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Trisulfonamide Calix[6]arene-Catalysed Michael Addition to Nitroalkenes

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We describe the application of a novel family of trisulfonamide calix[6]arenes TSA in general acid catalysis. Hydrogen-bonding interactions between acidic TSA and methanol boosted the reactivity of a Michael addition of indoles to nitroalkene derivatives. The transformation occurs at a low catalyst loading of 5 mol % allowing for the synthesis of nitroalkanes in good yields and functional group tolerance.

Calix[*n*]arenes represent a key structural motif in organic chemistry, and their properties have been broadly investigated particularly with the aim to synthesize synthetic receptors and working devices for the development of nanotechnologies.[1] Most of these systems, intensively studied for the preparation of rotaxane and catenane systems, exploited the presence of H-bonded donor moieties such as ureido groups anchored onto their upper rim.[2] In low-polar media, they are able to efficiently separate the ion pairs of mono- and dicationic salts, promoting the threading of these axles inside the π-rich aromatic cavity.[3] Another application, wherein their ability to establish non-covalent interactions has found broad success, is their use as catalysts. Indeed, calix[4]arene derivatives have been successfully employed as a "platform" to synthesize ligands for supramolecular organometallic catalysis or to link established organocatalysts.[4,5] In parallel, the dimensions and the hydrophobic character of tailored-designed calix[6]arenes have only recently been exploited to accelerate organic reactions under "on water" conditions.[6] The design of these novel "supramolecular" entities often allowed for the development of more selective and higher performing catalytic systems. Despite this considerable progress, the use of calix[6]arenes as a catalyst that means a "substance that increases the rate of a reaction", has been so far less exploited.[7] In this context, our group recently reported on the synthesis of a new generation of heteroditopic trisulfonamide (TSA) calix[6]arene receptors.[8] Interestingly, we found that their binding ability is highly influenced by the H-bonding interactions performed by the acidic NH sulfonamide moiety with the counterions of dialkylviologen-based guests. Prompted by these findings, we considered the possibility of employing for the first time the same features that govern threading processes for TSA calix[6]arenes in a general acid catalysis model reaction.[9]

At the outset of the investigation, we probed the reactivity of TSA calixarenes in a well-established Michael addition of electron-rich heteroarenes such as indole **2a** to a nitroalkene **1a**.[10] Hence, on using 5 mol % of TSA **A** in low-polarity solvents, where these are present in a typical cone conformation, low conversions were observed (Table 1, entries 1 and 2). Differently, with an aprotic polar solvent such as DMSO, the reactivity was completely shut down (entry 3). Using MeOH (pK_a = 15.5), under otherwise identical conditions, we observed an increased amount of product **3aa** (22%, entry 4).[11] However, upon performing the reaction without any TSA calixarene, at a working temperature of 50 °C, comparable low conversion and yield were observed, highlighting the presence of a background reaction (26 %, entry 5). We next probed the reactivity in the presence of differently substituted TSA, **C** and **D** presenting methoxy and chlorine substituent on the *para* position of the sulfonamide moiety, respectively. However, in all these cases, the outcome of the reaction followed suit (entries 6-8). On the other hand, increasing the H-donor ability of the calixarene with a nitro group as for **E**, a non-trivial increment in the reactivity was recorded (42%, entry 9). Since many examples of (thio) urea catalysed Michael addition are reported to date,[12] we probed the reactivity also in the presence of catalytic amounts of TPU calixarene **F**. However, we did not notice any significant improvement (entry 10). To test the effect of the supramolecular wheel **E**, we synthesised its monomeric analogue **G** and used it in the Michael addition with a loading of

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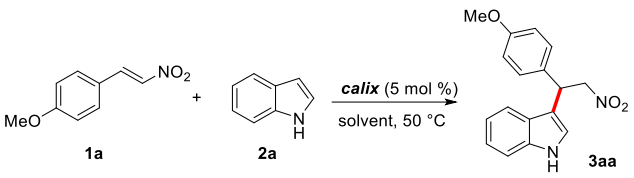
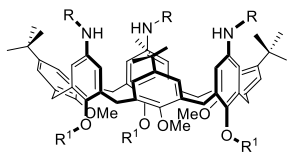
15 mol %. Hence, a lower efficacy in the reaction was observed (27%, entry 11).

