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Stabilization of Allylic Amine N-Oxide through Cocrystallization with Pyrogallol[4]arene

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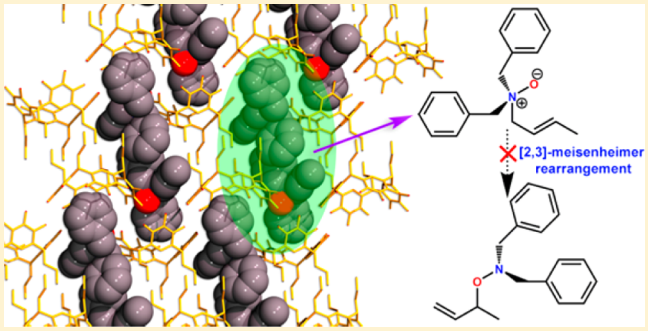
Supporting Information

ABSTRACT: An active allylic amine N-oxide (ANO) molecule was cocrystallized with pyrogallol[4]arene through intermolecular hydrogen bonds and $\pi\cdots\pi$ interactions. Interestingly, [2,3]-Meisenheimer rearrangement of the ANO was suppressed, which was analyzed in detail in the solid state by single crystal X-ray crystallography in varying temperatures. Additionally, this work provides not only a new strategy to stabilize reactive chemicals, but also a unique method to elucidate their structures.

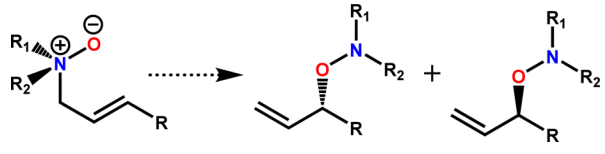


A cocrystal is a crystalline structure composed of more than two components, which interact through noncovalent interactions including hydrogen bonding, ionic interactions, van der Waals interactions, and $\pi\cdots\pi$ interactions.[1−4] Recent studies reveal that the cocrystallization strategy has been determined to be a powerful tool for tailoring the physiochemical properties of the individual components. Based on this strategy, less sensitive energetic explosives,[5−9] pharmaceuticals with enhanced bioavailability,[10−13] as well as other functional materials have been reported in recent years.[14−20]

C-Alkylpyrogallol[4]arene (abbreviating as PgC_n, where n is the length of the associated alkyl tail) contains four 1,2,3-trihydroxybenzene groups linked together by −CHR− units to form bowl-shaped molecules.[21] Along the upper rim of the molecule there are 12 hydroxyl groups, which have the ability to participate in not only coordinative bonding with different metal ions,[22−27] but also hydrogen bonding with various components.[28,29] In addition, the flexibility and affinity of the bowl also allow the PgC_ns to encapsulate other guest molecules.[30−39] These virtues make them ideal candidates to prepare cocrystals with interesting properties. For example, (1) the cocrystallization of pyrene butyric acid (PBA; a fluorescent probe molecule) with PgC_6 forms a hexameric nanocapsule.[30] Single-crystal X-ray diffraction suggests that two PBA guests were well separated in the host through specific interactions with the capsule walls, and spectroscopic studies reveal that the PBA molecules avoided quenching by the dimethylaniline (DMA), a known fluorescence quencher. (2) Pharmaceutical gabapentin can also cocrystallize with PgC_n to form active pharmaceutical ingredient (API) cocrystals.[31] Interestingly, the slight change of solvent or of the tail group in the PgC_n could affect the ratio of gabapentin and PgC_n in these supramolecular architectures. (3) The controlled crystallization of PgC_1 with ferrocene has resulted in the PgC_1Cferrocene dimer and nanotube frameworks, which provide an important prototype for exploring the relations between structures and magnetic properties.[32]

Stabilization of active species has attracted considerable attention,[40−44] which not only allows us to characterize and store these active species,[45−50] but also has potential applications such as drug delivery, catalysis reaction, and mechanistic research of chemical reactions.[13,51,52] Allylic amine *N*-oxides (ANOs), a kind of active species, can easily undergo thermal [2,3]-Meisenheimer rearrangement to produce synthetically useful allylic alcohol products (Scheme 1).[53−56] In the present work, the ANO and pyrogallol[4]arene chosen for cocrystallization are *N*,*N*′-dibenzyl-*N*-(trans-but-2-enyl)amine *N*-oxide (DBANO) and *C*-propylpyrogallol[4]arene (PgC_3), respectively (Figure 1). Interestingly, the [2,3]-Meisenheimer rearrangement of DBANO was suppressed, which was

Scheme 1. [2,3]-Rearrangement of Allylic Amine *N*-Oxides (ANOs)



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determined by single crystal X-ray crystallography at different temperatures.

