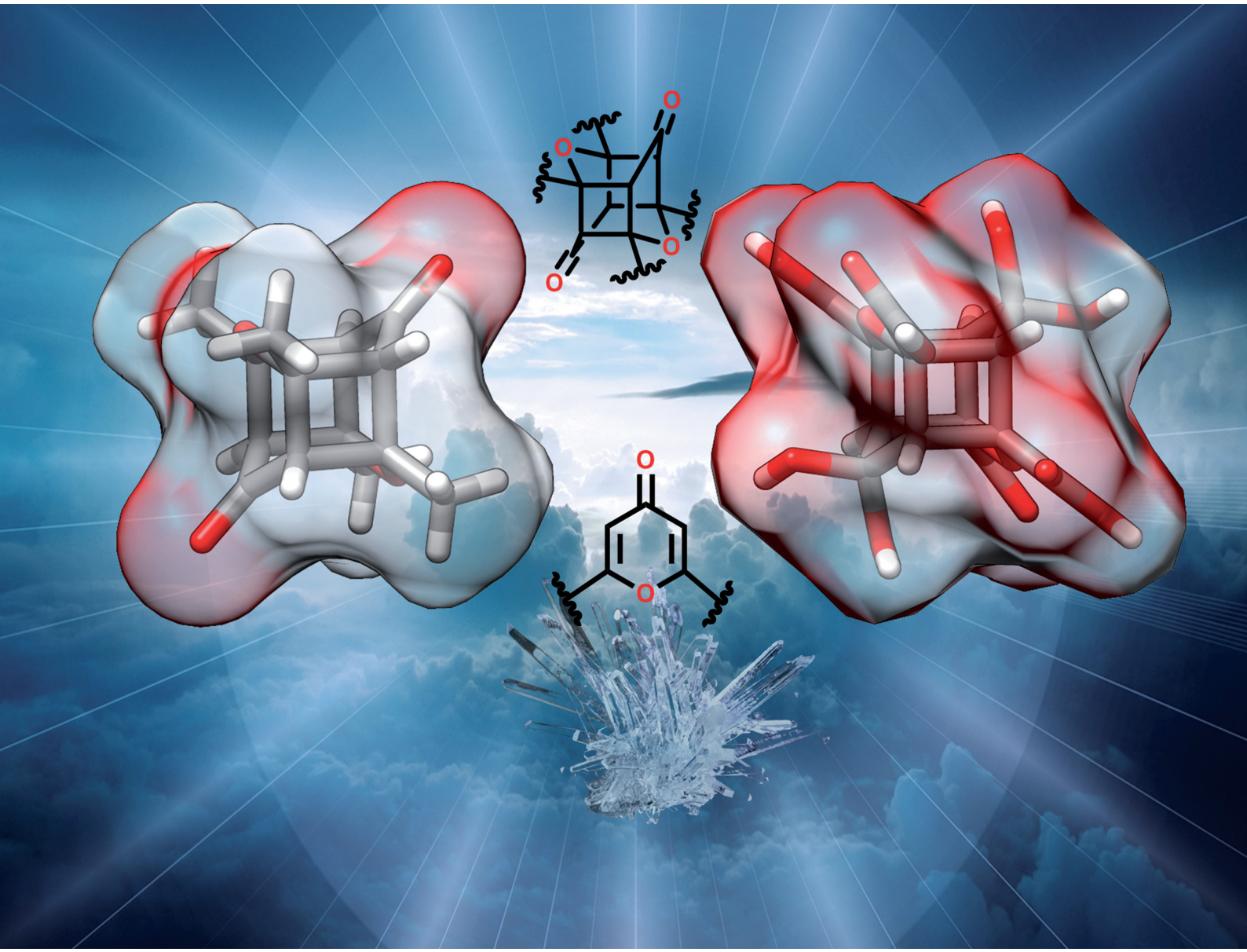
Volume 57
Number 55
14 July 2021
Pages 6697–6822

ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

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ChemComm

COMMUNICATION

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Cite this: *Chem. Commun.*, 2021, **57**, 6725

Received 25th May 2021,
Accepted 7th June 2021

DOI: 10.1039/d1cc02725e

rsc.li/chemcomm

Cubane-forming cyclic dienes that exhibit orthogonal reactivities in the solid state†

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Photoirradiation of a binary cocrystal composed of two different cyclic dienes generates a highly-symmetric cubane-like tetraacid cage regioselectively and in quantitative yield. The cage forms by a double [2+2] photodimerization of one of the diene cocrystal components. The second diene while photostable in the cocrystal reacts in a double [2+2] photodimerization as a pure form quantitatively to form a tetramethyl cubane-like cage. The stereochemistry of the cage is structurally authenticated.

