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Letter

Structure determination of tweezer-shaped π-extended tetraphenylenes by microcrystal electron diffraction

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Harshita Nagar

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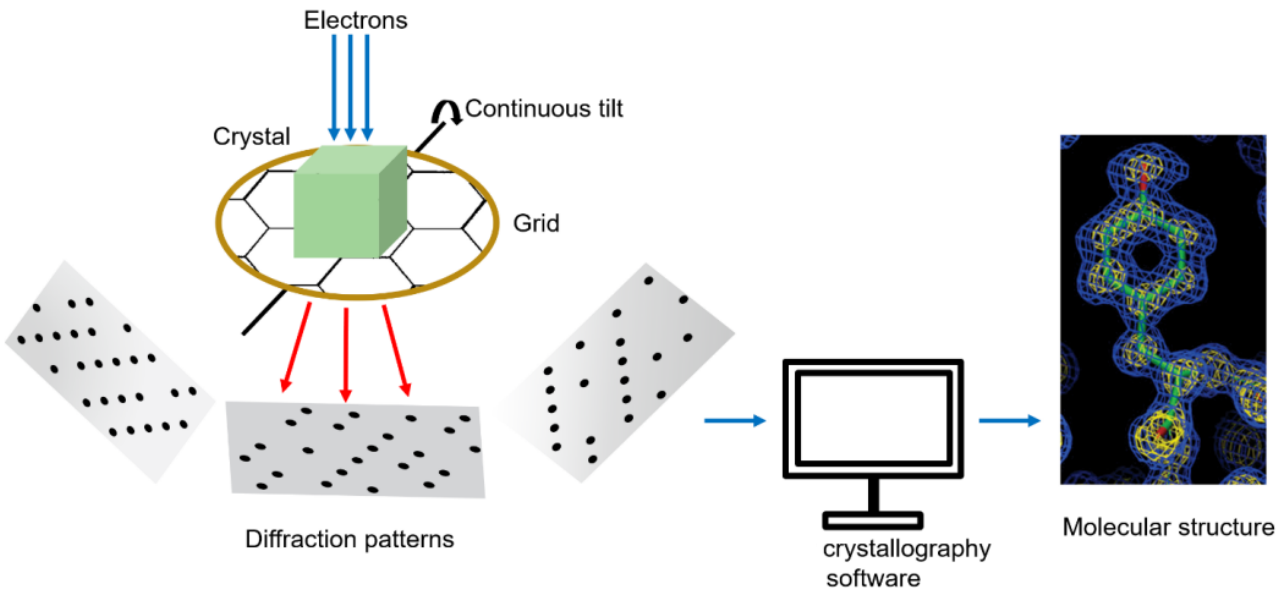
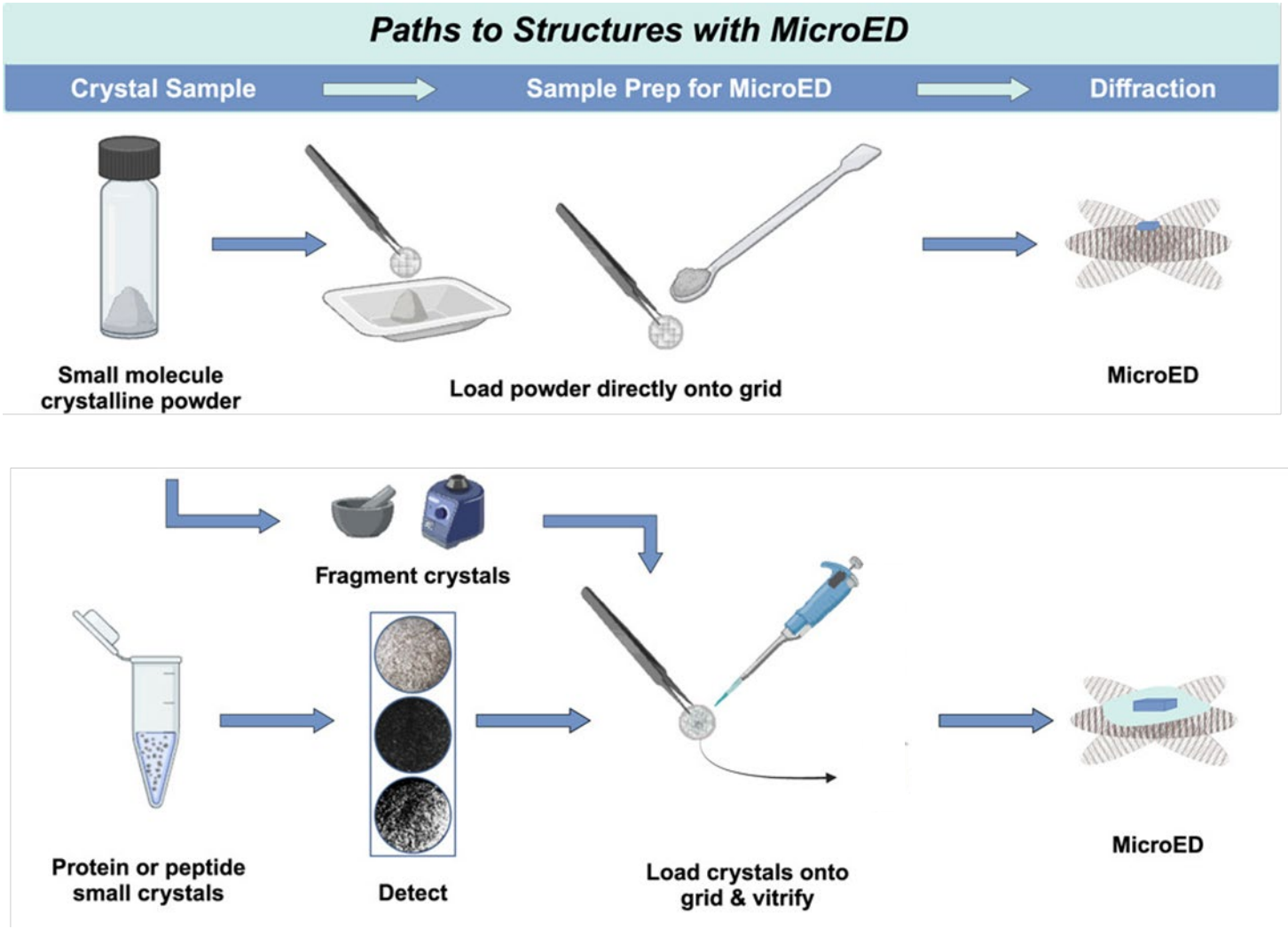
Microcrystal electron diffraction (MicroED)



