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Triazole: the Keystone in Glycosylated Molecular Architectures Constructed by a Click Reaction

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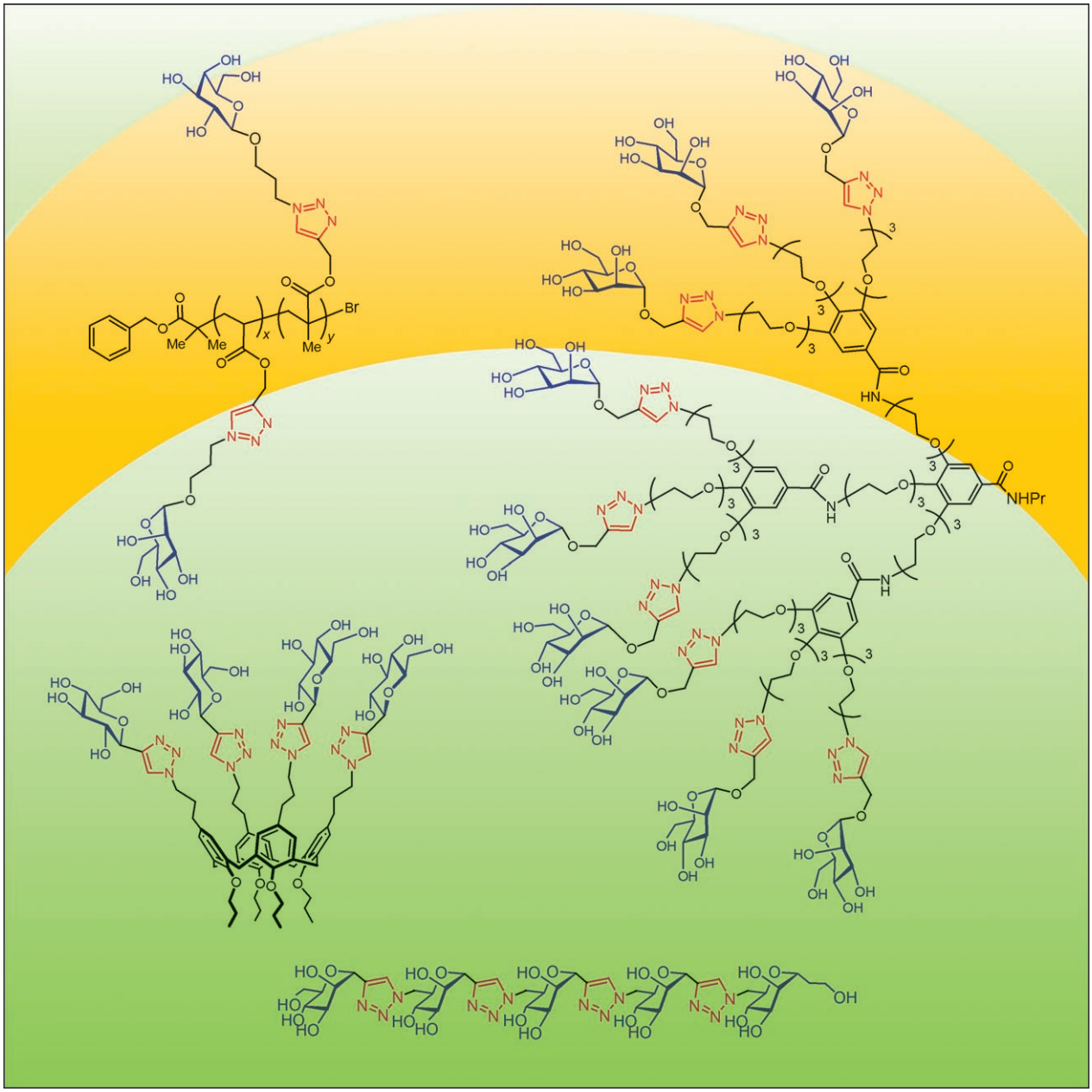
Dedicated to Professor Rolf Huisgen

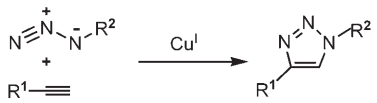


Abstract: The copper(I)-catalyzed modern version of the Huisgen-type azide–alkyne cycloaddition to give a 1,4-disubstituted 1,2,3-triazole unit is introduced as a powerful ligation method for glycoconjugation. Owing to its high chemoselectivity and tolerance of a variety of reaction conditions, this highly atom-economic and efficient coupling reaction is especially useful for the effective construction of complex glycosylated structures such as clusters, dendrimers, polymers, peptides, and macrocycles. In all cases the triazole ring plays a key role by locking into position the various parts of these molecular architectures. The examples reported and briefly discussed in this short review highlight the use of this reaction in carbohydrate chemistry and pave the way to further developments and applications.

