induced bending of either azide or the other analogs, the α - β - γ angle changed by at most 0.7° for the heteroallenes on going from solvent to the bound state (Table S3). This result is consistent with the near linearity of the azide groups in the X-ray structures of **2–6** in complex with **1**. Second, we used NBO calculations to look for donor-acceptor interactions between carbonyl oxygen lone pairs of the host and antibonding π orbitals of the guest-representative fragments. Initial calculations on formamide-formaldehyde complexes previously studied in the Raines group⁴⁴ served to validate the present approach, as the NBO results confirmed the interaction of the oxygen lone pair of the formaldehyde donor with the antibonding orbital of the C=O acceptor in formamide (Figure S18). In contrast, NBO analysis of the solvent-optimized methylenediurea complexes with the truncated guest molecules, **15–18**, indicates no significant $n \rightarrow \pi^*$ interaction. These findings (Figure S19) compare the donor-acceptor interactions between carbonyl oxygen lone pairs of the host and antibonding π orbitals across the various guest-representative fragments. In particular, no $n \rightarrow \pi^*$ delocalization above 0.07 kcal/mol were recorded. Thus, the present results indicate that $n \rightarrow \pi^*$ interactions do not contribute significantly to the attractive interactions studied here.

CONCLUSIONS

This study reports the discovery of a remarkable attractive interaction between organic azides and the portal carbonyls of cucurbiturils. Since this yet unexploited interaction could be more broadly useful as a driver of supramolecular assembly, we investigated it using a set of homologous bis- α,ω -azidoethylammonium alkanes. The interactions between these molecules and cucurbit[6]uril were studied by NMR, IR and X-ray crystallography, and by computational methods, all indicating that the attractive azide-carbonyl interaction is a general phenomenon that can be utilized for supramolecular applications in the cucurbituril family and other systems.

The crystallographic data show that while the distance between the portal plane and most atoms at the guest end groups increase progressively with the molecular size, the β -nitrogen atoms maintain a constant distance from the portal plane in all homologs, pointing at a strong attractive interaction between the azide group and the portal. Indeed, NMR evidence supports a specific electrostatic interaction between the carbonyl and the azide β -nitrogen, which stabilizes the canonical resonance form having positive charge on the β -nitrogen and negative charge on the γ -nitrogen.

Quantum computational analyses predict a substantial azide-carbonyl attraction, which is attributable largely to dispersion and electrostatic interactions, going beyond the weaker, primarily dispersive, attraction between a simple propadiene group and the host. The electrostatic component of the interaction traces largely to localization of positive charge on the β -nitrogen of the azide, and has the character of an orthogonal dipole-dipole interaction.²⁶ The alternative mechanism of $n \rightarrow \pi^*$ orbital delocalization does not seem to play a significant role in these interactions.

Analogous calculations for two other heteroallenes, isocyanate and isothiocyanate, suggest that these groups can inter-act with the host in much the same way as azide. This essentially unexploited attractive interaction could be more broadly utilized as a useful tool for supramolecular architecture, and further studies along these lines are currently under way in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Top and side views of crystal structure of *N,N'*-bis-(azidoethyl)-*p*-xylylene diammonium dichloride hosted in **1** (**9b** in ref. 13). Color code: C, gray; N, blue; O, red.

Figure 2.

A: ¹H NMR induced chemical shift differences ($\Delta\delta$) of the α' -methylene (blue circles) and the β' -methylene (red squares) upon formation of complexes between guests **2–6** and **1**. B: Intermolecular distances between either the azide β -nitrogen (red squares) or the α' -carbon (blue circles) and the closest carbonyl oxygen of the host. Data were derived from the crystallographic parameters (*vide infra*).

Figure 3.