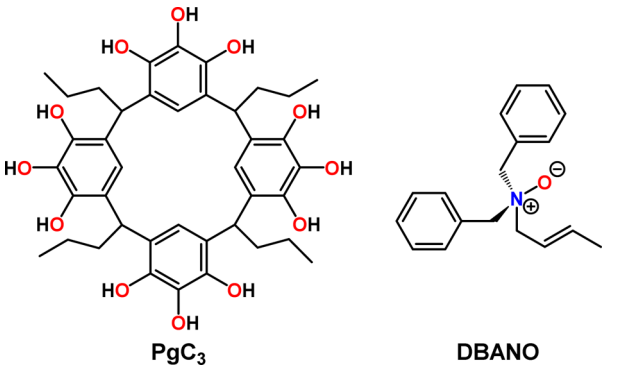

Figure 1. Chemical structure of *C*-propylpyrogallol[4]arene (PgC_3) and *N*,*N*′-dibenzyl-*N*-(trans-but-2-enyl)amine *N*-oxide (DBANO).

PgC_3 and DBANO are prepared according to the previously reported procedures. The former can be obtained by condensation reaction of Pg and butanal catalyzed by concentrated hydrochloric acid,[27] while the latter is synthesized in two steps: a Pd·Et_3B-catalyzed C−N bond formation reaction between dibenzylamine and 2-buten-1-o1 gave the dibenzyl-but-2-en-1-amine, which was further oxidized by metachloroperbenzoic acid (*m*CBPA) to afford the DBANO.[57,58] Since DBANO had the propensity to undergo thermal [2,3]-sigmatropic rearrangement at room temperature, the preparation of cocrystal **1** was under low temperature. Especially, cocrystal **1** was prepared by mixing 0.01 M methanol solution of DBANO and 0.01 M acetone solution of PgC_3 in a 1:1 ratio. The solution was permitted to crystallize by slow evaporation at 253 K for 3 days, and afforded colorless block crystals in 95% yield. Single-crystal X-ray diffraction studies at 273 K reveal that cocrystal **1** is crystallized in the triclinic space group $P\bar{1}$ with cell parameters a = 12.4557(3) Å, b = 15.7937(4) Å, c = 15.8516(4) Å, α = 74.969(2)°, β = 70.023(2)°, γ = 82.963(2)°, V = 2828.47(13) $Å^3$ (Table S1). The asymmetric unit contains one DBANO, one PgC_3 (Figure 2), and some disordered solvents, whose contribution has been subtracted from the diffraction data by the SQUEEZE command in PLATON.[59] One phenyl group of DBANO molecule is inside the bowl of the PgC_3 molecule. There are four intramolecular hydrogen bonds between upper-rim hydroxyl groups of the PgC_3 molecule with O···O distance in the range of 2.695−2.681 Å and angle of O−H···O in the range of 167.42−176.45° (Figure S1). The bowl is slightly pinched, and the cross-sectional separations (measured between the opposing, middle carbon atoms on the upper rim of the PgC_3) are 8.89 and 8.12 Å, respectively (Figure S2).

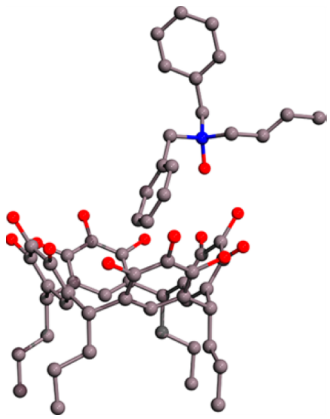

Figure 2. Asymmetric unit of cocrystal **1**. Hydrogen atoms are omitted for clarity. Blue (nitrogen), red (oxygen), and carbon (gray).

