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Structure and absolute configuration of liquid molecules based on adamantane derivative cocrystallization†

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Liquid molecules are difficult to crystallize, and their structures and absolute configurations cannot be directly determined by X-ray crystallography. We herein report the rapid cocrystallization of tetraaryladamantanes with liquid molecules. The structure of the liquid small molecules can be obtained by determining the crystal structure of the cocrystallized compound. The absolute configuration of chiral molecules can also be assigned, which cannot be accomplished by other methods such as nuclear magnetic resonance. In this paper, liquid compounds such as phenylethanol and phenylpropanol derivatives were selected. 1,3,5,7-Tetrakis(2,4-diethoxyphenyl)adamantane (TEO) powder was heated and dissolved in liquid molecules and allowed to stand overnight to undergo cocrystallization. The results show that the single-crystal structures and the absolute configurations of 16 liquid molecules were determined by cocrystallization, and the homochiral natures of chiral compounds were confirmed by solid circular dichroism spectral measurements.

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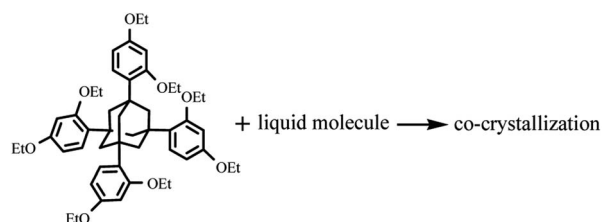
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Introduction

When a new compound is synthesized or isolated, it is usually characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and infrared spectroscopy, which provide essential information regarding its molecular formula, functional groups, and bond connectivities. However, the absolute stereochemistry of enantiomers was not obtained by the above methods. The most powerful method to determine molecular information is X-ray single-crystal diffraction. However, X-ray crystallography requires a crystal for analysis, and many small or highly flexible molecules, such as liquids or amorphous solids, do not crystallize readily. Chemists are searching for new methods to obtain accurate information on molecular structures. A particularly significant “crystalline sponge method” for the structural determination of noncrystalline compounds by X-ray single-crystal diffraction was reported by Fujita and coworkers.^{1–7} The crystal sponge most frequently employed in their studies was the metal–organic framework $\{[(\text{ZnI}_2)_3(\text{tris}(4\text{-pyridyl})\text{-}1,3,5\text{-triazene})_2]_x(\text{solvent})\}_n$. However, the crystal

sponges reported thus far are based on metal–organic frameworks, and their limitations are as follows: first, when the size of the target molecule is larger than one of the pores, the target molecule does not enter the crystal sponge. Second, it is difficult for hydrophilic molecules to enter the hydrophobic pores, and the “crystal sponge method” has been mainly applied to the determination of hydrophobic molecular structures. Several methods are being pursued to address these limitations. Recently, another particularly significant method using “cocrystallization chaperones” was presented. These crystallization chaperones, including tetraaryladamantanes^{8–19} and trimesic acid,^{20–27} readily form crystalline inclusion complexes with a range of guest molecules and provide accurate structural information on difficult-to-crystallize small molecules. Meanwhile, the high-throughput nanoscale crystallization of organic-soluble small molecules (encapsulated nanodroplet crystallization) was reported.²⁸ However, the cocrystallization of universal chaperones with various small molecules, such as porphyrins,



Scheme 1 Cocrystallization of TEO with liquid small molecules.

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calixarenes, or cyclodextrins, with a proven ability to obtain the structure of a broad range of different organic molecules is yet to be reported.¹² Here, we report the rapid cocrystallization of 1,3,5,7-tetrakis(2,4-diethoxyphenyl)adamantane (TEO) with liquid small molecules (Scheme 1), such as phenylethanol and phenylpropanol derivatives, and determine the absolute configuration of chiral small molecules.

Experimental section

Materials and physical measurements

1,3,5,7-Tetrakis(2,4-diethoxyphenyl)adamantane (TEO) was customized by WuXi AppTec (Tianjin, China). All of the other chemicals are commercially available and used without further purification. The solid circular dichroism (CD) spectra were recorded in the 200–350 nm region using a JASCO J-815 spectropolarimeter.

General methods for cocrystallization

Approximately 2 mg of solid TEO (0.0025 mmol) in a cylindrical sample bottle (1 mL) was added to approximately 40 mg of liquid analyte (2 drops). The resulting suspension was heated on a hot plate until a clear solution formed. The resulting solution was allowed to cool to room temperature with the sample bottle on the plate. After 12 h, colorless prism- or block-shaped crystals were obtained and then analysed by X-ray single-crystal diffraction.