Keywords: click reactions · cycloaddition · glycoconjugates · oligosaccharides · triazoles

1. Introduction

Today, organic chemistry, and organic synthesis in particular, is enjoying an exciting period of intense and fertile activity. A large part of research is carried out with a view to application in other fields, mainly biology, medicine, drug discovery, and functional materials. Hence, there is an evolving synergy between advanced organic chemistry and other disciplines with incommensurable advantages on both sides. The great potential of modern organic synthesis is a consequence of recent innovations in reactions, catalysts, and methodologies, as well as the advent of potent analytical techniques. The rediscovery of "old" reactions invented in the middle of the last century has also provided great stimulus to develop new chemistry. Two recent cases are emblematic. One is provided by olefin metathesis, pioneered by Natta, Banks, and Bailey in 1964, of which significance was highlighted by the award of the Nobel Prize to three organic chemists (Chauvin, Schrock, and Grubbs)[1] in 2005. The other is represented by asymmetric synthesis with metal-free chiral organocatalysts,[2] pioneered by two industrial groups (Hajos and Parrish; Eder, Sauer, and Wiechert) in the early 1970s and practically ignored until the 2000s. Both metathesis of unsaturated systems as a wide-scope carbon–carbon bond-forming reaction and organocatalysis as a fundamental synthetic methodology are nowadays privileged processes in organic synthesis. Another reaction that is the fruit of a reevaluation of earlier reported chemistry is copper(I)-catalyzed azide–alkyne coupling to give 1,4-disubstituted 1,2,3-triazole derivatives (Scheme 1). This reaction has garnered a significant amount of attention by researchers operating in disparate fields pertinent to the life and materials sciences.[3] It is amply documented in books and collections[4] that the uncatalyzed thermally induced reaction of organic azides (1,3-dipole) with acetylenes (dipolarophile) belongs to the vast repertoire of [3+2] concerted reactions (one-step pericyclic processes)[5] that have been systematized in the early 1960s by Huisgen under the name of 1,3-dipolar cycloadditions.[6] The discovery that catalytic Cu^I increases the reaction rate and controls the regioselectivity to give the 1,4-disubstituted triazole group while suppressing the formation of the 1,5-regioisomer was made independently in recent times by Sharpless[7] and Meldal[8] and their co-workers. Notably, under the new Cu^I-catalyzed conditions, the reaction does not retain its original concerted nature and proceeds through a multistep mechanism involving azide–copper and alkyne–copper complexes.[9] Hence, the improved version of the Huisgen-type reaction turned out to be a remarkable example of chemical efficiency, because besides being operatively simple and tolerant to atmospheric conditions, it transforms readily the reagents into a single product in high yield and with the maximum level of atom economy. For these reasons, the reaction was identified as the premier ex-



Scheme 1. Cu^I-catalyzed azide–alkyne coupling.

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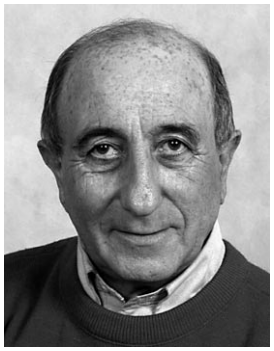
ample of a "click reaction", an onomatopoeic expression (click is the sharp sound that is made by snapping one's fingers, for example, to point to a facile and quick operation) coined by Sharpless and co-workers[10] "to indicate a near-perfect chemical process for the assembly of specially designed building blocks". In a similar figurative manner, we consider the triazole unit as a solid keystone[11] that holds separate units together in complex molecular architectures, just as the keystone in an arch secures the whole structure (Figure 1).

Figure 1. Etruscan arch in the city of Volterra, Tuscany (Italy).



Alessandro Dondoni *graduated at the Univ. of Bologna in 1960 under the supervision of Prof. F. Montanari. After a postdoctorate (1961–62) with Prof. S. I. Miller at the Illinois Institute of Technology in Chicago, he returned to the Univ. of Bologna first as Assist. Prof., then as Assoc. Prof. He moved to the Univ. of Ferrara as a Full Prof. of Organic Chemistry in 1975. He has received many awards, such as the Japan Society for the Promotion of Science Award (1988) and the Lincei National Academy Prize in Chemistry (1999). His present research interests include asymmetric and diastereoselective synthesis, heterocycles as synthetic auxiliaries, and carbohydrate chemistry.*