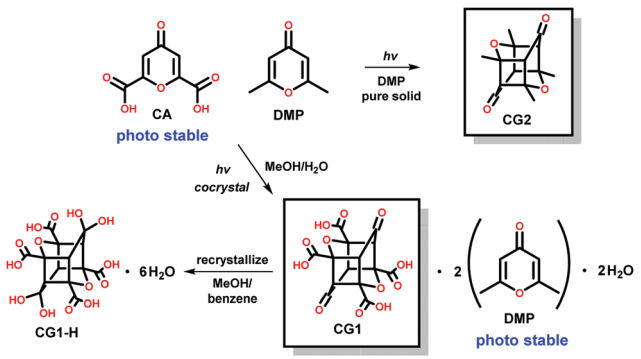
Cocrystals are proving successful to support the assembly of alkenes in the solid state that undergo intermolecular [2+2] photocycloadditions.[1] In addition to rules on geometry criteria for a photocycloaddition to occur as delineated by Schmidt,[2] the last century witnessed work that described the formation of rigid three-dimensional (3D) cubane-like cages from photodimerizations of cyclic dienes, and more specifically pyrones, in the solid state.[3] Uses of cocrystals to enable photodimerizations in organic solids have typically involved linear alkenes cocrystallized with photoinert coformers (*e.g.*, resorcinols),[4] and there has been only a single report on the formation of a cage using the cocrystal approach.[5]

Here we report a novel binary cocrystal composed of two cyclic dienes with one component that reacts to generate the photodimeric cubane-like tetraacid cage **CG1**.[6] The cocrystal consists of chelidonic acid (**CA**) and 2,6-dimethyl-4-pyrone (**DMP**) with the diacid undergoing a double [2+2] photodimerization to generate **CG1** regioselectively and in quantitative yield (Scheme 1). We are unaware of a cocrystal composed of two 4-pyrones. We also report on the first structural authentication of the cubane-like tetramethylated cage **CG2** that has hitherto remained unreported and is generated from pure solid **DMP**.[3a,c]

Cubanes,[7] and cubane-like cages (*i.e.*, tetraasterane,[8] hexaprismane,[9] basketane[10]), are important constructs[11] and structural motifs in organic synthesis,[12] medicinal chemistry,[13] and material science.[14] Carboxylic acid functionalized cubanes, for example, can find applications as crosslinking agents for drug delivery.[15] Despite many efforts, however, accessibility to cage compounds analogous to cubane and related hydrocarbons remains limited.[12] Indeed, efforts toward the syntheses of highly functionalized cubane structures can offer new opportunities to pharmaceutics and beyond.

We initially determined diacid **CA** (Honeywell Research Chemicals) to be photostable as a pure form. When **CA** (55 mg, 0.30 mmol) was crystallized from tetrahydrofuran (THF) (5 mL), colorless irregular prisms of **CA·THF** formed upon slow evaporation over a period of 2 days.

A single-crystal X-ray analysis (SCXRD) (150 K) showed **CA** and the THF molecules to crystallize in the monoclinic space group $P2_1/c$ (Fig. 1). The asymmetric unit contains one **CA** and one THF molecule that interact *via* O–H(acid)···O (solvent) hydrogen bonds (O4···O7 2.581(2) Å). The diacids self-assemble as bent dimers that form a tape structure sustained by O–H···O hydrogen bonds (O2···O3 2.560(2) Å) (Fig. 1a). The tapes run parallel to the *b*-axis with neighboring **CA** molecules



Scheme 1 Solid-state constructions of **CG1** (binary cocrystal) and **CG2** (pure solid).

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† Electronic supplementary information (ESI) available. CCDC 2082537–2082540. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc02725e

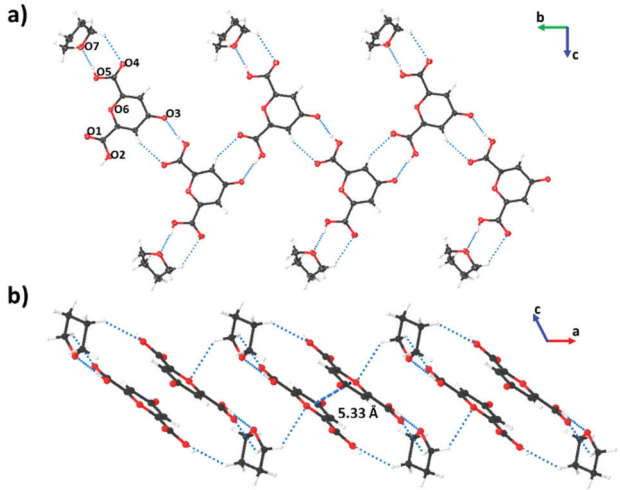

Fig. 1 X-Ray structure **DMP·THF**: (a) tape and (b) ht-stacked **CA** of adjacent tapes.

stacked offset face-to-face and head-to-tail (ht). The shortest distance between two stacked **CA** rings is 5.33 Å (plane-to-plane) (Fig. 1b).