X-ray crystallography

Single-crystal data were collected on a Bruker Apex II diffractometer at 296 K using Mo-K α radiation ($\lambda = 0.71073$ Å) or on a SuperNova Dual AtlasS2 diffractometer at 150 K using Cu-K α radiation ($\lambda = 1.54184$ Å). All empirical absorption corrections were applied by the SADABS program²⁹ or CrysAlisPro (Rigaku, V1.171.39.46, 2018). The structures were solved by direct methods, which yielded the positions of all nonhydrogen atoms. These were refined first isotropically and then

anisotropically. All nonhydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model. All calculations were performed using the SHELXTL system of computer programs.³⁰ Most of the guest molecules are disordered in cocrystallization. The crystallographic data are summarized in Table S1.† CCDC reference numbers 2126622 to 2126637 for **1–16**, respectively. See <http://www.rsc.org/suppdata/> for crystallographic data in CIF or other electronic format.

Results and discussion

We chose structurally similar liquid analytes, such as phenylethanol and phenylpropanol derivatives, for cocrystallization experiments with TEO. A mixture of the analytes and TEO without any solvent was heated for approximately 30 s on a laboratory hotplate until a clear solution formed. The resulting solution was left to cool to room temperature. Colourless crystals for X-ray diffraction were obtained after crystallization overnight, and the crystal structures of the liquid analytes were confirmed by X-ray crystallography. With most guest molecules, triclinic crystal systems and a host/guest ratio of 1 : 1 were found. However, with 1-(4-chlorophenyl)ethanol and 2-(4-methylphenyl)-1-propanol, TEO crystallized in a trigonal crystal system (Table S1†).

Successful examples can be found from the full list of 16 liquid small molecules tested in this study (Table 1), including a series of phenylethanol derivatives (**1a–1e**) (Fig. 1), phenylpropanol derivatives (**2a–2d**) (Fig. 2), ethylbenzylamine (**3a–3c**)

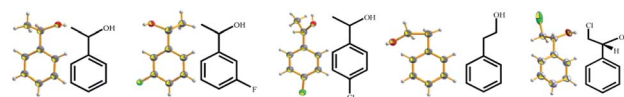


Fig. 1 X-ray crystal structures of liquid phenylethanol derivatives obtained by cocrystallization with TEO (ORTEP plots of the encapsulated molecules at the 50% probability level).

Table 1 Cocrystallization experiments of TEO and analytes

Serial No.	Analytes	Crystal system	R1	Flack values	Sample No.
1	Phenylethanol	Triclinic	0.064		1a
2	1-(3-fluorophenyl)ethanol	Triclinic	0.060		1b
3	1-(4-chlorophenyl)ethanol	Trigonal	0.081		1c
4	2-Phenylethanol	Triclinic	0.074		1d
5	(R)-(–)-2-chloro-1-phenylethanol	Triclinic	0.096	0.124(14)	1e
6	1-Phenyl-1-propanol	Triclinic	0.066		2a
7	(S)-(–)-1-phenyl-1-propanol	Triclinic	0.045	–0.01(4)	2b
8	(R)-(+)-1-phenyl-1-propanol	Triclinic	0.041	0.04(3)	2c
9	2-(4-methylphenyl)-1-propanol	Trigonal	0.071		2d
10	α -ethylbenzylamine	Triclinic	0.076		3a
11	(R)-(+)- α -ethylbenzylamine	Triclinic	0.048	0.06(5)	3b
12	(S)-(–)- α -ethylbenzylamine	Triclinic	0.067	0.03(8)	3c
13	2-Chloropyridine	Triclinic	0.062		4a
14	3-Chloropyridine	Triclinic	0.066		4b
15	Styryl acetate	Triclinic	0.065		5
16	Methacrylic acid	Triclinic	0.097		6



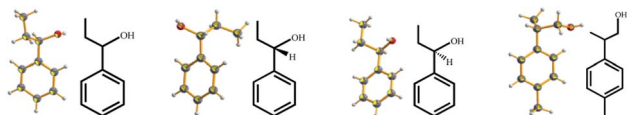


Fig. 2 X-ray crystal structures of liquid phenylpropanol derivatives obtained by cocrystallization with TEO (ORTEP plots of the encapsulated molecules at the 50% probability level).

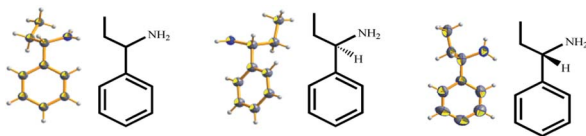


Fig. 3 X-ray crystal structures of liquid α -ethylbenzylamine obtained by cocrystallization with TEO (ORTEP plots of the encapsulated molecules at the 50% probability level).