The high affinity of the azide[12] for the alkyne group (chemoselectivity) and, by contrast, the inertness of both functionalities toward the majority of functional groups connected to the core of a variety of biomolecules (bioorthogonality), as well as the stability of the triazole ring toward chemical and enzymatic degradation,[13] are all features that concur to make this click reaction particularly suitable for covalently linking bioactive molecular entities, an operation in which mild and neutral conditions are a prerequisite. The potential of this coupling reaction in bioconjugation[14] appears to be comparable to that of the Staudinger reaction between azides and phosphines,[15] a ligation reaction that in a reengineered form was highlighted by Bertozzi and co-workers as a means of selectively modifying cell-surface glycans with exogenous probes.[16] The two methods are complementary. However, the triazole residue produced in the Huisgen-type reaction is more robust than the amidic tether formed in the Staudinger reaction and can participate in hydrogen-bonding and dipole interactions, which can favor the binding to biomolecular targets and improve solubility.[17] Hence, the copper(I)-catalyzed Huisgen-type ligation did not escape the attention of synthetic carbohydrate chemists in their continuous efforts to devise new tools that might allow molecular glycobiologists to clarify the role of carbohydrates at the molecular or cellular levels in biological events.[18] Alternatively, these tools can be advanced structures for the developments of new therapeutics[19] or carbohydrate-based vaccines[20] against largely diffuse human diseases such as cancer, inflammation, and viral infections. Herein, I report and comment on some triazole-based glycosylated structures whose construction relies on the readiness and efficiency of the copper(I)–azide–alkyne-coupling (CAAC) process. The presence of carbohydrate systems with their delicate structure rich in functionalities and stereocenters makes these structures one of the most severe testing benches on which to validate the utility of this reaction. Although this account is not meant to be a comprehensive overview, the achievements from different laboratories that bear substantial witness to the versatility of the CAAC reaction will be illustrated.

2. Early Applications: Triazole-Based Glycosylated Arrays and Glycoclusters

Wong[21] and Santoyo-Gonzáles[22] and their co-workers were timely in reporting in 2002, the same year of the discovery of the Cu^{I} catalysis,[7,8] the efficient ligation of carbohydrates with non-carbohydrate substrates by the CAAC process. Wong and co-workers[21] described the construction of glycosylated arrays on the surface of microtiter wells (Scheme 2). Quite remarkably, they not only exploited the azide–alkyne ligation to attach oligosaccharides to a hydrocarbon chain that was not covalently bound to the microtiter plate, but also showed that the glycosidic portion could be modified, for example, fucosylated, by an enzymatic reaction. Various biological assays were also carried out, thus demonstrating

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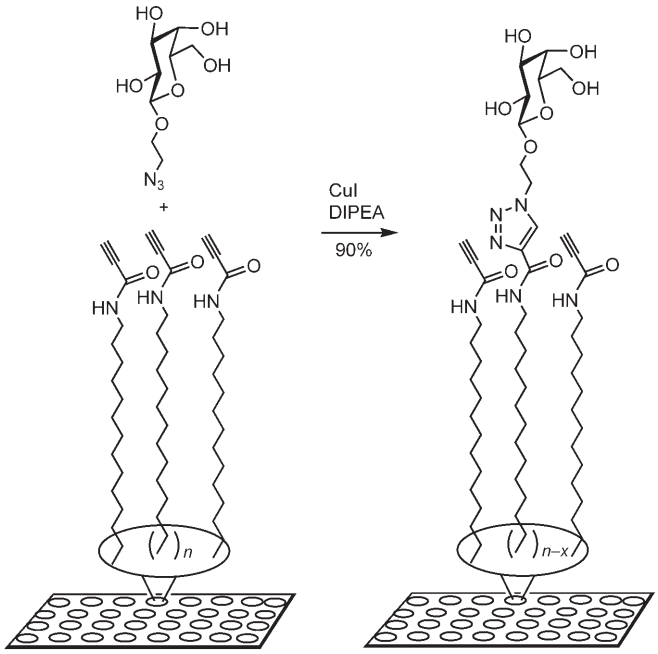
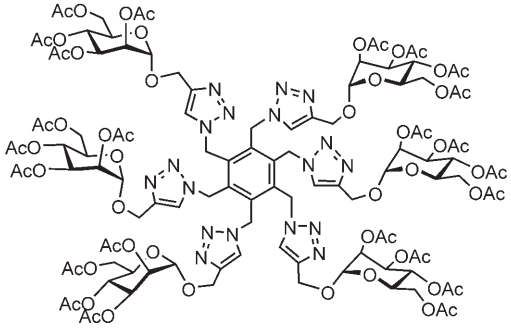


Scheme 2. Formation of a glycosylated array in a microtiter plate by the CAAC process.[21] DIPEA = diisopropylethylamine.

that the carbohydrate arrays were suitable for high-throughput studies of protein interaction and enzyme-inhibitor screening. The road was thus paved for the synthesis of other carbohydrate arrays by the CAAC process.[23] In all cases, the presence of the triazole ring, with its impervious nature to degradation by external agents, was crucial to robust ligation between the glycosylated fragment and the molecular unit immobilized on the solid surface.

Santoyo-Gonzáles and co-workers[22] prepared a range of glycoclusters anchored to various scaffolds. An example of these compounds is shown in Scheme 3. This pioneering work was also important in many respects as it demonstrated the fidelity of CAAC chemistry in a program directed toward the introduction of several sugar fragments in a single molecular residue.