Further inspection of the environment of the DBANO molecule, it is found that two nearby DBANO molecules are assembled through $\pi\cdots\pi$ interaction with a distance of 4.341 Å to form a supramolecular dimer, which is surrounded by eight PgC_3 molecules (Figure 3a). The above-mentioned two molecules have the same environment, and thus we only provide one as a generic description. Except for the aforementioned $\pi\cdots\pi$ interactions between the DBANO supramolecular dimer, there still exists one hydrogen bond, one $\pi\cdots\pi$ interaction, and two C−H···π interactions (Figure 3b). The hydrogen bond is between the phenolic hydroxyl group of PgC_3 molecule and the oxygen of DBANO molecule with O···O distance of 2.625 Å and O−H···O angle of 170.2°. The $\pi\cdots\pi$ interaction is between the inside aromatic group of the DBANO and one aromatic group of PgC_3, which is almost parallel to the former one, with a distance of 3.979 Å. The C−H···π interactions are between two hydrogen atoms on the inner DBANO molecule's phenyl group and two aromatic groups from PgC_3 molecule with C−H···π distances of 2.598 and 3.058 Å, respectively. It can be speculated that these weak interactions would stabilize the active DBANO molecule.

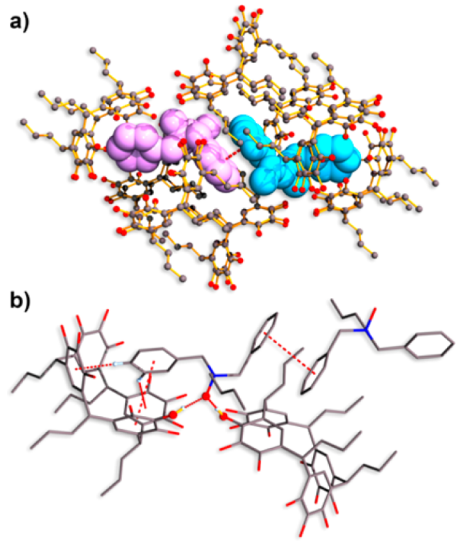

Figure 3. (a) Surrounding environment of DBANO supramolecular dimer, and (b) Intermolecular hydrogen-bonding pattern, $\pi-\pi$ and C−H···π effect pattern in cocrystal **1**.

The examination of the extended structure of cocrystal **1** reveals that the PgC_3 molecules assemble into a skewed bilayer array (Figure 4), which is typical in the PgC_n cocrystal system.[36] The interstices of the bilayer are filled with DBANO supramolecular dimers and disordered solvent molecules.

As mentioned above, DBANO is reactive and can undergo thermal [2,3]-Meisenheimer rearrangement to produce allylic alcohol product under room temperature. Surprisingly, single crystal X-ray crystallography revealed that the cell parameters of cocrystal **1** changed slightly in the range of 273−353 K, and the DBANO molecules in cocrystal **1** maintained its structure

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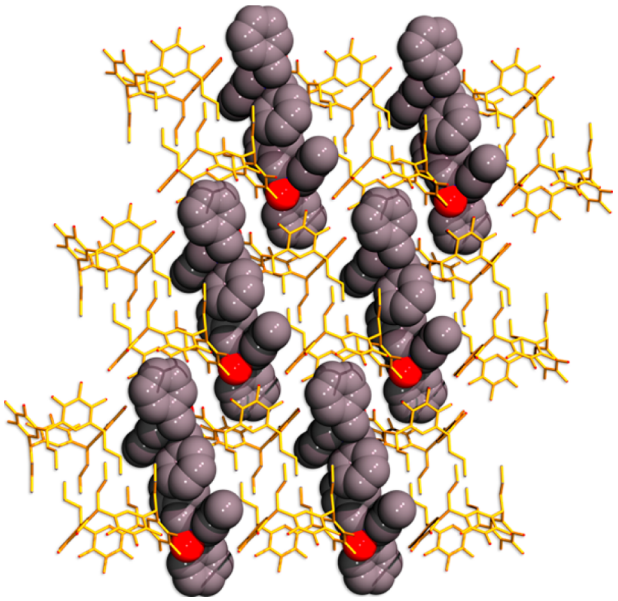

Figure 4. Packing of cocrystal viewing along *a* axis; DBANO molecules are shown in space-filled representations.