Table 1 Optimisation of Reaction Conditions

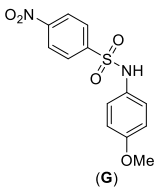


Entry[a]	*Calix*	Solvent	Conv (%)	Yields (%)
1	**A**	toluene	8	6
2	**A**	$CHCl_3$	9	7
3	**A**	DMSO	--	--
4	**A**	MeOH	23	22
5	--	MeOH	28	26
6	**B**	MeOH	26	25
7	**C**	MeOH	28	22
8	**D**	MeOH	32	30
9	**E**	MeOH	43	42
10	**F**	MeOH	36	33
11[b]	**G**	MeOH	33	27
12[c]	**E**	MeOH	86	83 (81)
13[c]	--	MeOH	68	58
14[c]	--	*t*-BuOH	36	31
15[c]	**E**	*t*-BuOH	25	20
16[c]	**E**	H_2O	85	82

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), ***calix*** (5 mol %), solvent (0.5 ml, 0.2 M), 50 °C, 24 h. Yields calculated by ^{1}H-NMR integration using 1,3,5-trimethoxybenzene as an internal standard. [b] **G** (15 mol%) was employed. [c] **2a** (0.3 mmol), solvent (0.25 ml, 0.4 M). The isolated yield is shown in brackets.



R = 4-MeC$_6$H$_4$SO$_2$ R^1 = *n*-Oct (**A**)
R = 4-MeC$_6$H$_4$SO$_2$ R^1 = (CH$_2$)$_2$OEt (**B**)
R = 4-MeOC$_6$H$_4$SO$_2$ R^1 = *n*-Oct (**C**)
R = 4-ClC$_6$H$_4$SO$_2$ R^1 = *n*-Oct (**D**)
R = 4-NO$_2$C$_6$H$_4$SO$_2$ R^1 = *n*-Oct (**E**)
R = C$_6$H$_5$NH(CO) R^1 = *n*-Oct (**F**)

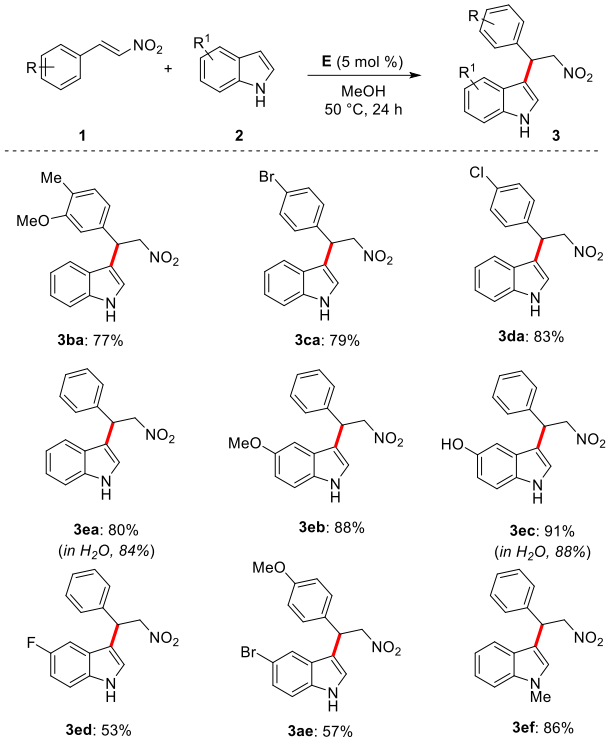


(**G**)

Finally, by just increasing the amount of nucleophile (3 equiv.) and the concentration up to 0.4 M, product **3aa** could be obtained in good yields (entry 12). For the sake of comparison, a similar reaction performed in MeOH, in the absence of any calixarene, led to the formation of **3aa** in lower yields (58%, entry 13). Noteworthy, on employing *t*-BuOH (pK_a = 18.5) as the solvent, the reaction in the presence of **E** was worse than the background reaction, highlighting how the acidity of the medium plays an important role under present conditions (entries 14 and 15).[13] Finally, H_2O was found as a suitable solvent for the TSA-catalysed Michael addition, yielding **3aa** with comparable efficacy (82%, entry 16).