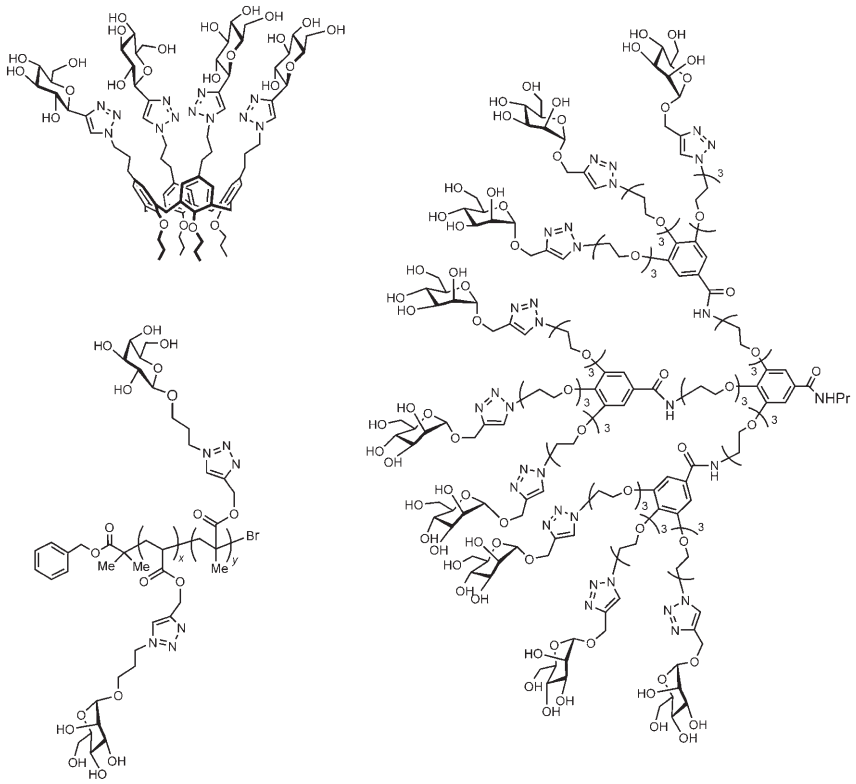
Scheme 3. Glycocluster prepared from hexakis(azidomethylbenzene) and propargyl *O*-mannoside.[22]

3. Other Triazole-Based Glycoclusters, Glycodendrimers, and Glycopolymers

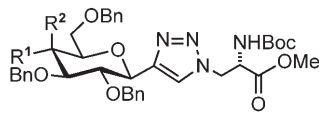
The synthesis of multivalent neoglycoconjugates is currently promoted by the extensive findings of multiple ligand–receptor interactions that occur in nature and by the phenomenon generally referred to as the glycoside cluster effect.[24,25] A number of papers have appeared in 2005 and 2006 that deal with the CAAC-based synthesis of various types of densely glycosylated molecular architectures, such as glycoclusters,[26] glycodendrimers,[27] and glycopolymers[28] (Scheme 4). The preparation of these saccharide constructs involved the equipping of a suitable scaffold with several azide or ethynyl groups and then treatment with a glycosylated residue holding the complementary functionality for performing concomitant copper(I)-catalyzed Huisgen-type reactions. From the numerous substrate combinations employed and the high yields of the multivalent glycoconjugates obtained, it appears that each CAAC reaction proceeded quite efficiently regardless of the structure and complexity of the substrate to which the azide and ethynyl groups were bound. Surprisingly, however, there was no apparent concern about the stability of compounds displaying an *O*- or *N*-glycosidic bond to connect the carbohydrate moiety, either directly or through a suitable spacer, to the triazole ring. It is a common tactic in glycochemistry to replace the *O*- and *N*-glycosidic residues with *C*-[29] or *S*-glycosidic analogues[30] to induce high stability toward chemical and enzymatic degradation without compromising biological activity. In accordance with this concept, this structural feature was introduced in the calix[4]arene-based *C*-glycocluster shown in Scheme 4 and in other similar products reported in the same publication from our laboratory.[26c] This improvement should avoid serious drawbacks such as the easy removal of the carbohydrate fragments from glycoclusters when they are employed, for example, as probes in glycobiology or biosensors in nanodevices under conditions that are not tolerated by the weak *O*- and *N*-glycosidic bonds.

