Organic &
Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

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Cite this: *Org. Biomol. Chem.*, 2025, **23**, 10684

Received 26th September 2025,
Accepted 12th November 2025

DOI: 10.1039/d5ob01545f

rsc.li/obc

C–H amination reactions inside α-cyclodextrin supramolecular capsule

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We describe the photochemical generation of an alkoxycarbonylnitrene species in a supramolecular capsule and its reactivity. 2-Adamantyl-carbonazidate was co-crystallized in a supramolecular capsule consisting of two α-cyclodextrins (α-CDs) interacting through a hydrogen bond network. Irradiation of the co-crystal with UV light (254 nm) in the solid state or in suspension resulted in the extrusion of a nitrogen molecule and the corresponding nitrene formation inside the capsule. This reactive species provides selective C–H amination of the capsule wall, specifically at carbon 5 of the α-CD unit. The supramolecular assembly fixes the geometry of both reactants, the nitrene and the C–H bond, in line, mimicking the transition state for the triplet nitrene H-atom-abstraction reaction. Enantioselective intramolecular formation of a minor product, a carbamate, occurring concomitantly in the CD capsule, helps clarify the mechanisms of C–H amination reactions.

The study of electron-deficient nitrene species as reactive intermediates in amination reactions dates back to their first preparation and structural elucidation in the first half of the last century.[1] The reactivity of nitrene species varies according to the attached group and the distribution of the six electrons around the nitrogen atom.[2] Many precursors have been designed to provide nitrene intermediates in response to thermal, electromagnetic or chemical stimuli. If metals are involved in the generation and transfer of nitrenes, then such species are called metal nitrenoids.[3]

Among the most common precursors for C–H amination reactions[4–6] of alkanes or aziridination[7,8] of alkenes are alkoxycarbonylnitrenes[9,10] with the structural formula ROCON for the preparation of cyclic or acyclic carbamates (Fig. 1). Such nitrenes can be prepared by formal oxidation of carbamates ($ROCONH_2$),[11–14] by formal elimination of an ROH group from *N*-substituted carbamates ($R^2OCONHOR$)[15,16] or by nitrogen extrusion from carbonazidates ($ROCON_3$).[9,17–19] The reactivity of nitrene species depends on the electronic configuration of nitrogen,[20] *e.g.*, singlet species undergo insertion reactions into C–H bonds, whereas triplet species undergo amination reactions through hydrogen-atom abstraction and a subsequent radical rebound process.[21] Carbonazidates are typical precursors for thermal or photolytic nitrogen extrusion reactions. The key idea of this work was to encapsulate such a precursor into a supramolecular assembly that is transparent to UV light and enables the generation of the nitrene species inside the cavity. Several studies have demonstrated photochemical transformations in different types of molecular containers,[22,23] including cyclodextrins (CDs).[24] CDs[25] are widely used supramolecular hosts that are known to form strong inclusion complexes[26] predominantly in water and with lipophilic compounds. The most common CDs are α-, β- and γ-CD, cyclic oligosaccharides consisting of 6, 7 and 8 D-glucose units connected by α-1,4 glycosidic bonds.

The shape of the CD resembles a truncated cone, being hydrophilic outside its cavity (due to OH groups) and lipophilic inside its cavity (due to C3–H, C5–H and C–O–C bonds). Many studies describing the inclusion complexes of CDs with

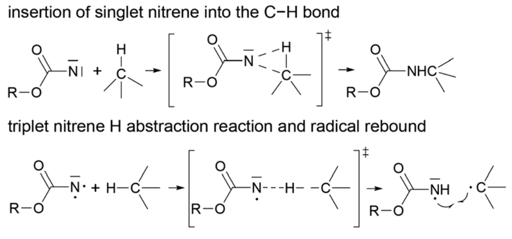

Fig. 1 Reactivity of singlet and triplet nitrenes with C–H bonds.

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adamantane derivatives[27] have been published,[28] often reporting large binding constants, especially with β-CD.[29–31] We have recently described[32] a strong binding and conformational study of selected C_S-symmetric adamantane derivatives with α-CD. To the best of our knowledge, we are the first to present an encapsulated nitrene precursor in a cyclodextrin capsule.