Attracted by the features of the protocol and to probe a general applicability of the methodology, we synthesised a small library of nitroalkane derivatives of type **3**.

Table 2 Scope for the catalytic Michael addition



Particularly, substituted and unsubstituted nitrolefines **1a-e** were converted smoothly into the corresponding products **3aa-3ea** (83-77%). Noteworthily, the reaction outcome was not influenced by the presence of halogen functional groups as for **3ca** and **3da**. Differently substituted indole derivatives could be applied as well. Hence, indoles with EDGs such as ethers and hydroxyl groups (**3eb-ec**) reacted giving high yields (88-91%), while the inherently less reactive fluorine- and bromine-substituted ones **2d-e** delivered **3ed-3ae** in synthetically useful yields (53-57%). Finally, the methodology could be applied also in the presence of *N*-protected indole derivative **3ef** (86%) (Table 2). In order to get more insights on the features of calixarene **E** in the reaction and to compare its effect with respect to the background reaction, we analysed the kinetic profile of parallel reactions conducted in the presence of catalytic amounts of **E** and in solely methanol (Fig. 1).

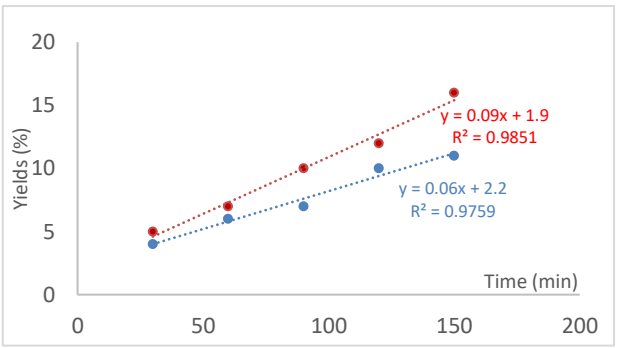


Fig. 1. Kinetic profile of parallel reactions (MeOH, 0.02 M) in the presence of **E** (red line) and without **E** (blue line)

For both cases, we obtained a linear slope that had not reached its plateau, with a moderate $k_y^1/k_y^2 \approx 1.5$. This finding proved the catalytic role of **E** in boosting the reactivity of the Michael addition in terms of chemical yields (see entries 12 and 13 in Table 1). Subsequently, to investigate the role of methanol in the catalytic system, we performed a control experiment by running a model reaction in a sealed glass tube, using toluene as the solvent (see Fig. S1 in ESI). After stirring the mixture for 1 h, a small aliquot of the crude was analysed by NMR. Reasonably, no product formation was observed. We thus added 1 equiv. of MeOH keeping the mixture at 50 °C for an additional hour. After that, the crude mixture was analysed, highlighting trace formation of **3aa** (Figure 2, a).

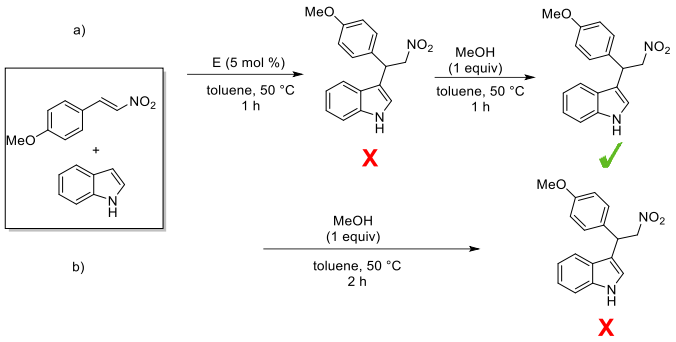


Fig. 2 Comparing the effect of MeOH: a) with catalyst **E**; b) without the catalyst.