An outline of MicroED data acquisition and processing

- MicroED is a cryo electron microscopy technique used to determine structure of nano and microcrystals.
- Due to strong interaction between electrons and matter, crystals can be as small as few tens of nanometer.

Sample preparation



Acehan, D. *etal.*, *Cell Reports Physical Science*, **2024**, *5* (6), 102007.

Why this paper ?

- Structure determination of large **π**- conjugated molecules using microcrystal electron diffraction.
- Aromatic compounds have several applications owing to their diverse structure-dependent properties.
- Understanding their molecular structures and packing patterns is essential. However, **π**- conjugated compounds are sometimes difficult to purify and recrystallize due to their poor solubility.

Background work

ACS central science

2024

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Article

Reactive Noble-Gas Compounds Explored by 3D Electron Diffraction: XeF_2–MnF_4 Adducts and a Facile Sample Handling Procedure

Klemen Motaln, Kshitij Gurung, Petr Brázda, Anton Kokalj, Kristian Radan, Mirela Dragomir, Boris Žemva, Lukáš Palatinus,* and Matic Lozinšek*

RESEARCH ARTICLE

2023

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Unraveling the Structure of Meclizine Dihydrochloride with MicroED

*Jieye Lin, Johan Unge, and Tamir Gonen**

ACS chemical biology

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Articles

MicroED as a Powerful Tool for Structure Determination of Macrocyclic Drug Compounds Directly from Their Powder Formulations

Emma Danelius,[⊥] Guanhong Bu,[⊥] Lianne H. E. Wieske, and Tamir Gonen*

Background work

RESEARCH ARTICLE 2024

ADVANCED BIOLOGY
www.advanced-bio.com

Polymorphic Structure Determination of the Macrocyclic Drug Paritaprevir by MicroED

*Guanhong Bu, Emma Danelius, Lianne H.E. Wieske, and Tamir Gonen**

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Crystal structure and orientation of organic semiconductor thin films by microcrystal electron diffraction and grazing-incidence wide-angle X-ray scattering†

