Experimental and Computational NMR Strategies to Identify Constrained Conformers of Modified Calix[4]arenes

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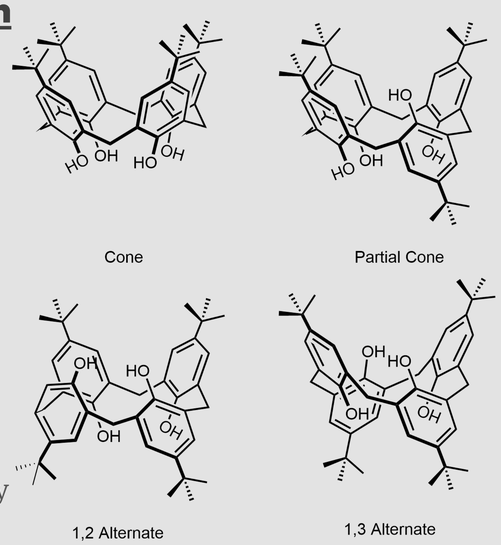
Introduction

~Calixarene derived from p-hydrocarbyl phenols

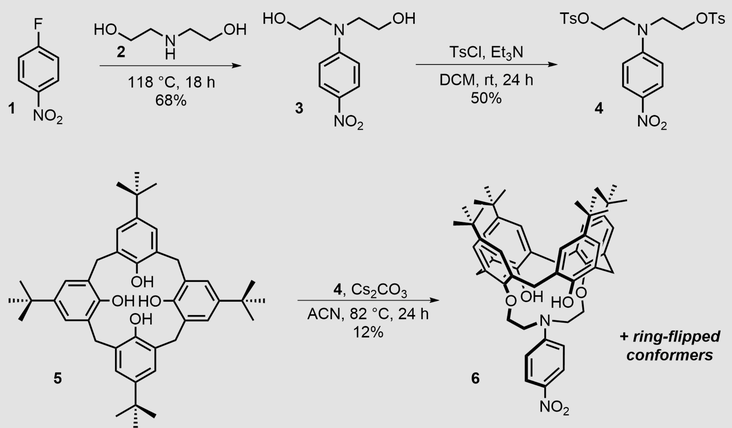
~Applications include enzyme mimetics, ion sensitive electrodes, drug delivery and Ion binding

~Conformationally dynamic



[1] Hyun No, K. et al J. Org. Chem 1982, 47, 2713–2719.
[2] Zhang, D. et al Tetrahedron 2008, 64, 9843–9849.
[3] Van Dienst, E. et al Pure Appl. Chem. 1993, 65, 387–392

Synthesis



[4] Xie, R. et al Bioorg. Med. Chem. Lett 2017, 27, 4415–4420.
[5] Li, G. et al Spectrochim. Acta A 2020, 239, 118465.
[6] Gutsche, C. D. et al Org. Syn. 2003, 68, 234–234

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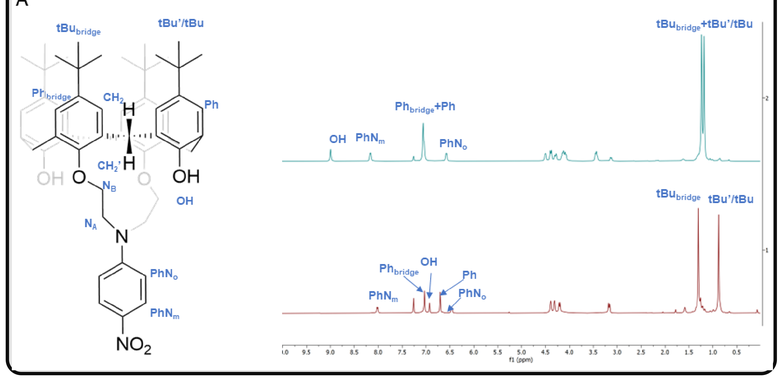
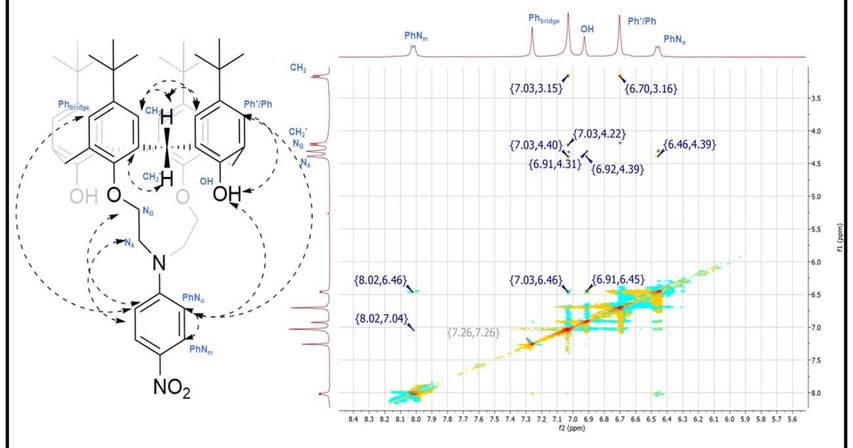