In our study, 2-adamantanol was converted into the corresponding carbonazidate using triphosgene and sodium azide in a one-pot reaction (Fig. 2). Crystallisation of this compound in a 1 : 2 ratio with α-CD in a water/ethanol mixture at 60 °C provided the desired co-crystal. This co-crystal was subjected to X-ray diffraction analysis, and the resulting set of atom coordinates was used for computational studies (Fig. 3). The UV irradiation (254 nm) of the crystal was performed either in the solid state or in a suspension of the crystals in *n*-hexane at room temperature for two hours. Then, the suspension was treated with an ethylacetate–water mixture to extract the organic compounds into the organic solvent and cyclodextrin derivatives into the water phase. HRMS analysis revealed the presence of two compounds. The covalently modified CD derivative **2**, which was isolated, *i.e.*, separated from the unmodified CD part of the capsule **2c** using column chromatography on silica gel (75% isolated yield; see SI page 7), and its structure were confirmed by NMR, along with carbamate **3**, which is a known compound (Fig. 4). Carbamate **3** was isolated, and its enantiopurity was measured using HPLC with a chiral stationary column. This minor product was formed in a yield of around 5% with a stable 75 : 25 ratio of enantiomers. This clearly demonstrates that the α-CD capsule creates an anisotropic environment for the trapped prochiral compound, as evidenced by the observed enantiomeric excess of the intramolecular amination reaction.

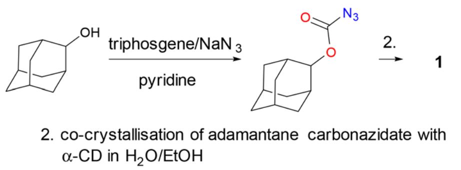

Fig. 2 Synthesis of 2-adamantyl-carbonazidate and its co-crystallisation with α-cyclodextrin towards supramolecular assembly **1**. This assembly of two α-cyclodextrins with a molecule of 2-adamantyl-carbonazidate inside the capsule is depicted in Fig. 3.

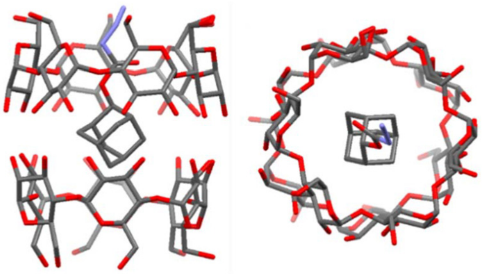

Fig. 3 X-ray data analysis of **1**, the assembly of two α-cyclodextrins with a molecule of 2-adamantyl-carbonazidate inside the capsule, side and top views.

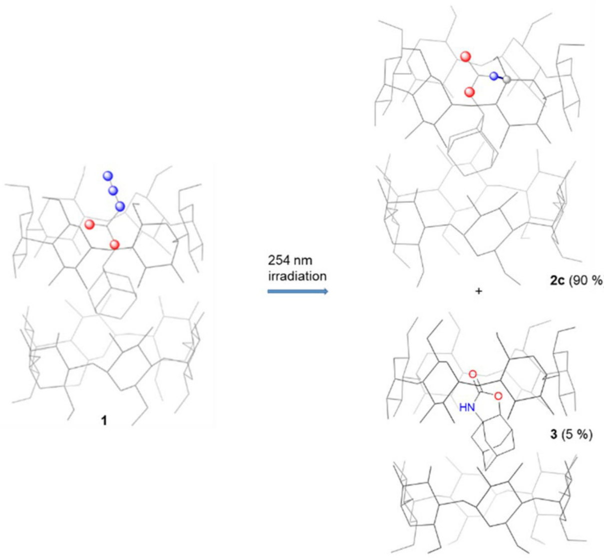

Fig. 4 UV irradiation of co-crystal **1** and the C–H amination reaction leading to major product **2c** that is formed in yields of over 90%. Oxygen atoms of $OCON_3$ are depicted in red and nitrogen atoms in blue. The generated nitrene intermediate inserts selectively into the C(5)–H bond of α-cyclodextrin. The resulting C–N bond is depicted in black. The covalently modified α-cyclodextrin is described as compound **2**. The capsule consisting of the modified cyclodextrin and unmodified cyclodextrin is denominated as **2c**. Enantioenriched carbamate **3** as a result of intramolecular C–H amination inside the α-cyclodextrin capsule is a minor product (5% yield) that is formed with 50% enantiomeric excess.