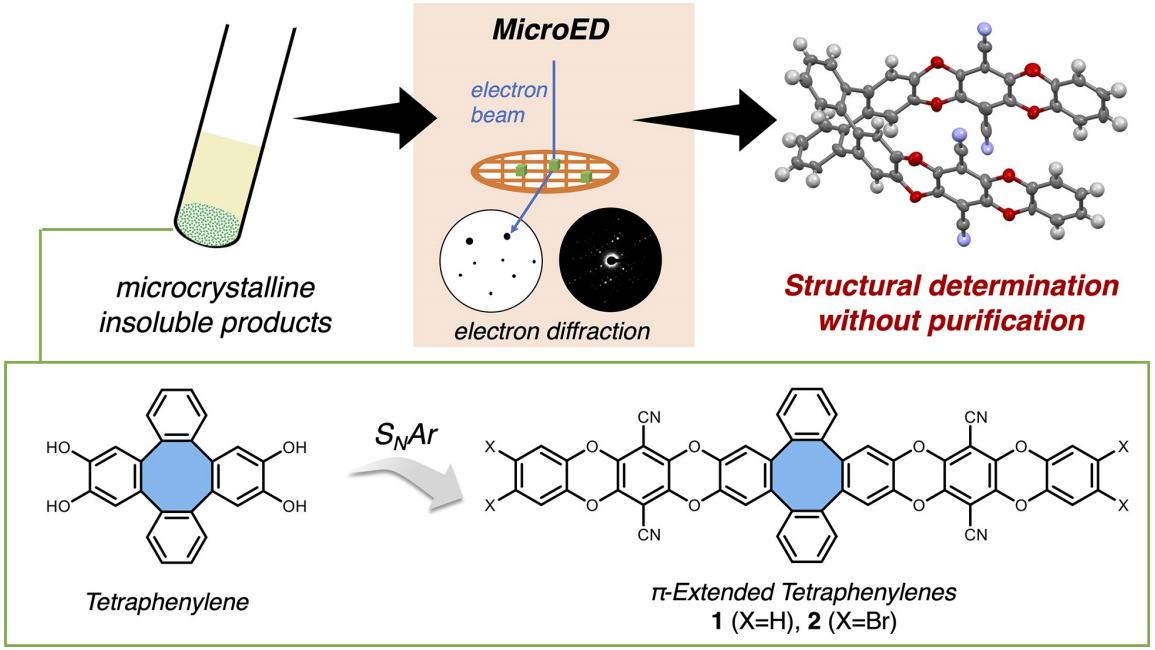
Andrew M. Levine, [abc] Guanhong Bu, [de] Sankarsan Biswas, [abc] Esther H. R. Tsai,*[f] Adam B. Braunschweig *[abc] and Brent L. Nannenga *[de]

Introduction

- In this work, they determined the structures of tweezer-shaped **π**- extended tetraphenylenes using MicroED without purification or recrystallization.

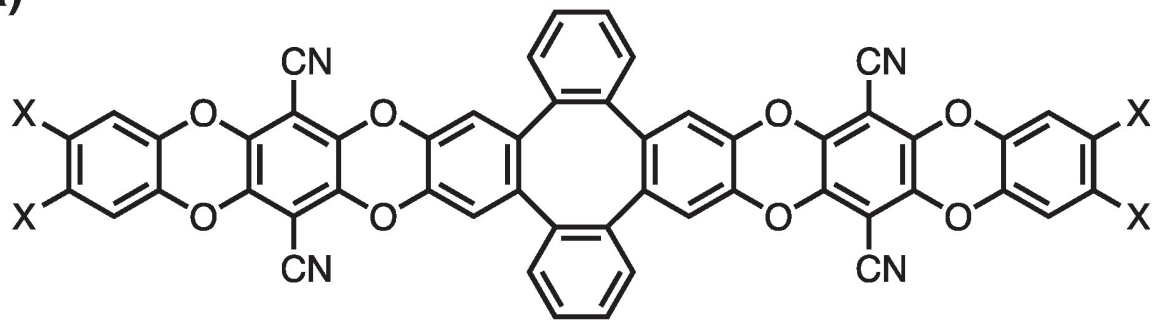
- Two types of **π**- extended tetraphenylenes **1** and **2** were synthesized via nucleophilic aromatic substitution reactions of tertrahydroxy tetraphenylene **3** with phthalonitrile derivatives **4** and **5**, respectively.

- The study analyzed two variations of these molecules, showing how small differences in their chemical composition affected their 3D structures and packing arrangements.



