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Multifold Post-Modification of Macrocycles and Cages by Isocyanate-Induced Azadefluorination Cyclisation

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Keywords: macrocycles, cages, Azadeflorination cyclization (ADFC), isocyanates, membranes.

Who are the corresponding authors and what are their research areas?

Bernd M. Schmidt

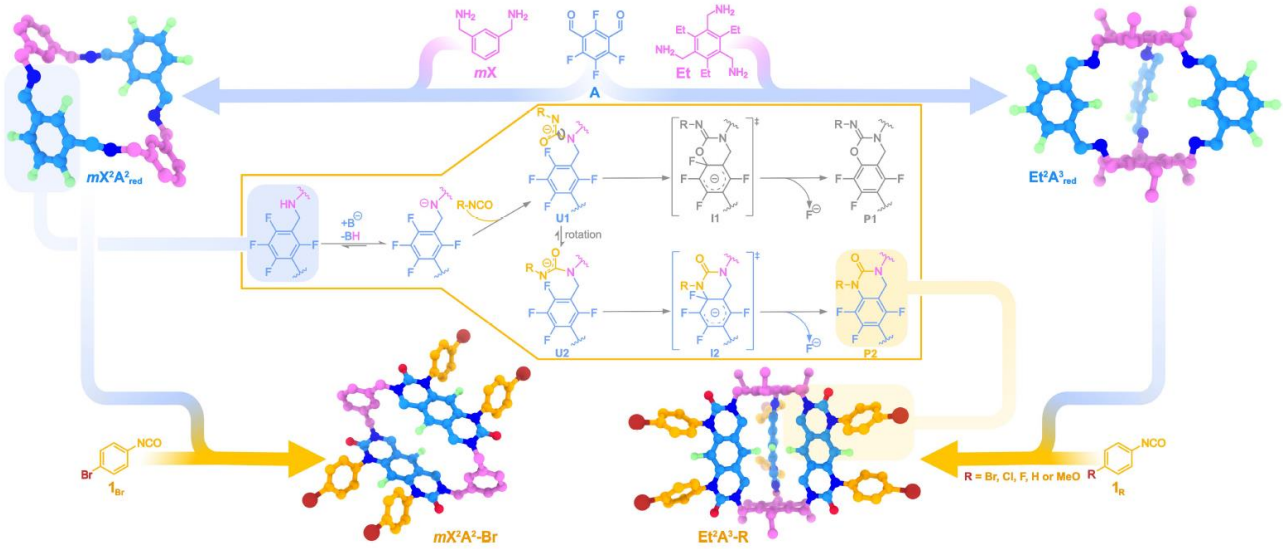
Junior PI at the University of Heinrich Heine (HHU)

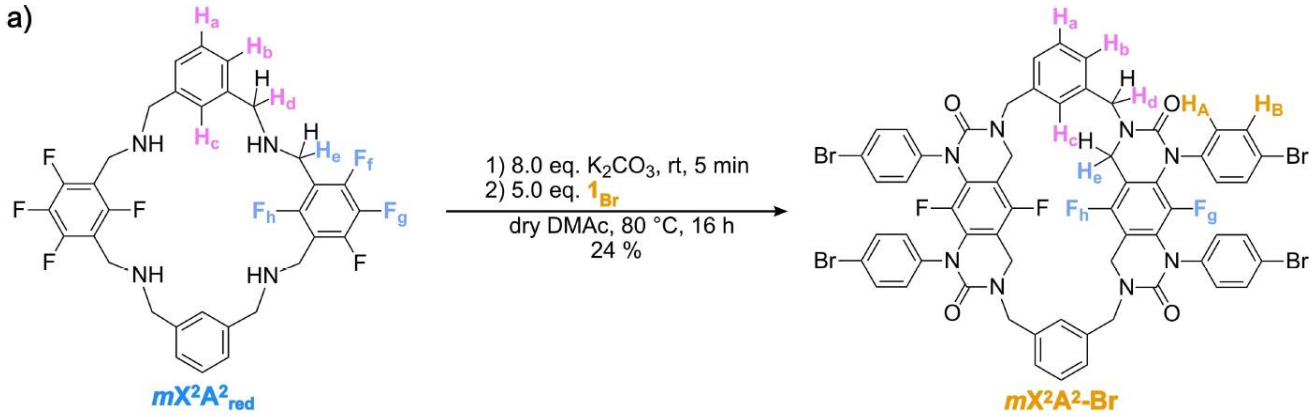
Joint postdoc between University of Tokyo and Humboldt University in Berlin