4. Triazole-Tethered Glycosyl Amino Acids and Peptides

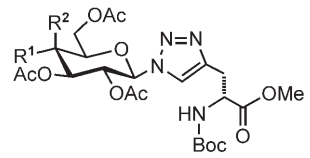
Another issue that was successfully addressed by CAAC chemistry was the synthesis of nonnatural glycopeptides. Extensive findings demonstrate that anomerically *O*- and *N*-linked carbohydrate residues play a key role in the folding and biological activity of glycopeptides.[23a,31] Consequently, chemically and metabolically stable analogues composed of *C*-glycosyl α-amino acids are important synthetic targets because they can serve as probes in studies of biochemical pathways and leads for the development of potential drugs.[32] Hence, the synthesis of a new class of *C*-glycosyl α-amino acids that contain the triazole ring as a linker of the sugar fragment and the amino acid moiety (Scheme 5) was reported independently by us and Rutjes and co-workers.[33] Interestingly, the comparison of the thermal and copper(I)-



Scheme 4. Examples of triazole-linked multivalent neoglycoconjugates: glycocluster[26c] from tetrakis(azidopropylcalix[4]arene) and ethynyl *C*-glucoside (left top), glycodendrimer[27b] from polyazidogallic acid–triethylene glycol dendrimer and propargyl *O*-mannoside (right), and glycopolymer[28] from a copolymer with alkyne side chains and azidopropyl *O*-glycoside (left bottom).



a; R^1= H, R^2 = OBn
b; R^1= OBn, R^2 = H



a; R^1= H, R^2 = OAc
b; R^1= OAc, R^2 = H

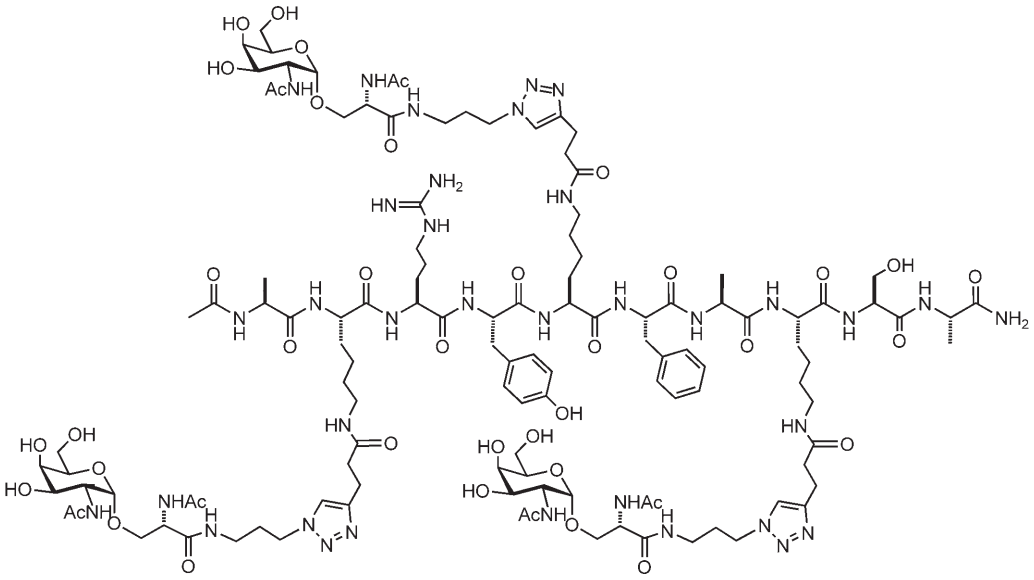
Scheme 5. *C*-glycosyl[33a] and *N*-glycosyl[33b] triazolylalanines (top and bottom, respectively) prepared by the CAAC process. BOC = *tert*-butoxycarbonyl.

catalyzed reactions between ethynyl *C*-glycosides and azide-equipped amino esters[33a] demonstrated the total 1,4-regioselectivity of the latter process,[34] whereas the uncatalyzed reaction afforded the two 1,4- and 1,5-triazole regioisomers in comparable amounts. More extensive work by Rutjes and co-workers[33b] was carried out in the synthesis of triazolyl amino acids and peptides, all of which display the glycosyl fragment bound to a nitrogen atom of the heterocyclic ring.

Very recently, carbohydrate-decorated polypeptides (Scheme 6) constructed by the CAAC process were reported by Danishefsky and co-workers.[35] This is an important and notable contribution to the ongoing research on the synthesis of carbohydrate-based antitumor vaccines. These substances could either be conjugate systems composed of oligosaccharides covalently linked to immunogenic proteins or simply polysaccharide antigens.[20] These systems could induce an immune response because cancer cells typically display aberrant levels and patterns of cell-surface glycosylation.[20a] The strategy employed by Danishefsky and co-workers involved the introduction of the azide group at the end of a glycopeptide chain followed by carry-on multiple copper(I)-catalyzed couplings of this substrate with a polypeptide equipped with pendant alkynyl groups. However, in contrast to that observed in simple model systems, the construction of such large architectures from highly sensitive substrates revealed that the key CAAC process needed optimized conditions. The reaction time was thus reduced from days to hours, and the yields of the desired adducts were increased from low to excellent values by the use of nanosized Cu particles in slightly basic water.