To compare this result, we performed a second reaction in the presence of 1 equiv. of MeOH, without **E**. After 2 h, analysis of the crude by NMR did not reveal any significant presence of nitroalkane **3aa** (Fig. 2b). This supported once more that the interplay between TSA **E** and MeOH was crucial for enhancing the catalytic process. Finally, to probe a possible hydrophobic effect, a 1:1.5 mixture of TSA **E** and nitroalkene **1a** was evaluated by ^{1}H-NMR. No shift of the proton resonances of **1a** was observed, excluding at this stage any role of the electron-rich calixarene cavity (see Fig. S2 and S3 in ESI).[14] Since the results acquired are suggestive of a necessary cooperation between TSA calixarenes and MeOH to improve the performances of the catalytic reaction, we first investigated the possible conformations assumed by our model TSA **A** in this protic solvent. We previously observed that TSA calixarenes adopt, in apolar solvents such as $CDCl_3$ and d_6-benzene, a pseudo-cone conformation. This geometry was confirmed by the upfield shift of the ^{1}H NMR resonances of methoxy signals and the AX system of two doublets at δ = 4.4 and 3.4 (^2J = 15.5 Hz), related to the bridging pseudo-axial and pseudo-equatorial methylene groups of the macrocycle (Fig. 3a). Furthermore, the absence of NH signals of the sulfonamide moieties led us to hypothesise the presence of an homodromic H-bonding domain existing on the upper rim of the cavity.[15] This was supported by a preliminary geometry optimisation of TSA **A**, carried out at the PM6-DH+ level12 using the Mopac 2016 program. Indeed, intrannular NH---O bonds (2.765-2.817 Å) were crucial for maintaining TSA calixarenes in their typical cone conformation, in apolar solvents (see Fig. S4 in ESI). Interestingly, the situation completely changed when we analysed the conformation of TSA **A** in d_4-methanol.