(Table 1 and CIFs (CCDC 1568808−1568813). Notably, the increment in the cell volume (cal. 84.3 Å^3) of cocrystal **1** at 353 K with respect to 273 K was studied by Hirshfeld surface analyses (Figures S3−S5 in SI).[60,61] The dispersive H···H interactions have the greatest participation in the crystal structure of cocrystal **1** compared to the other interactions, and the increment in the cell volume can be mainly ascribed to the change of H···H interactions in the above-mentioned temperatures (60.5% and 59.8% in cocrystal **1** at 353 and 273 K, respectively). Moreover, the crystals of cocrystal **1** did not lose crystallinity even keeping them at room temperature for a year, and the DBANO molecules could also be observed by single crystal X-ray crystallography. These results suggest that cocrystal **1** was stable and the [2,3]-Meisenheimer rearrangement of DBANO in cocrystal **1** was suppressed. We consider that the supramolecular interactions including intermolecular hydrogen bonds, $\pi\cdots\pi$ as well as the C−H···π interactions between DBANO and PgC_3 molecules hamper the rearrangement of DBANO. To the best of our knowledge, encapsulation of the reactive species in supramolecular containers including metal coordination capsules, covalently bonded capsules and hydrogen-bonded capsules, has been documented to be an excellent method to stabilize them.[43] In contrast, exploration on stabilization of reactive species through host−guest interaction by utilizing supramolecular macromolecules is still minimal.[62,63] In addition, although PgC_ns can assemble with different guests to form cocrystals with functional properties, stabilization of reactive chemicals with PgC_ns by utilizing cocrystallization method has still not been reported. Thus, cocrystal **1** provides not only a unique example to stabilize thermally unstable chemicals, but also a new method to solve their structures.

In summary, we present the preparation of novel cocrystal composed of DBANO and PgC_3 molecules. Single crystal X-ray diffraction studies suggest that the cocrystal was very stable and the [2,3]-Meisenheimer rearrangement of DBANO was suppressed, which may be ascribed to the supramolecular interactions between these two components. Further work is focusing on stabilization of different reactive chemicals by using this cocrystallization method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b01136.

Synthetic details, characterization, and additional figures (PDF)

Accession Codes

CCDC 1568808−1568813 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Table 1. Crystal Data and Structure Refinement for Cocrystal 1 at Different Temperatures[a]

T/K	*a* (Å)	*b* (Å)	*c* (Å)	*α* (deg)	*β* (deg)	*γ* (deg)	V (Å^3)	R_1	wR_2
273	12.4557(3)	15.7937(4)	15.8516(4)	74.969(2)	70.023(2)	82.963(2)	2828.47(13)	0.0512	0.1495
293	12.5877(4)	15.8623(5)	15.9762(4)	74.963(3)	69.967(3)	82.728(3)	2891.83(16)	0.0527	0.1503
293[b]	12.5863(5)	15.8464(5)	15.9829(4)	74.985(3)	69.991(3)	82.864(3)	2890.84(17)	0.0540	0.1548
313	12.5928(5)	15.8214(5)	15.9924(4)	75.015(3)	69.981(3)	82.878(3)	2889.74(17)	0.0534	0.1530
333	12.6358(7)	15.6845(9)	16.1021(9)	74.940(5)	69.525(5)	82.580(5)	2884.3(3)	0.0626	0.1663
353[c]	12.6965(16)	15.7676(13)	16.0920(11)	74.969(7)	69.575(9)	82.507(8)	2912.8(5)	0.0717	0.1742

[a]Note: Cocrystal **1** was kept at the desired temperature for 30 min before data collection. [b]Cocrystal **1** was put at room temperature for a year before data collection. [c]Cocrystal **1** was put in 353 K for 5 h before data collection.

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