5. Triazole-Carbohydrate Hybrid Macrocycles

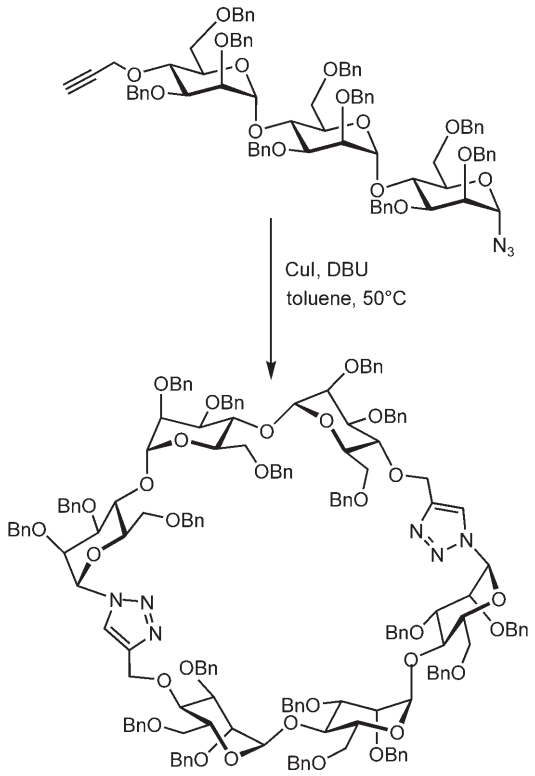
Recent papers provided evidence on the utility of the CAAC process in the synthesis of cyclic oligomers. Inspired by the general tactic of Fürstner and Müller in cyclic glycolipid synthesis by ring-closing metathesis,[36] Dörner and Westermann reported the preparation of triazole-tethered carbohydrate macrocycles.[37] Dimeric carbohydrate–triazole fragments bearing a carbon–carbon double bond at each end were first prepared by the CAAC process. These intermediates were then subjected to macrocyclization via intramolecular olefin metathesis promoted by the first-generation Grubbs ruthenium–carbene complex. Besides paving the way to libraries of carbohydrate–heterocycle hybrid macrocycles, this work furnished an important result as it



Scheme 6. Example of polypeptide with three side chains bearing a triazole ring and a terminal *O*-glucoside residue.[35]

demonstrated the compatibility of the triazole ring with the conditions of olefin metathesis. This finding can be of great utility in the design of new synthetic strategies and projects.

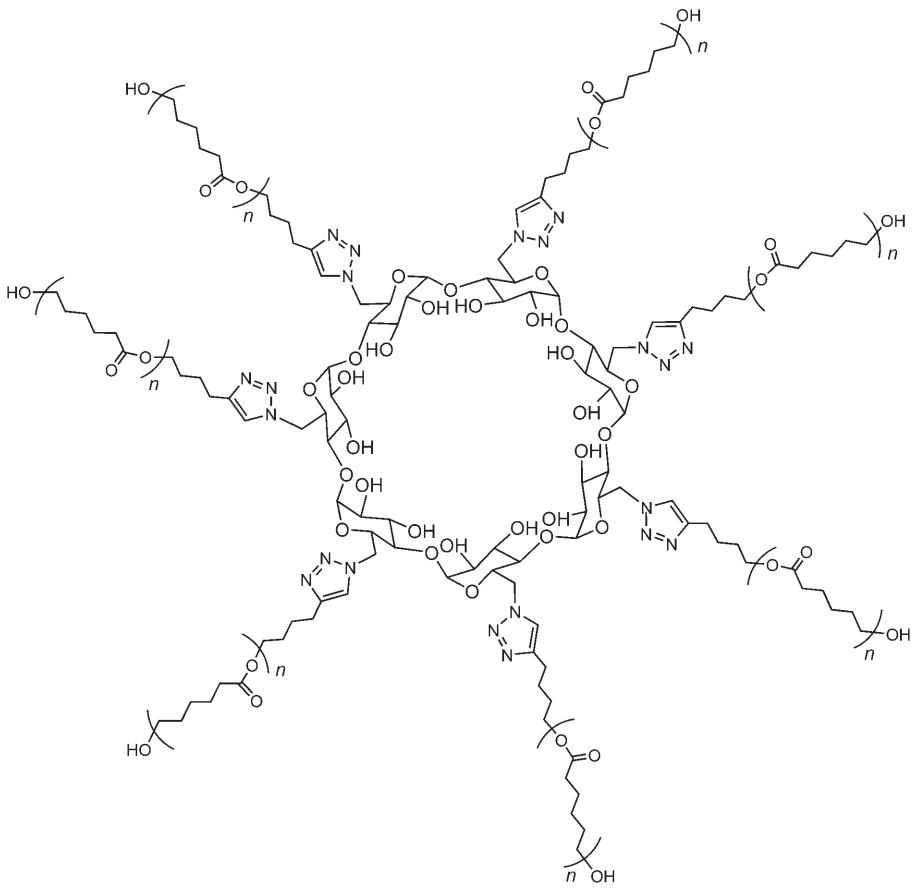
A highly convergent approach based exclusively on CAAC chemistry was employed by Gin and co-workers in the preparation of cyclodextrin analogues that display two or more triazole residues as part of the ring.[38] A notable example is provided by the synthesis of an oligosaccharide macrocycle that involved the cyclodimerization of a trisaccharide carrying an azide group at one terminal and an ethynyl group at the other (Scheme 7). The reaction was effectively promoted by CuI and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene. On the other hand, in the absence of the copper catalyst, the reaction was very sluggish and afforded the target oligosaccharide in small amounts together with multiple products. The same synthetic route was followed by Billing and Nilsson for the cyclooligomerization of bifunctional (azide and ethynyl) monosaccharide–dipetide substrates to give macrocyclic carbohydrate–dipeptide hybrids.[39] In this case, the most efficient conditions were found by the use of CuI and *N,N*-diisopropylethylamine in MeCN. Hence, this and the other cases illustrated above indicate that despite its simplicity, the CAAC reaction applied to multifunctionalized systems require optimized conditions especially with respect to the generation of the copper(I) catalyst.