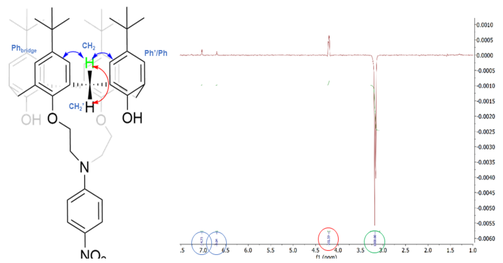
2D analysis



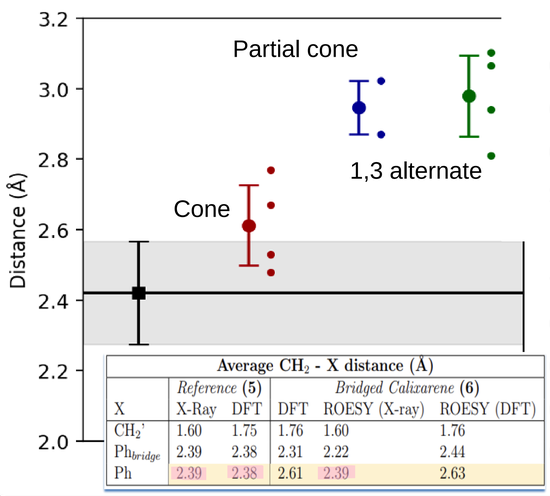
Nuclear Overhauser Effect Spectroscopy (NOESY) of Bridged Calixarene

~Arrows correlate to labeled cross peaks showing proton interactions through space

~Although promising, this data is inconclusive and requires more studies to determine conformations



~Rotating frame Overhauser affect spectroscopy (ROESY) was performed in order to calculate proton distance through space



Average CH_2 - X distance (Å)

	Reference (5)		*Bridged Calixarene* (6)		
X	X-Ray	DFT	DFT	ROESY (X-ray)	ROESY (DFT)
CH_2'	1.60	1.75	1.76	1.60	1.76
Ph_{bridge}	2.39	2.38	2.31	2.22	2.44
Ph	2.39	2.38	2.61	2.39	2.63

~These were compared to computationally derived distances

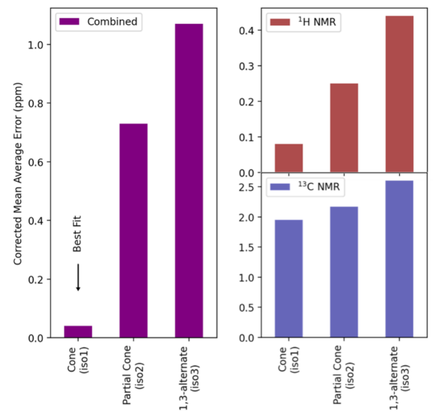
Computational analysis

		CMAE (ppm)	R^2	uDP4+	sDP4+	DP4+
^{1}H	*iso 1*	0.08	0.9981	87.97%	100.00%	100.00%
	iso 2	0.25	0.9848	12.02%	0.00%	0.00%
	iso 3	0.44	0.9352	0.01%	0.00%	0.00%
^{13}C	*iso 1*	1.95	0.9979	96.07%	97.71%	99.90%
	iso 2	2.17	0.9973	3.93%	2.29%	0.10%
	iso 3	2.60	0.9955	0.56%	0.00%	0.00%
Combined ^{1}H and ^{13}C	*iso 1*	0.40	0.9980	99.44%	100.00%	100.00%
	iso 2	0.73	0.9936	0.56%	0.00%	0.00%
	iso 3	1.07	0.9829	0.00%	0.00%	0.00%

~Conformer and ensemble sampling tool(CREST) was utilized for predictive NMR

~Results point overwhelmingly towards cone.

~Computational chemical shift values were compared to experimental values and corrected mean average was graphed and compared.



Conclusion

~Utilized NMR and computational methods to determine cone conformation

Acknowledgements

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References

[1] Hyun No, K. et al J. Org. Chem 1982, 47, 2713–2719.
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