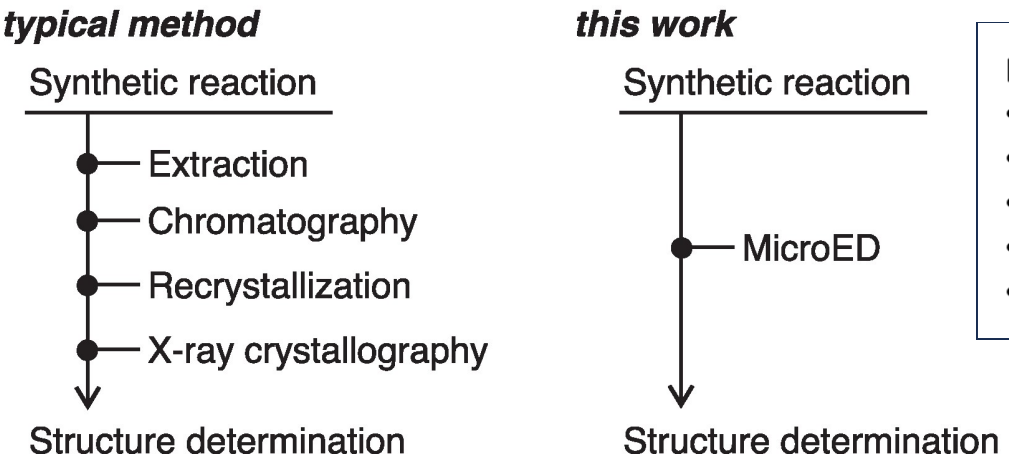
Results and discussion

(a)



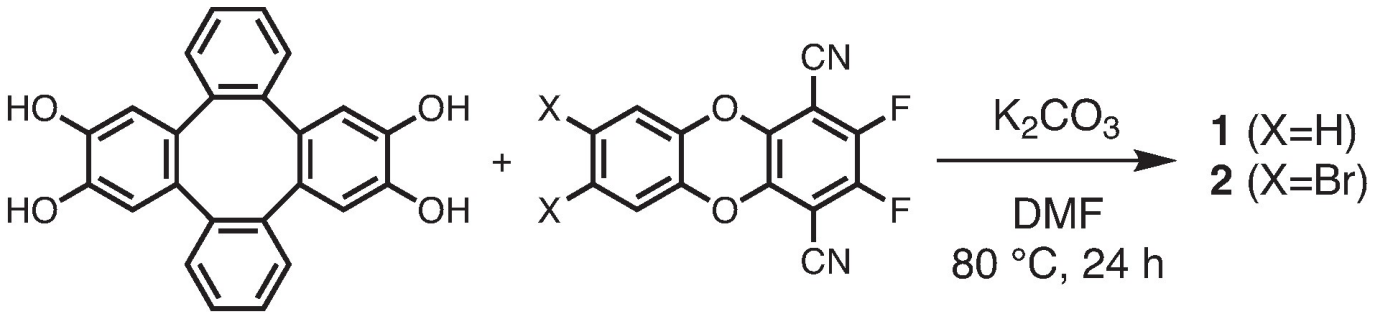
1 (X=H), **2** (X=Br)

(b)



Electron crystallography
- Krios G4 Cryo - TEM
- Accelerating voltage : 300kV
- Dose rate : 0.04 e $Å^{-2}$ sec^{-1}
- Stage rotation : -50° to 50° at 1°
- Crystal size : 0.1 µm

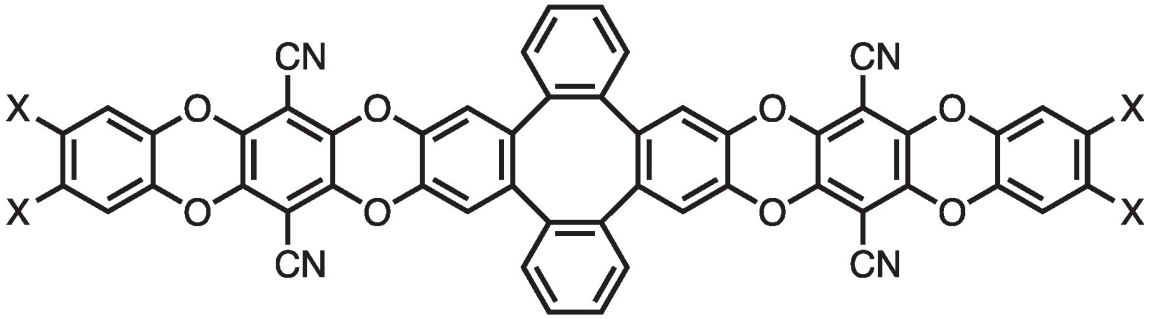
Figure 1. a) Structures of tweezer-shaped **π**- extended tetraphenylenes **1** and **2.**
b) A typical method for determining the molecular structures of the reaction products and the method used in this work.