Scheme 7. Synthesis of a triazole-linked oligosaccharide macrocycle by the CAAC process.[38]

6. Cyclodextrin with Triazole-Tethered Polymer Chains

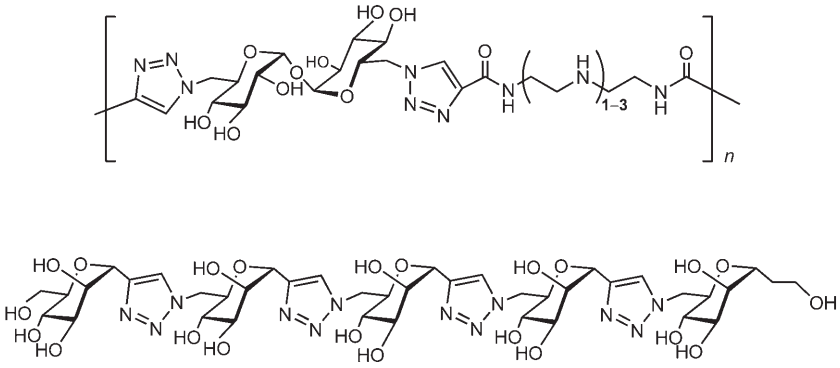
The enduring interest of many researchers for cyclodextrin functionalization led to the application of the CAAC process to this natural macrocyclic oligosaccharide as well.[40] Hence, β-cyclodextrin functionalized with seven azide groups, one for each glucose residue, and an excess of acetylene poly(ε-caprolactone) under Cu^{I} catalysis and microwave acceleration afforded the star-shaped macromolecule shown in Scheme 8.



Scheme 8. Heptakis(poly(ε-caprolactone)-β-cyclodextrin) with triazole tethers.[40]

7. Glycopolymers with Triazole Rings in the Chain

Open-chain glycopolymers with incorporated triazole units were constructed by Reineke and co-workers[41] in early 2006 (Scheme 9). The key operation for polymer formation consisted of multiple Cu^{I}-catalyzed coupling reactions (click polymerization) between trehalose bis(azide) and dialkyne oligoamine monomers. Three polymers were constructed by varying the amine number between the trehalose moieties.



Scheme 9. Triazole-containing glycopolymer[41] (top) and oligosaccharide[42] (bottom) constructed by the iterative CAAC process.

The synthesis of these compounds represents another remarkable success of the CAAC process in the preparation of complex glycosylated architectures with planned biological activity. In fact, the glycopolymers were synthesized to promote nucleic acid delivery into cells in the presence of serum. Therefore, the polymeric structures were designed with a special role for each constituent in mind. In particular, the heterocycle–amide groups were thought to promote complexation with nucleic acids through hydrophobic, van der Waals, and H-bonding interactions. For similar reasons we prepared the triazole-linked oligosaccharide triazolopentamannose[42] (Scheme 9). This new type of carbohydrate–heterocycle hybrid, which displays only *C*-glycosidic linkages, represents an anomerically stable imitation of natural mannooligosaccharides that constitute the essential substructure of mycobacteria lipoglycans. Hence, these artificial oligosaccharides may act as inhibitors of the growth of these organisms, which are the cause of diseases such as tuberculosis.[43] The triazole–mannose oligomer was prepared by four repetitions of a reaction sequence comprising the CAAC process under microwave irradiation and azidation of the resulting product. This iterative process appears to be perfectly suited to the preparation of sugar oligomers with a well-defined composition. For simplicity as well as chromatography-free and high-yield reactions in each cycle, this reaction is likely to be carried out in an automated apparatus.