The mole ratio of products **2** and **3** formed upon irradiation remains consistent when the reaction is replicated, but the overall yield varies depending on the crystal size. The release of N_2 during irradiation turns the transparent crystal into a powder, which causes a variation in conversion. The exclusive formation of compounds **2** and **3**, as well as the observed ratio of compounds **2** and **3** (*i.e.*, the ratio of intermolecular amination and intramolecular amination and the ratio of enantiomers for the intramolecular amination reaction), was explained using quantum chemical computations. *Ab initio* calculations were performed utilizing the ORCA software package[33,34] using the M06L DEF2-SVP D3ZERO DEFGRID3 method[35–39] either for the guest (2-adamantyl-carbonitrene → carbamate **3**) itself or for its complexes with two α-cyclodextrins (Fig. 5). Because the resulting complexes are too large for free-energy calculations, the energies from either optimizations or scans of chosen reaction coordinates are provided. The crystal structure was the starting point for the geometry optimisation of complex **A**, consisting of two α-cyclodextrins and 2-adamantyl-carbonitrene (formed by cleavage of N_2 from 2-adamantyl carbonazidate) (Fig. 5).

Similarly, the geometries of complexes **B**, **C**, and **D** were optimized for three conformers of 2-adamantyl-carbonitrene,

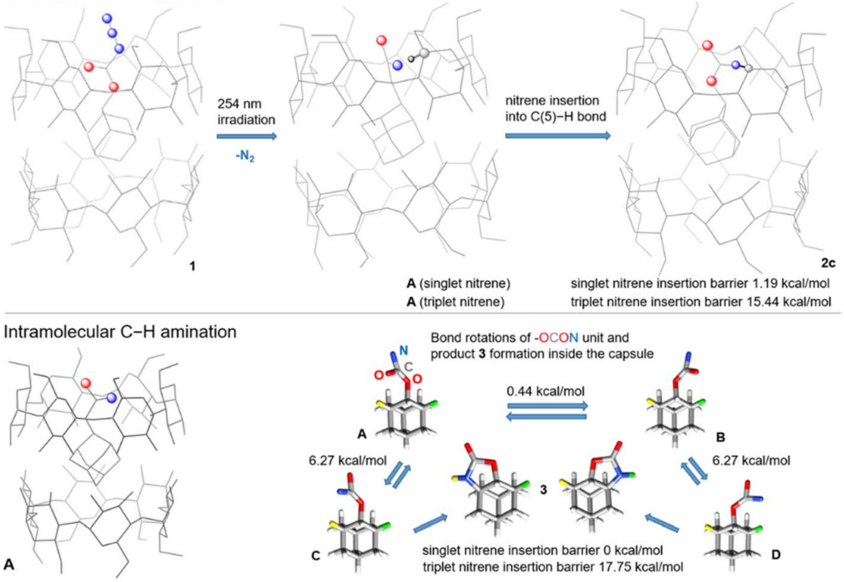

Fig. 5 Model structure **A**, the reactive nitrene intermediate, was generated from the X-ray structural analysis of **1**. For clarity, the computationally modelled (M06L DEF2-SVP D3ZERO DEFGRID3) complexes **B**, **C** and **D** are visualised without the host capsule. Product **3** that is generated inside the capsule is also visualised without the host capsule.

which were formed by rotating the C–O–C–H torsion angle (from ∼−47° to +41°) or by rotating the N–C–O–C torsion angle by 180°. An ∼0.44 kcal mol^{-1} energy barrier must be overcome during the transition between conformers **A** and **B**. During the transitions between conformers **A** and **C** (or **B** and **D**), an energy barrier of ∼6.27 kcal mol^{-1} must be overcome.

For the singlet nitrene, the resulting energies of complexes **A**, **C**, and **D** are almost the same (*ca.* 10 kcal mol^{-1} above the triplet ground state **A**). In the case of conformer **B**, the arrangement of the complex is stable only if the length of the C–H bond at the nearest cyclodextrin hydrogen is fixed. If it is not fixed, the spontaneous formation of the intermolecular product **2** occurs. In the case of conformers of 2-adamantyl-carbonitrene **A**, **C**, and **D**, the formation of the intermolecular product cyclodextrin derivative **2** occurs after overcoming a small energy barrier of ∼1 kcal mol^{-1}. 2-Adamantyl-carbonitrene can always react with several surrounding (C5–H) hydrogens of α-cyclodextrin, which are at almost the same distance. Conformers of 2-adamantyl-carbonitrene **C** and **D** also enable the formation of the intramolecular product carbamate **3**. This is a nearly barrier-free process.