3
Tertrahydroxy tetraphenylene

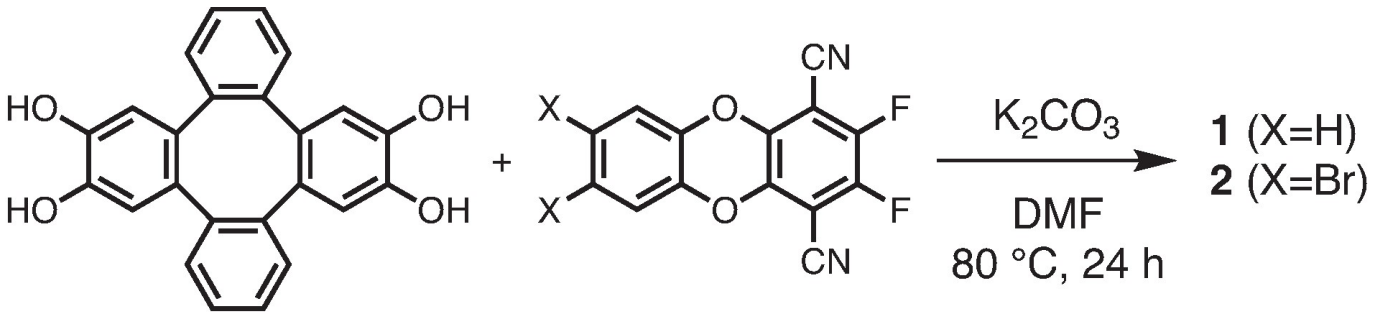
4 (X=H), **5** (X=Br)
Phthalonitrile derivatives

Figure 2. Synthesis of **1** and **2.**



1 (X=H), **2** (X=Br)

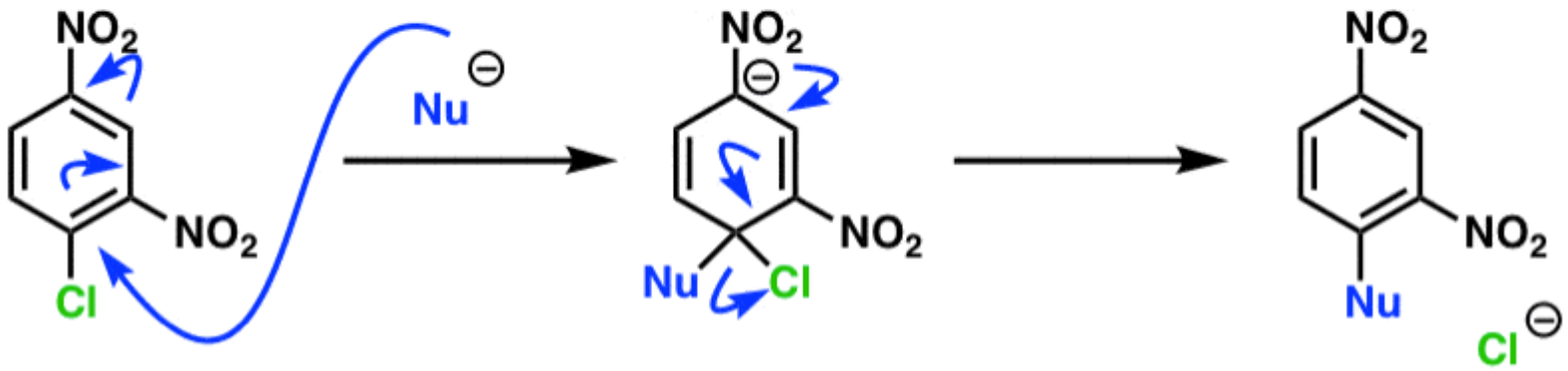
Synthesis



3 **4** (X=H), **5** (X=Br)

Nucleophilic Aromatic Substitution

In this reaction, a nucleophile (**Nu**) attacks an electron-poor aromatic molecule, resulting in the substitution of a leaving group:



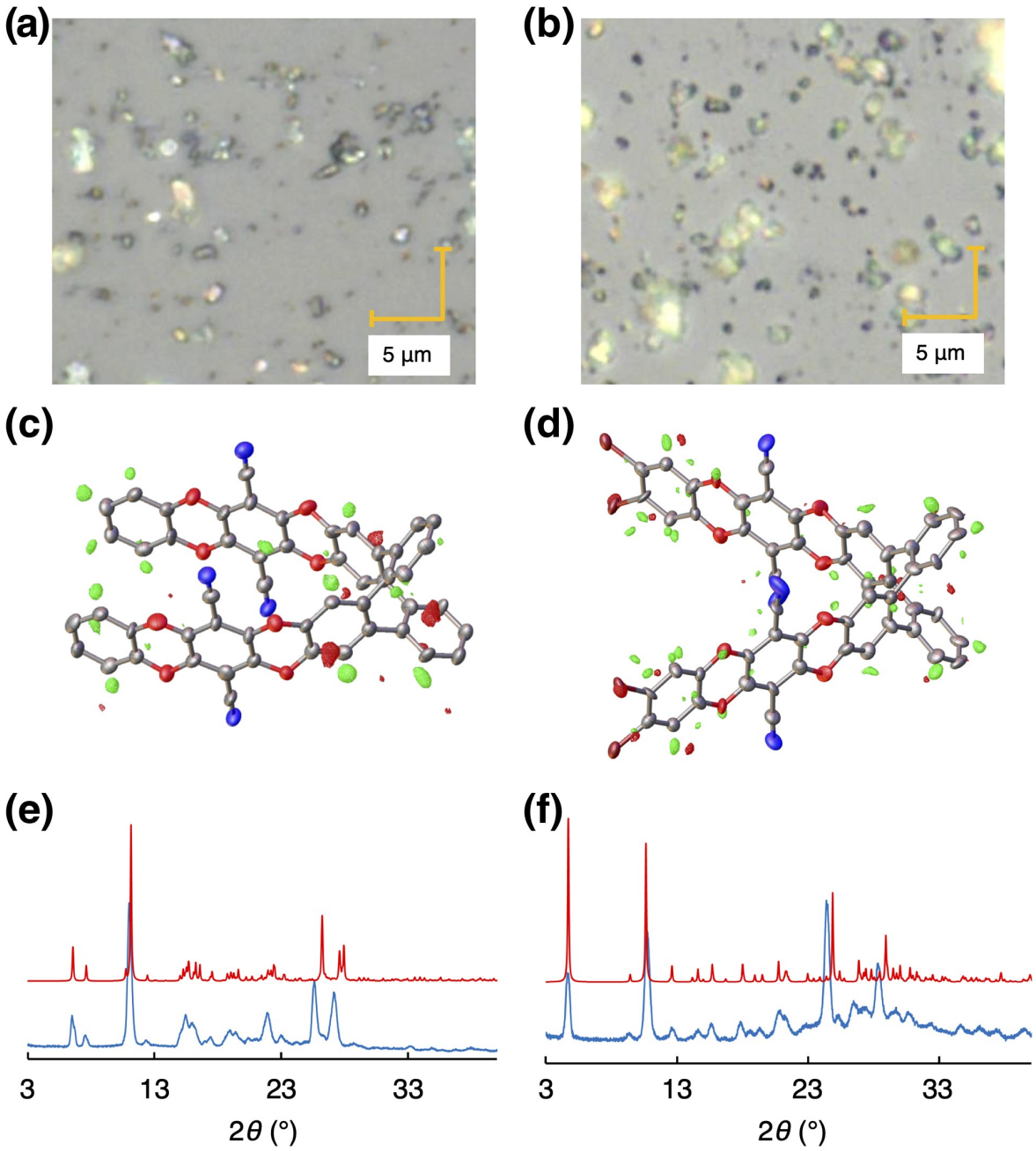


Figure 3. (**a**) and (**b**) Optical microscopy images of 1 and 2. (**c**) and (**d**) Difference Fourier maps of the crystal structures of 1 and 2, where red and green spheres indicate the missing and excess electron density areas, respectively. (**e**) and (**f**) Observed (blue) and calculated (red) PXRD patterns of 1 and 2.