IR vibrational frequencies (KBr pellet) of urea and azide groups. A. Ureido carbonyl stretching frequency of **1** (black circle), and of complexes **2@1**, **4@1** and **6@1** (red circles). B: Azido stretching frequencies of guests **2-6** in the absence of **1** (blue circles), and of complexes **2@1**, **4@1** and **6@1** (red circles).

Figure 4.

X-ray crystal structures of a) **2@1**, b) **3@1**, c) **4@1**, d) **5@1** and e) **6@1**. The host, **1**, is presented in a cross-sectional, space-filling format. Atom doubling and missing bonds indicate disordered structures.

Figure 5.

Crystallographic distances. A: The intramolecular distances between the ammonium nitrogen atoms in the fully extended conformation of free guest molecules (blue circles) and in the corresponding complexes (red squares). B: The inter-molecular distances between the portal plane and selected atoms at the guest end group. For the non-symmetrical complex **5@1**, the data points represent an average between the two sides of the complex.

Figure 6.
Definition of geometrical parameters θ and $d_{\text{N}\cdots\text{O}}$.

Figure 7.

A: Scatterplot correlation between $\theta(^{\circ})$ and $d_{N...O}$ (Å), extracted from the X-ray structural data. The red circles refer to the interactions with the azide β -nitrogen atom and blue circles refer to the γ -nitrogen. B. Scatterplot correlation between θ and $d_{N...O}$ (all referring to the azide β -nitrogen) extracted from the CSD database. The red circles refer to intramolecular interactions whereas the red circles with dark margin describe intermolecular interactions.

Scheme 1.

Synthesis of **2–6**. Reagents and conditions: a) NaN_3 , H_2O , 80°C , 24 h; b) $(\text{Boc})_2\text{O}$, Et_3N , CH_2Cl_2 , RT , 16 h; c) α,ω -dibromoalkane, NaH , DMF , RT , 48 h; d) HCl (4N), EtOH , RT , 16 h.

Scheme 2.

¹H NMR induced chemical shift differences upon formation of 1:1 complexes between guests **2–6** and **1** at room temperature in D₂O-DCI containing traces of DMSO (δ =2.71 ppm) as an internal standard. The shielding effect (– δ , ppm, upfield shift) is shown in bold, whereas deshielding (+ δ , ppm, downfield shift) is shown in italics.

Scheme 3.

Canonical structures of organic azides.

Scheme 4.

Various guest molecules equipped with heteroallene end-groups

Interaction energies and interaction energy decompositions (kcal/mol) of the host-guest interactions between **14** and **15–18**. Results are provided for the geometries of both ends of each guest, as their geometries are somewhat different; the one with the shortest host-guest distance is reported first in each case.

Table 1

Guest	Total Interaction Energy			SAPT2+3 Decomposition			
	MP2	MP2-PCM	SAPT2+3	elst	exch	ind	disp
15	-5.6	-2.9	-4.9	-2.9	3.6	-1.3	-4.3
	-5.3	-3.2	-4.3	-1.7	2.3	-0.8	-4.0
16	-5.1	-2.3	-5.0	-2.9	3.0	-1.2	-3.9
	-4.9	-2.7	-4.5	-2.1	2.3	-0.8	-3.8
17	-6.9	-3.1	-6.4	-3.6	2.9	-1.4	-4.3
	-7.3	-3.6	-6.7	-3.8	2.8	-1.1	-4.6
18	-2.6	-1.3	-1.8	-0.1	4.2	-1.4	-4.5
	-4.6	-3.0	-3.6	-1.9	4.7	-1.3	-5.1

Natural atomic charges of guest functional groups, expressed in *e*. For **18**, the α and γ charges are the sum of the C and H charges.

Table 2

Guest	Natural Atomic Charge		
	α	β	γ
15	N	0.3224	-0.1218
		0.3088	-0.1022
16	N	1.0407	-0.6430
		1.0290	-0.6348
17	N	0.4292	-0.2318
		0.4176	-0.2167
18	CH	0.0889	-0.1081
		0.0744	-0.0856