(Fig. 3), isomers such as 2-chloropyridine (**4a**) and 3-chloropyridine (**4b**), styralyl acetate (**5**) used in fragrance and flavor, and methacrylic acid (**6**) (Fig. 4) applied to organic chemical raw materials and intermediates of polymers (Fig. 5). There are no covalent bonds or strong mutual interactions, such as hydrogen bonding between host and guest molecules in the asymmetric unit of the complex (Fig. 6). The liquid small molecules solidified and crystallized with the aid of TEO, and most of the liquid molecules were disordered due to the lack of mutual interactions with the host during cocrystallization. TEO can rapidly crystallize, perhaps due to its shape and symmetry, in which alkoxy groups can adopt different conformations to accommodate different guest molecules.¹⁴ However, a crystalline sponge needs to be preformed with a suitable crystal lattice for accommodating analytes. TEO solvated by liquid molecules can crystallize without any special interactions and encapsulate

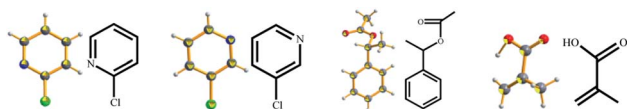


Fig. 4 X-ray crystal structures of other liquid analytes obtained by cocrystallization with TEO (ORTEP plots of the encapsulated molecules at the 50% probability level).

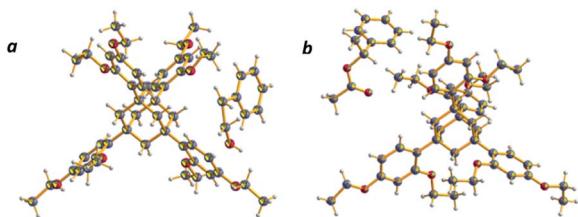


Fig. 5 Structure of representative cocrystals and 50% probability displacement ellipsoids for non-H atoms: (a) 2-phenylethanol/TEO and (b) styralyl acetate/TEO.

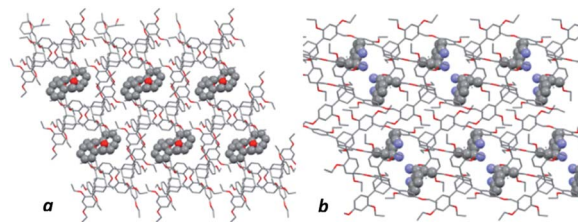


Fig. 6 Packing arrangement in representative cocrystals: (a) 1-phenyl-1-propanol/TEO and (b) α -ethylbenzylamine/TEO.

a broad range of molecules and would be a potential candidate for extended crystalline sponges.

Structurally similar liquid phenyl alcohols or amines were selected, including two pairs of enantiomers, namely, (*R*)- and (*S*)-1-phenyl-1-propanol (**2b** and **2c**) and (*R*)- and (*S*)- α -ethylbenzylamine (**3b** and **3c**). Flack parameters were in the range of $-0.01(4)$ to $0.124(14)$ (Table 1), allowing for the unambiguous assignment of absolute configuration. The absolute structure parameters are critical for determining the correct absolute configuration of the chiral guest molecule. The initial structural model was solved using SHELXTL programs, and the intensity data appeared to be centrosymmetric due to the strong reflexes originating from host molecules, although the encapsulated guest molecule was chiral. To resolve this conflict, it is necessary to introduce particular treatments according to previous reports.¹⁸ Compared to the above reports, the homochiral natures of chiral compounds were further confirmed by solid CD spectrum.

Circular dichroism spectra

The crystal samples were filtered, dried, and determined after grinding and pressing on a JASCO J-815 spectropolarimeter. The results of the selected solid circular dichroism measurements are consistent with the results of the X-ray crystal structures. As shown in Fig. 7a, the bulk crystals of **3b** showed negative and positive Cotton effects at 207 and 273 nm, respectively, and those of **3c** also showed positive (208 and 231 nm) and negative Cotton effects (296 nm). The selected corresponding UV spectra of **3b** in Fig. S1.†

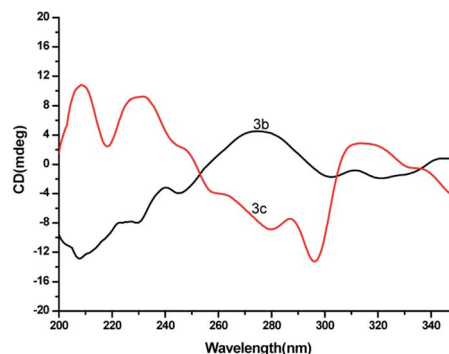


Fig. 7 Solid CD spectra of TEO-*S*- α -ethylbenzylamine (**3b**) and TEO-*R*- α -ethylbenzylamine (**3c**).

Conclusions

In summary, we report a rapid method for the structure determination of liquid small molecules. These liquid small molecules can cocrystallize rapidly with 1,3,5,7-tetrakis(2,4-diethoxyphenyl)adamantane without covalent bonds or strong directional interactions and can be used to determine the absolute configuration of chiral liquid molecules. Unfortunately, most liquid molecules are disordered during cocrystallization, increasing the difficulty of structural analysis. 1,3,5,7-Tetrakis(2,4-diethoxyphenyl)adamantane can cocrystallize rapidly with liquid molecules and encapsulate a broad range of molecules, demonstrating its potential application in extended crystalline sponges.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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