	1	**2**
Crystal system	Triclinic	Monoclinic
Space group	P-1	C2/c
a (Å)	10.124	17.097
b (Å)	13.766	6.512
c (Å)	14.482	38.68
α	111.1	90
β	91.83	103.72
γ	90.47	90
Number of merged crystals	14	5
R_1	0.217	0.219

Table 1 . Crystallographic data and structure refinement details of **1** and **2.**

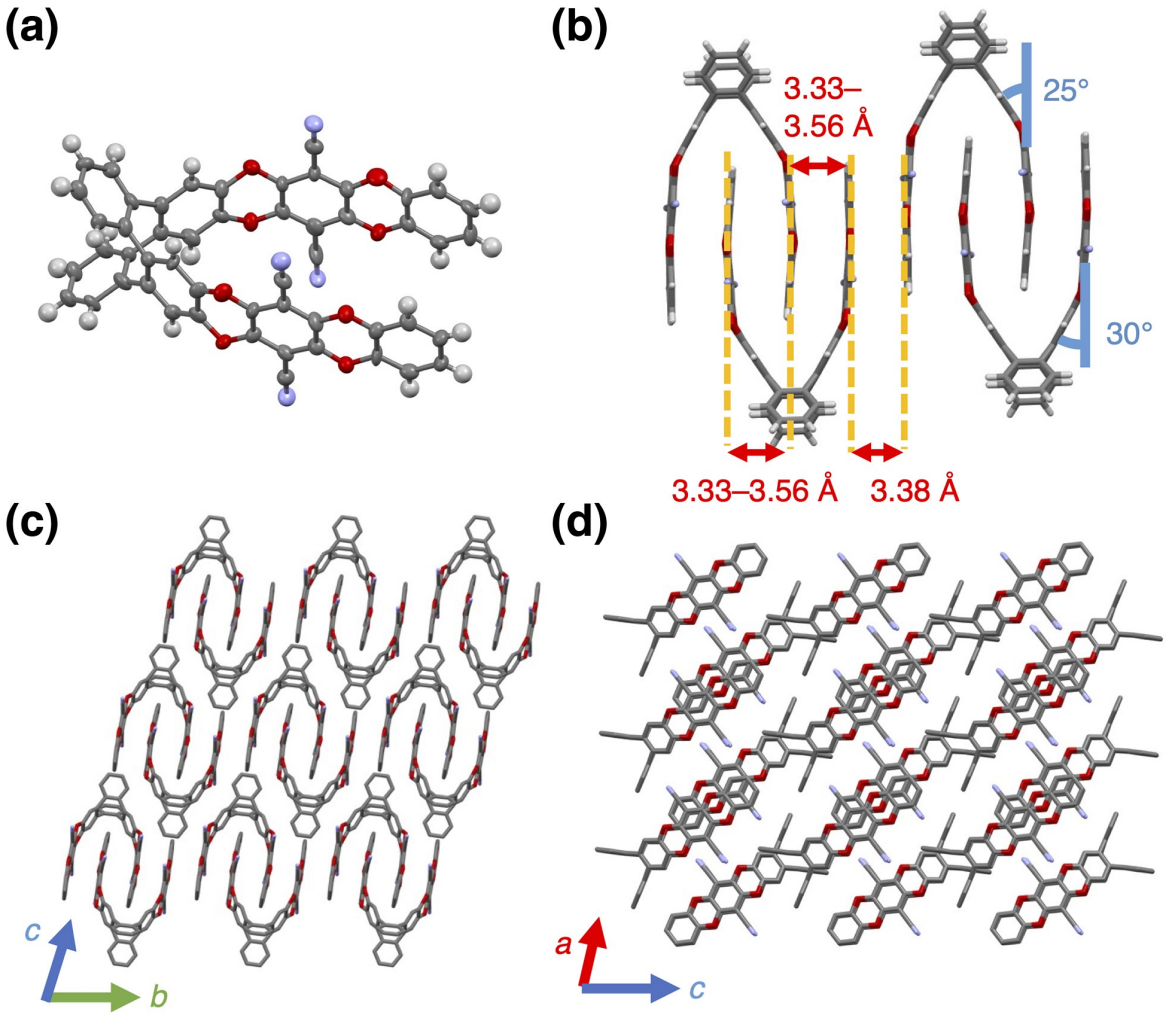


Figure 4. MicroED analysis of the crystal structure of 1. (**a**) Molecular structure of 1. (**b**) Intermolecular π–π stacking. (**c**) and (**d**) The packing of 1; hydrogen atoms and solvent molecules are omitted for clarity.