CA·THF loses the entrapped THF solvent molecules under ambient conditions to generate non-solvated **CA** within periods of minutes. Powder X-ray diffraction (PXRD) showed the resulting solid to be of the same crystalline phase as the commercial solid (Fig. S4, ESI†). When subjected to UV-radiation (150 h), both the desolvated and commercial solids were photostable (Fig. S1, ESI†).

By contrast, cocrystallization of **CA** with **DMP** affords the cocrystal dihydrate **CA·DMP·2H$_2$O** wherein **CA** is photoactive. Single crystals as colorless prisms were obtained by slow evaporation of a MeOH/H$_2$O (1 : 1) solution of **CA** (50 mg, 0.27 mmol) and **DMP** (33.7 mg, 0.27 mmol) over a period of 3 days. The composition of **CA·DMP·2H$_2$O** was confirmed by SCXRD and ^{1}H NMR spectroscopy (Fig. S3, ESI†).

The components of **CA·DMP·2H$_2$O** crystallize in the triclinic space group $P\bar{1}$ (Fig. 2). The asymmetric unit consists of one **CA**, one **DMP** and two H$_2$O molecules. **CA** and **DMP** interact *via* a combination of O–H···O (O4···O7 2.451(3) Å) and C–H···O (C14···O3 3.390(3) Å) hydrogen bonds. The primary **CA·DMP** unit is extended along the *c*-axis to form a planar structure with hydrogen-bonded water dimers in interstices, interacting by O–H···O (O9···O10 2.653(2) Å) hydrogen bonds (Fig. 2a). **CA** also interacts with one water molecule by an O–H···O (O1···O9 2.471(2) Å) hydrogen bond. Adjacent planar structures assemble such that **CA** molecules stack face-to-face and in a ht geometry (Fig. 2b). The C=C bonds of each ht stacked **CA** pair lie approximately parallel and separated by 3.65 Å (centroid–centroid), which conforms to the criteria for a [2+2] photodimerization.[2] **CA** molecules also participate in offset face-to-face stacks with neighboring **DMP** molecules, being in a head-to-head (hh) geometry with C=C bonds separated by 4.52 and 4.71 Å (centroid–centroid). Overall, the structures display offset ABBA-like stacking (dark/light gray) approximately parallel to the *ab*-plane (Fig. 2c).

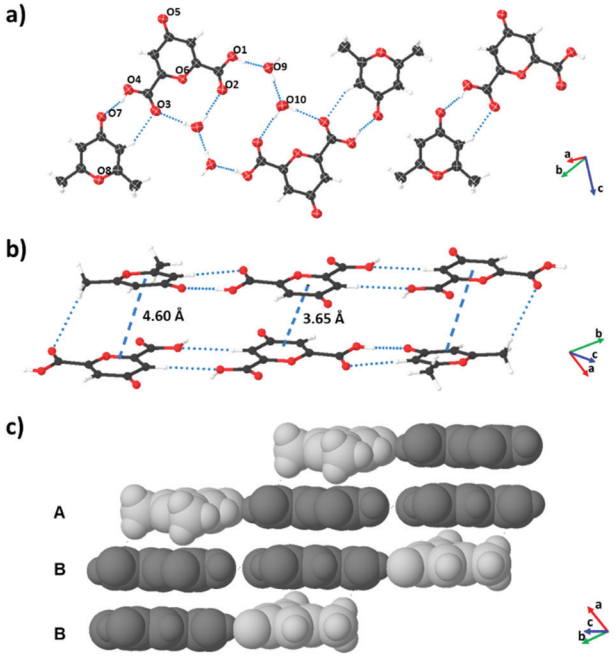

Fig. 2 X-Ray structure **CA·DMP·2H$_2$O**: (a) hydrogen-bonded layer, (b) ht stacking of **CA**, and (c) space-filling of diene stackings (**CA** pairs highlighted dark).

When a powdered crystalline sample of **CA·DMP·2H$_2$O** was subjected to UV-radiation (450 W medium pressure Hg lamp) for a period of 90 hours, the C=C bonds of **CA** reacted quantitatively. The generation of a photoproduct was evidenced in an ^{1}H NMR spectrum by disappearance of the olefinic signal of **CA** at 7.01 ppm and appearance of a cyclobutane signal at 3.56 ppm in D$_2$O (Fig. S3, ESI†). The position of the cyclobutane peak is consistent with a double photodimerization of **CA** to form **CG1**.[16]

The stereochemistry of **CG1** was confirmed by SCXRD. Specifically, when the photoreacted solid (40 mg) was recrystallized in hot MeOH and benzene (2 : 1, v/v), single crystals as colorless plates formed over a period of 3 days.