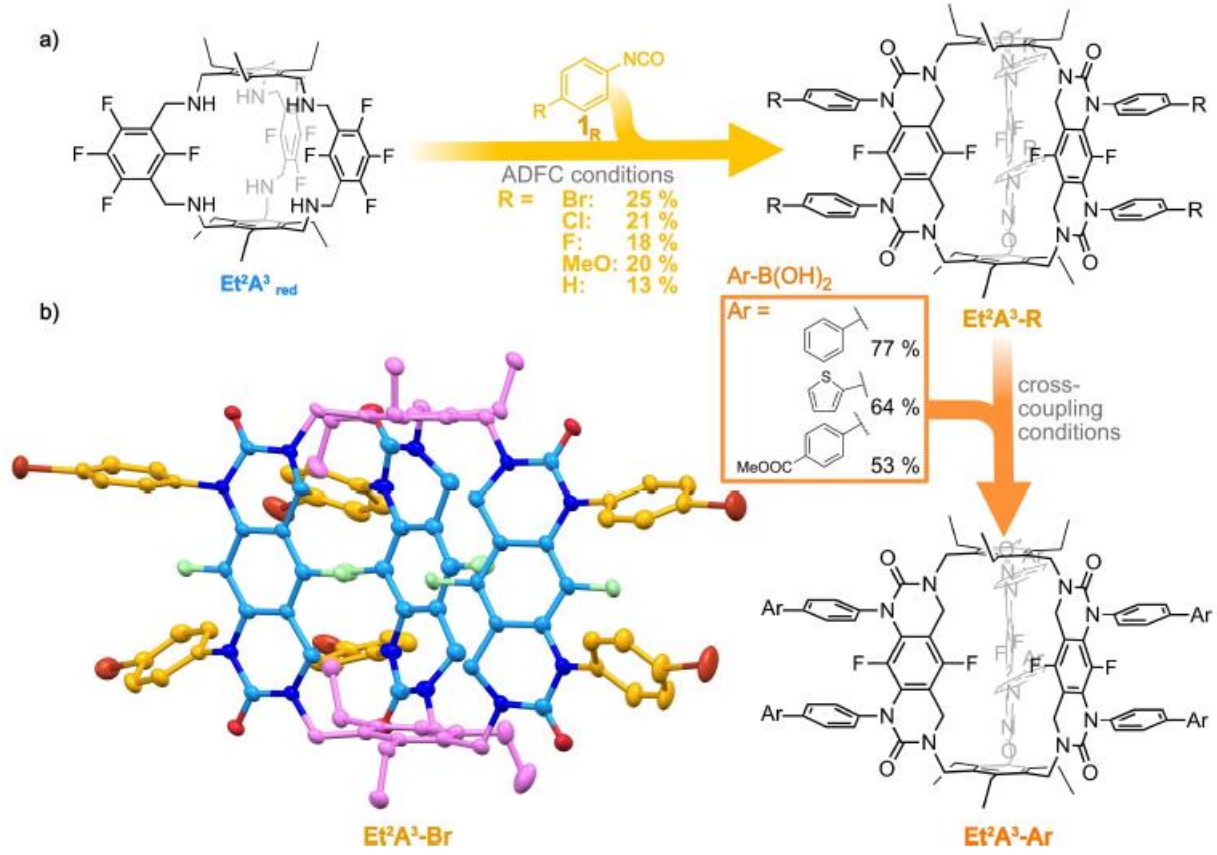
PhD at the Fluorine Chemistry Research Training Group Freie University, Berlin

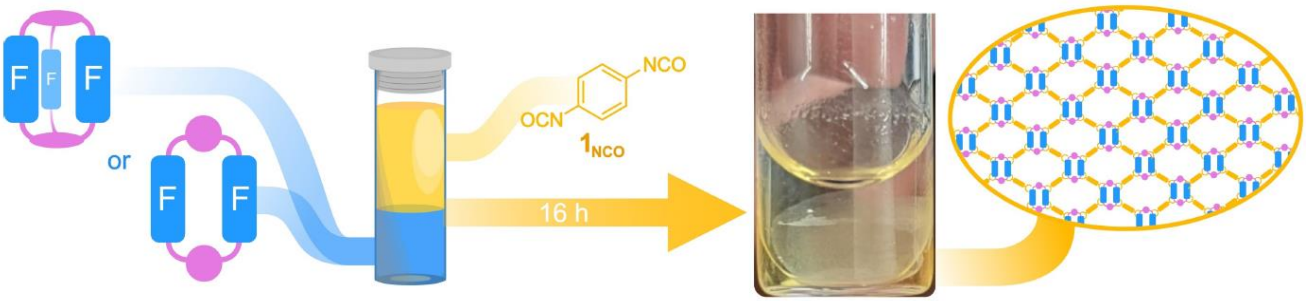
What is the main claim of the article?