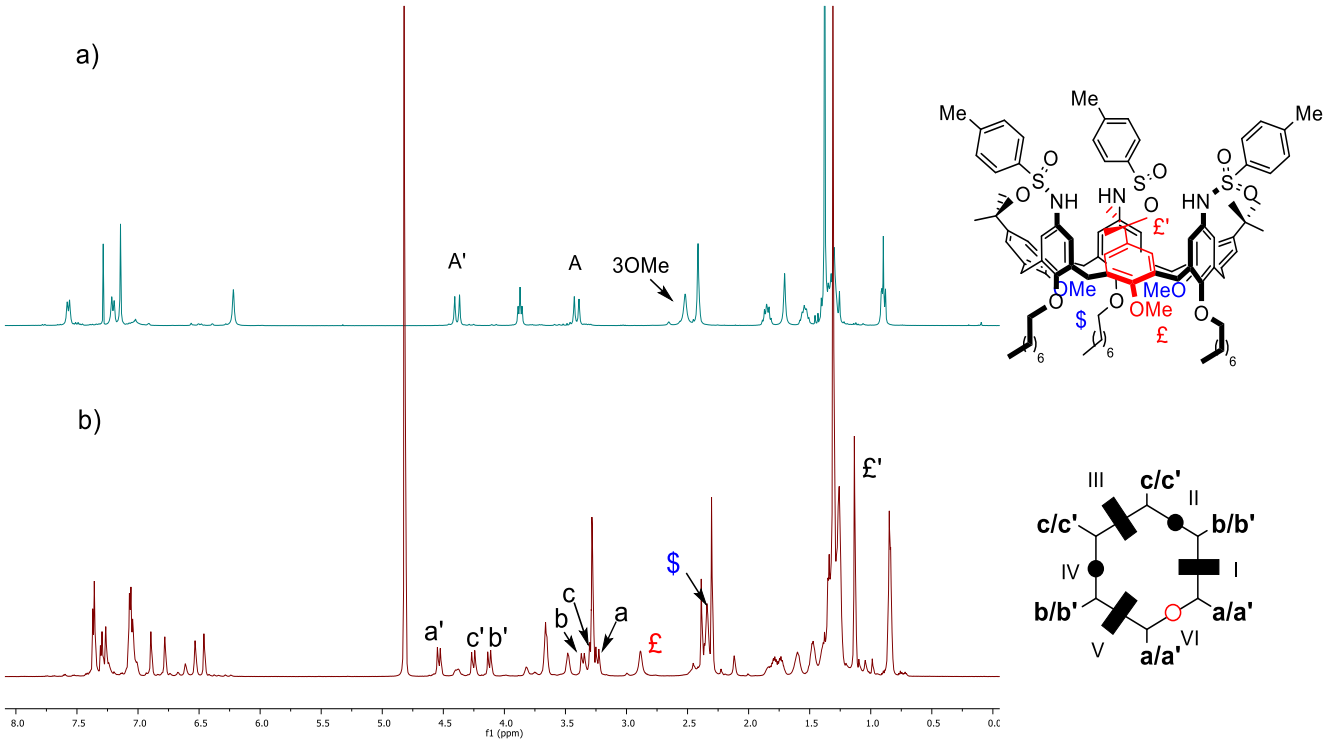


Fig. 3 ^{1}H NMR spectra (400 MHz, 298 K) of a) calixarene **A** in $CDCl_3$, b) calixarene **A** in MeOH-d_4. At the bottom right are schematic representations of **A**. The colors of the ovals and rectangles indicate the relative position of the phenolic substituent with respect to the plane defined by the bridging methylene groups (hexagon) (black, upward; white outward). The rectangle identifies the phenolic ring substituted with the octyloxy chains, while the circle those with the methoxy groups.

Its ^{1}H-NMR clearly showed a "flipping" of one phenolic ring with the methoxy substituent (£) that was pushed outside from the π-rich aromatic cavity. This was highlighted by a "down-field" shift of its proton signal (£, 0.8 ppm) along with an "up-field" shift of its parental *t*-Bu (£', 0.3 ppm). The different conformation was further established by a new pattern for the methylene bridging protons. The two doublets (ax + eq, A + A') present in the pseudocone conformation, split in six doublets, with geminal coupling, three for the axial and three for the equatorial, in a 1:1 ratio (Fig. 3b). The appearance of two signals (2:1 ratio) for the acidic NH bonds of **A** were suggestive of the breaking of the homodromic domain and their engagement in intermolecular interactions with the protic solvent. This "distorted" cone conformation was finally confirmed through a complete NMR analysis (see Fig. S5-S10 in the ESI for more details).

The ability of TSA calixarenes to perform intermolecular H-bonding interactions was further investigated in the solid state. Indeed, we succeeded in obtaining a single crystal of TSA **B**, which present three ethylethyloxy alkyl chains, through slow evaporation of a methanol solution (Fig. 4).

The molecular structure of **B**, determined *via* microfocus X-ray diffraction, assumes a geometry compatible with a "distorted" 1,2,3-alternate conformation (see Fig. S11-18 in the ESI).[16,17]

Interestingly, each NH moiety of the tosylamide groups is engaged in H-bonding interactions with crystallisation water molecules (Table 3). The donor-acceptor distances NH---O_{water} ranging from 2.807(8) to 2.943(5) Å could be categorise as "moderate, most electrostatic" according to Jeffrey's classification.[18]

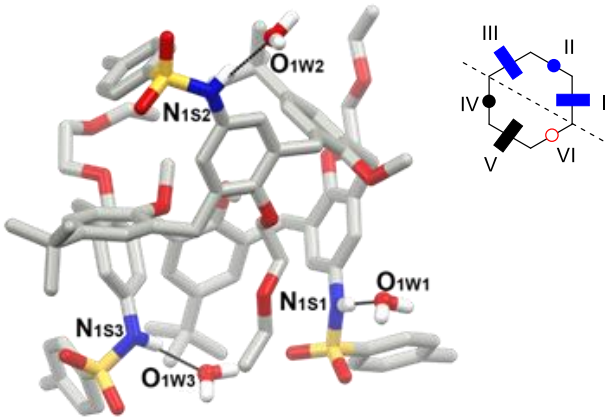


Fig. 4 X-ray molecular structure of TSA **B**. The colours of the ovals and rectangles indicate the relative position of the phenolic substituent with respect to the plane (black, upward; white, outward, blue, downward).