It should be mentioned that information is lacking on whether the 2-adamantyl carbonitrene is in the singlet or triplet state after irradiation of 2-adamantyl carbonazidate and N_2 cleavage. Studies whether experimental[20] or theoretical[40,41] are relatively scarce. Based on them, it can be concluded that a transition to the singlet excited state should primarily occur, which merges with the ground singlet state at larger distances between N_2 and the nitrene.[40,41] Thanks to the crossing of energy surfaces and the so-called singlet–triplet coupling, transitions to the energetically lower-lying triplet state gradually occur.[40,41] Therefore, we performed *ab initio* calculations for the triplet state as well.

The **B**, **C**, and **D** conformers lie slightly above (+1.07–5.71 kcal mol^{-1}) the **A** ground state. Calculations show that the triplet reaction mechanism is relevant; however, during hydrogen abstraction, a non-negligible energy barrier of ∼15.44 kcal mol^{-1} must be overcome, which should be significantly lowered due to the tunneling effect.[42–48] Nevertheless, it does not seem that the triplet reaction mechanism should prevail or even be exclusive for the formation of the intermolecular cyclodextrin derivative **2** product. We expect that the singlet and triplet reaction channels rather combine and complement each other. Similarly, regarding the intramolecular product carbamate **3**, *ab initio* calculations show that in the case of the triplet nitrene, H-abstraction is hindered by a large energy barrier of ∼17.75 kcal mol^{-1}.

In summary, with the help of computer modelling, we obtained structures of complexes consisting of two α-cyclodextrins and either singlet or triplet 2-adamantyl-carbonitrene in conformations **A**, **B**, **C**, and **D**, with several products of either intermolecular (cyclodextrin derivative **2**) or intramolecular reactions (both enantiomers of carbamate **3**) and transition states along the reaction paths. The energies explain why different products are differently populated, *i.e.*, intermolecular cyclodextrin derivative **2** (95%), the major intramolecular carbamate **3** enantiomer (0.75 × 5%) and the minor intramolecular carbamate **3** enantiomer (0.25 × 5%).

The formation of the dominant intermolecular cyclodextrin derivative product **2** occurs because the highly reactive nitrene, whether in its singlet or triplet form, always has several α-cyclodextrin (C5–H) hydrogens in its vicinity to react with. The positioning of the reaction intermediate in the crystal structure is ideally suited for the formation of this intermolecular cyclodextrin derivative product **2**. For the formation of the intramolecular carbamate product **3**, one or two conformational changes of 2-adamantyl-carbonitrene must occur with energy barriers higher than the energy barriers of the singlet reactions themselves. It seems that the formation of reaction products can occur predominantly with the singlet nitrene.

Taken together, the relative population of reaction products is determined by the height of the energy barriers that need to be overcome during the conformational transitions that precede the insertion reaction. Questions that have not yet been answered, because they push the limits of experimental and computational accuracy, are whether the conversion of singlet to triplet nitrene is faster than the C5–H singlet nitrene insertion reaction and the ratio of insertions proceeding *via* the singlet and triplet pathways. From a synthetic point of view, this work represents the first regioselective C–H functionalisation of the interior of the α-cyclodextrin cavity. This C–H functionalisation method *via* the insertion reaction of electron-deficient species generated inside a supramolecular assembly can be applied to other cyclodextrins in the future and is not limited to amination reactions. The critical step is the co-crystallisation of the photochemically labile precursor inside the cyclodextrin capsule. The resulting derivatives, in which the guest molecule is covalently bound to the cyclodextrin and permanently fills its cavity, can be used in applications where weak host–guest interactions are undesirable.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): experimental procedures, compound descriptions, X-ray data and copies of NMR spectra. See DOI: https://doi.org/10.1039/d5ob01545f.

CCDC 2411472 contains the supplementary crystallographic data for this paper.[49]

Acknowledgements

This work has been supported by the Charles University within the Cooperatio Program.

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