The crystallization resulted in the hydration of the keto groups of **CG1** to form crystalline (**CG1-H**)**·6H$_2$O**. The cage and water molecules assemble in the triclinic space group $P\bar{1}$ with half a **CG1-H** molecule and three waters in the asymmetric unit. The cubane-like cage, which sits on a crystallographic center of inversion, is defined by four oxane rings interlinked by two parallel cyclobutane rings (Fig. 3a). The oxane rings are in an approximate boat-shaped conformation, with the four carboxylic acid groups pointing away at the corners. **CG1-H** interacts with the water molecules *via* a network of O–H···O hydrogen bonds to give a 3D hydrogen-bonded framework (Fig. 3b) (O1···O3A 3.124(4) Å; O1···O2A 3.233(5) Å; O2···O1A 2.623(2) Å; O3···O3A 2.801(6) Å; O4···O2A 2.688(7) Å; O5···O3A 2.657(5) Å; O5···O7 2.605(5) Å; O6···O2A 2.871(6) Å; O7···O3A 3.151(5) Å; O7···O5 2.605(5) Å).

While **DMP** is photostable in **CA·DMP·2H$_2$O** and effectively serves to enable photoactivity of **CA**, as a pure solid is photoactive. **DMP** (CSD refcode: HAXDAL)[17] stacks face-to-face in a ht

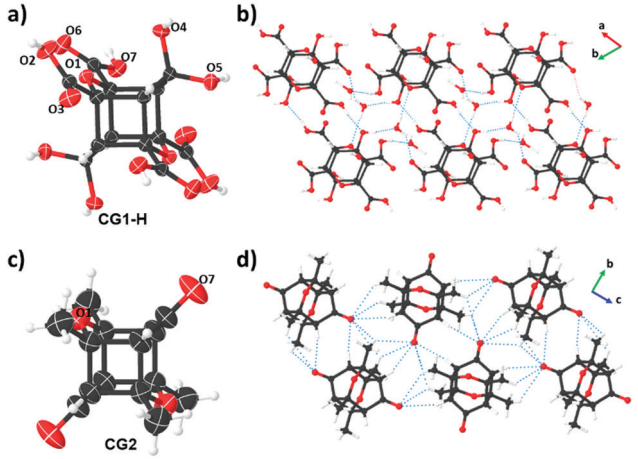

Fig. 3 X-Ray structures cubane-like cages: (a) **CG1-H**, (b) hydrogen-bonded framework of **CG1-H** with water, (c) **CG2**, and (d) hydrogen-bonded framework of **CG2**.

orientation with the C=C double bonds parallel and separated by 3.46 Å. When pure **DMP** was irradiated for a period of 140 hours **CG2** formed in quantitative yield, which contrasts the original report (yield: *ca.* 30%).[3a,c]

When the photoreacted solid (20 mg) was recrystallized from chloroform (5 mL), colorless prisms formed. A SCXRD analysis revealed **CG2** to crystallize in the orthorhombic space group *Cmce* (Fig. 3c). Similar to **CG1-H**, **CG2** is composed of two cyclobutane rings and four boat-shaped pyrone rings. In contrast to **CG1-H**, adjacent **CG2** cages interact through intermolecular C–H···O hydrogen bonds (O1···C6 3.652(2) Å; O7···C3 3.537(3) Å; O1···C5 3.527(2) Å; O1···C6 3.745(2) Å; O1···C6 3.652(2) Å) to form, as compared to **CG1-H**, a 3D hydrogen-bonded framework (Fig. 3d).

In conclusion, we have revealed the solid-state construction of a cubane-like tetraacid cage **CG1** from **CA**, which is photostable as a pure solid, *via* a binary cocrystal composed of two cyclic dienes. While **DMP** is photostable in the cocrystal, pure **DMP** reacts to generate the cage **CG2**. The orthogonal reactivities of the dienes provide an intriguing example of a relationship between structurally similar molecules with a capacity to photodimerize as pure solids *versus* cocrystals. We expect our study to expand fundamental principles and applications of cocrystals as organic materials to access complex cyclobutane products, and particularly cubanes. We are currently exploring the crystal landscape of cocrystals based on cyclic dienes and higher-order cyclic alkenes.

We gratefully acknowledge the National Science Foundation (LRM DMR-1708673 & CHE-1828117) and University of Iowa Graduate College (CAL Fellowship) for financial support.

Conflicts of interest

The authors declare no conflicts of interest.

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