The conformational rearrangement observed in solution, along with the information acquired by solid state analysis, supported the ability a TSA to undergo H-bonding with protic solvents. Based on these studies, we hypothesised H-bonding interactions between TSA and methanol as responsible for the observed boosted reactivity of the Michael addition to nitrolefines.

Table 3 Geometrical patameters for intermolecular hydrogen bonds in TSA **B**

Interaction	Distance D---A (Å)	Distance DH---A (Å)	Angle D-H---A (°)
N1S1---O1W1[a]	2.843(6)	1.96(5)	164.(6)
N1S2---O1W2[a]	2.807(8)	1.98(7)	153.(5)
N1S3---O1W3[a]	2.943(5)	2.083(4)	165.6(3)
O1S1---O1W2[b]	2.874(8)	2.064(6)	146.9(3)
O1S2---O1W3[b]	3.057(7)	2.168(5)	165.0(3)
O2E1---O1W1[c]	2.828(5)	1.990(3)	162.0(4)
O2E2---O1W2[c]	2.877(6)	1.984(5)	170.7(4)

[a] NH tosylamide as hydrogen bond donor, [b] O tosylamide as hydrogen bond acceptor, [c] O ethoxy group as acceptor.

It is a matter of fact these secondary interactions produce several modifications of the physical and chemical properties of organic molecules, including acidity. Although subtle, we could parallel this effect to the one investigated for polyols, where the stabilisation of the charged oxygen centre by H-bonding network, induced an acidity enhancement that was exploited, as we herein reported, for Brönsted acid-catalysed Michael addition reactions.[19] Thus, a plausible catalytic cycle could be depicted.[20] The H-bonding interactions between catalytic amounts of TSA **E** and MeOH induce an acidity amplification of the former, sufficient to work as a Brönsted acid catalyst. The activation of nitroolefin **1a** enables a subsequent nucleophilic attack by the indole. Finally, intermediate **3aa'** undergoes a hydrogen transfer process to deliver the corresponding Michael product **3aa** (Fig. 5).

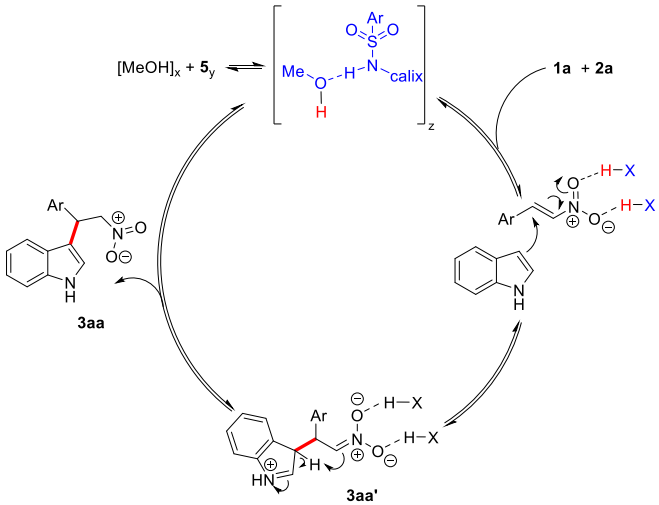


Fig. 5 Proposed mechanism for Michael addition

Conclusions

We offered a proof of principle concerning the application of TSA calixarenes in general acid catalysis. Mechanistic hints supported a supramolecular cooperation between TSA and methanol, established by H-bonding interactions, able to

improve the catalytic performances of a Michael addition to nitroalkenes. At the same time, we demonstrated how the solvent plays an important role in dictating the application of this class of calix[6]arenes. While in apolar solvents, the H-bonding domain has been exploited for the synthesis of supramolecular receptors, here the use of a protic solvent opened access to the unprecedented application of these systems in catalysis.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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17 CCDC 2009420 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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