8. Labeling of DNA Strands

A postsynthetic method was employed for the introduction of molecular labels in DNA strands by CAAC chemistry.[44] The method was first applied to designed alkyne-modified oligodeoxyribonucleotides, which were subjected to multiple coupling with suitable azide-bearing labels such as glucose, cou-

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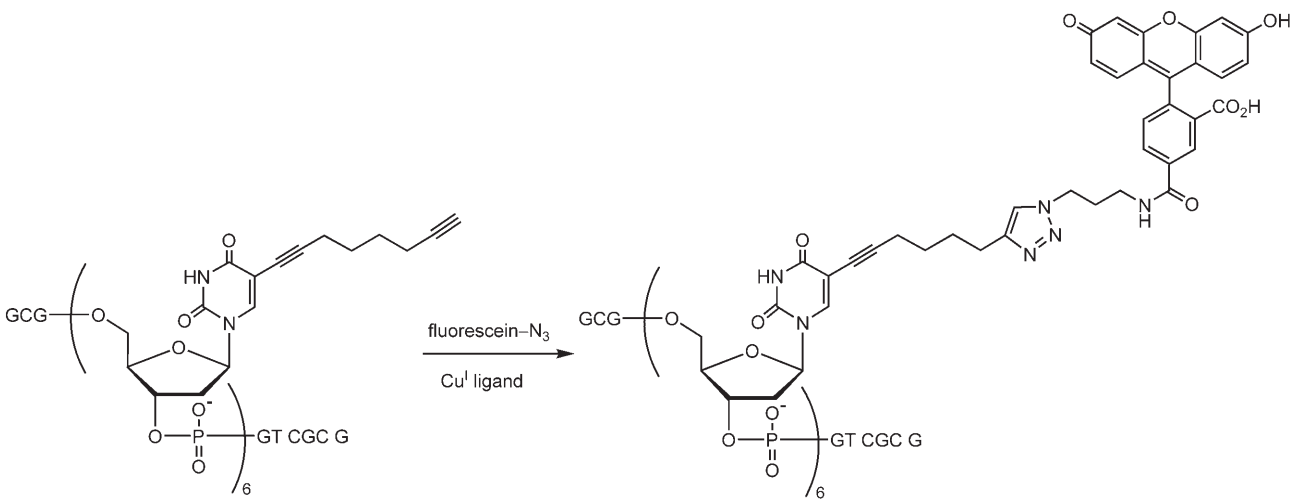

Scheme 10. Synthesis of fluorescein-labeled oligodeoxyribonucleotide by multiple CAAC processes.[44]

marin, and fluoroscein (Scheme 10). As strand breaks occurred in the presence of Cu^{I}, this inconvenience was avoided by the use of the Cu^{I}-stabilizing ligand tris(benzyltriazolylmethyl)amine, which is known to protect biomolecules from side reactions in water that involve Cu^{I} ions. The CAAC reaction also proved effective with alkyne-containing long DNA fragments obtained by enzymatic processes such as the polymerase chain reaction (PCR) without the DNA cleavage. This postsynthetic modification was introduced as a means of allowing the decoration of DNA for isolation and identification according to the nature of the probe.

9. Conclusions

In summary, the Huisgen-type azide–alkyne cycloaddition promoted by copper(I) is a powerful tool in new strategies for complex glycoconjugate synthesis. The reaction has been employed especially in the preparation of glycosylated substrates for studies of carbohydrate-based molecular-recognition processes and for advancement in the synthesis of designed glycoconjugates to prevent diseases of social relevance such as cancer. In all cases in which the reaction was interrogated, it gave a positive response and showed its superior value relative to the thermally induced process. Concomitant multiple cycloadditions allowed the decoration of complex scaffolds such as dendrimers and polymers with numerous carbohydrate residues. Repetition of the reaction in oligosaccharide synthesis by a linear-homologation strategy showed unvarying efficiency over several consecutive cycles. The role of the triazole group as a robust keystone that firmly holds disparate types of molecular fragments emerged in all circumstances. Finally, although the main contribution of this reaction is mainly manifested in the realm of organic synthesis, the skepticism about its application in living systems owing to the noxious copper catalyst is being dissolved by the successful live-cell labeling carried out by Link and Tirrell[45] as well as Bertozzi and co-workers.[46]

Acknowledgements

I thank my co-workers, Prof. A. Marra and Dr. A. Massi, and students for their collaboration in this specific field of carbohydrate chemistry, and I am grateful to the University of Ferrara for financial support.

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[3] Almost 600 papers have been published since 2002, the year of the discovery of the copper(I) catalysis (personal communication by K. B. Sharpless).

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[11] In architecture, the keystone is the central wedge-shaped block of an arch that locks its parts together. The semicircular arch was present in Etruscan structures around 700 BC and was then developed by the Romans in the vaults and domes of their monumental buildings.

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