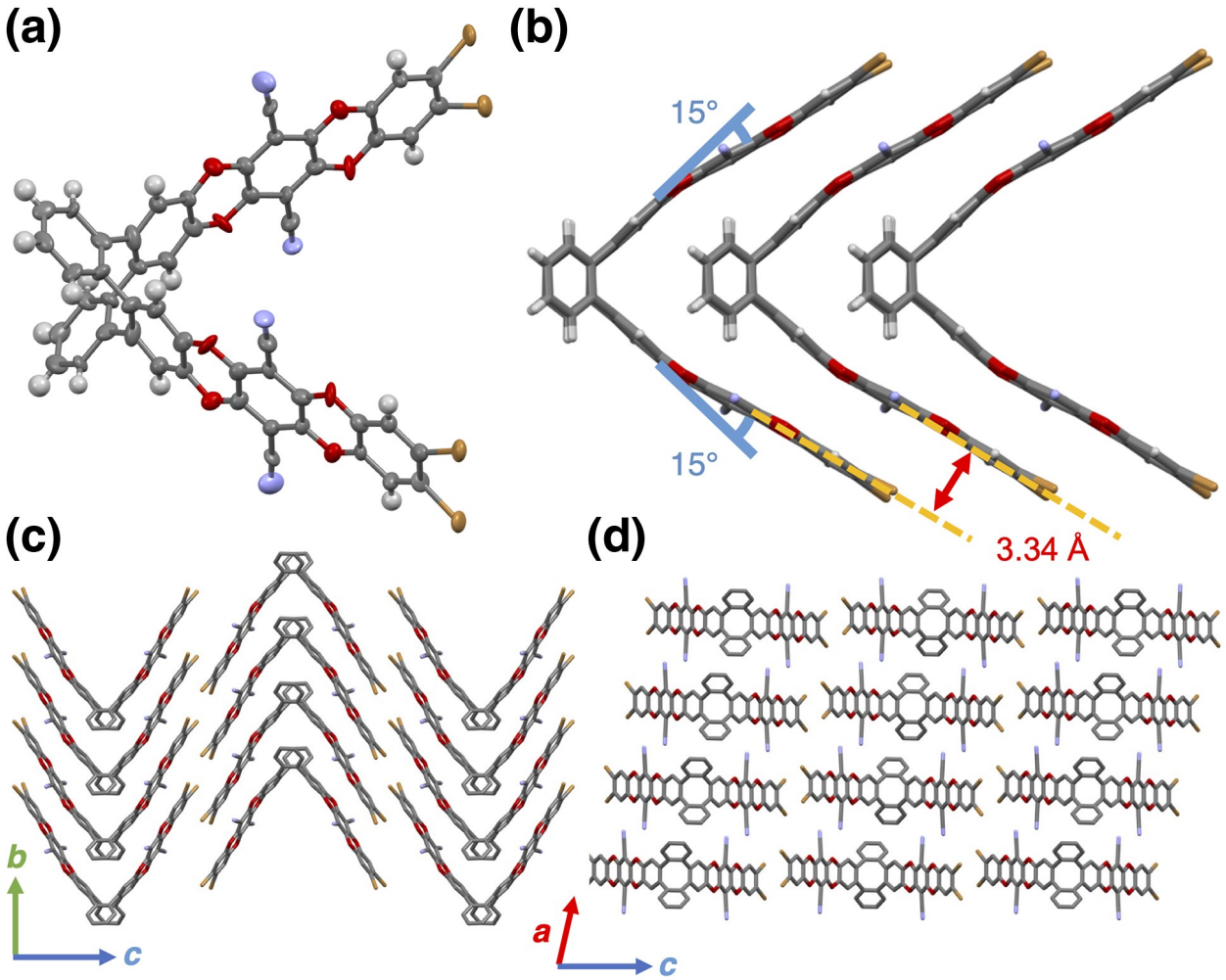


Figure 5. MicroED analysis of the crystal structure of 2. (**a**) Molecular structure of 2. (**b**) Intermolecular π–π stacking. (**c**) and (**d**) The packing of 2; hydrogen atoms and solvent molecules are omitted for clarity.

Conclusion

- This study presented the synthesis of two tetraphenylene derivatives with extended **π**-planes.
- They reported the molecular structures and crystal packing of **Compounds 1 and 2** using MicroED.
- **Compound 1** has a **U-shaped** structure, with two flat regions (called π-planes). This stacking creates a layered arrangement in the crystal.
- **Compound 2** has a **V-shaped** structure, form a zigzag pattern due to their shape and interactions with the bromine atoms.
- This was achieved without requiring purification or crystallization, which are often time - consuming and difficult for poorly soluble molecules like these tetraphenylenes.