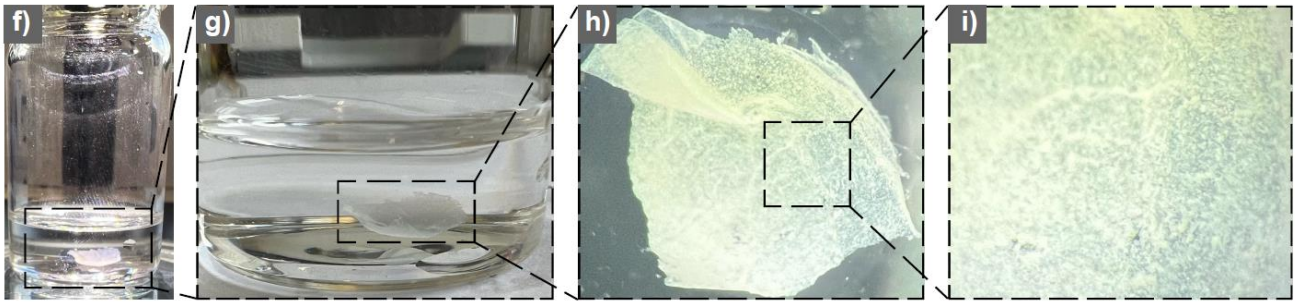
They developed a strategy to post-functionalize macromolecules and cages in four- or six-fold fashion with similar decent yields (70 to 79% per side corresponding to 24 to 25% overall yield). The products show excellent stability and robustness to further modifications depending on the starting material used. The strategy was exploited to form membranes between two immiscible solvents.




a)
1) 8.0 eq. K2CO3, rt, 5 min
2) 5.0 eq. 1Br
dry DMAc, 80 °C, 16 h
24 %
mX2A2red
mX2A2-Br


a)
Et2A3 red
NCO
1R
ADFC conditions
R = Br: 25 %
Cl: 21 %
F: 18 %
MeO: 20 %
H: 13 %
Et2A3-R
Ar-B(OH)2
Ar =
77 %
64 %
53 %
MeOOC
cross-coupling conditions
b)
Et2A3-Br
Et2A3-Ar





How is it demonstrated?

- *Reactions characterized by MALDI-TOF to identify the progress of the reaction*
- *the compounds were isolated on silica gel chromatography and analyzed by ^{1}H and ^{19}F NMR*
- *HRMS data coincide with the masses expected for the claimed compound*
- *DOSY NMR showed a reduced diffusion coefficient due to an increase in the size of the formed species*
- *Crystals suitable for X-ray Chromatography confirmed the structures of the compounds*
- *DFT calculations to understand the mechanism of the multi-fold post-functionalisations*
- *Membranes visible by naked-eye and were characterized by microscopy*

What are the typical experimental conditions?

Azadefluorination cyclizations ADFC:

*Dry solvents (N,N-dimethylacetamid **DMAc** for T = 80°C or N-méthyl-2-pyrrolidone **NMP** for T = 85°C -100°C)*

8 equiv. base K_2CO_3 ; 5 equiv isocyanate with four-fold post functionalization of macrocycle

12 equiv. base K_2CO_3 ; 10 equiv. isocyanate with six-fold post functionalization of cage

Suzuki-Miyaura cross-coupling on modified macrocycles:

12 eq. K_2CO_3, rt, 5 min; 25 eq. Ph-$B(OH)_2$; 37 mol% $Pd(OAc)_2$, 72 mol% MePhos; THF/H_2O (9:1), 85 °C, 3 d

Suzuki-Miyaura cross-coupling on modified cages:

12 eq. K_2CO_3; 35 eq. Ph-$B(OH)_2$; 40 mol% $Pd(OAc)_2$, 80 mol% MePhos; THF/H_2O (9:1), 85 °C, 2-3 d

Membrane synthesis:

Macrocycle or cage in DMF (0.5 to 5wt%)

Ditopic Isocyanate in Cyclohexane (1.0 to 0.05wt%; low solubility)

Higher concentrations of isocyanate yields gels.

Which are the key related papers?

Incorporation of supramolecular architectures in membrane formation:

Calix[4]pyrrole-Crosslinked Porous Polymeric Networks for the Removal of Micropollutants from Water
X. Wang, L. Xie, K. Lin, W. Ma, T. Zhao, X. Ji, M. Alyami, N. M. Khashab, H. Wang, J. L. Sessler, *Angew. Chem. Int. Ed.* **2021**, *60*, 7188

Functional Supramolecular Polymeric Networks: The Marriage of Covalent Polymers and Macrocycle-Based Host-Guest Interactions
D. Xia, P. Wang, X. Ji, N. M. Khashab, J. L. Sessler, F. Huang, *Chem. Rev.* **2020**, *120*, 6070–6123

The cyclization step

Efficient Synthesis of Pyrimido[1,2-*c*] [1,3]benzothiazin-6-imines and Related Tricyclic Heterocycles by S_NAr-Type C–S, C–N, or C–O Bond Formation with Heterocumulenes
T. Mizuhara, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2010**, *75*, 265–268

Additional notes:

Peculiarities:

Simple macrocycle/cage synthesis from amines and aldehydes

Wide scope of isocyanates: tolerance

Decent yields of multi-functional post-modifications

Robust and tolerant to mild acidic conditions (TFA)

Decomposes in concentrated acidic media (HCl)

I don’t understand the reactivity of the methoxy-isocyanate in requiring higher temperatures to undergo the ADFC although the amine is more rich in electrons