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**Authors:** Rui Ning, Yu-Fei Ao, De-Xian Wang, and Qi-Qiang Wang



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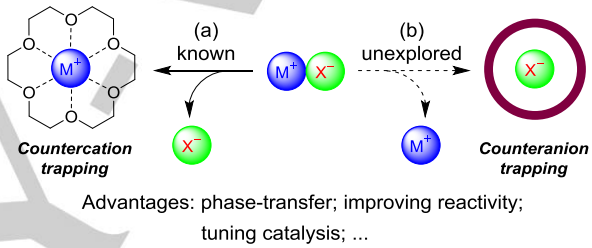
# Macrocycle-Enabled Counteranion Trapping for Improved Catalytic Efficiency

Rui Ning,[a,b] Yu-Fei Ao,[a] De-Xian Wang,[a,b] and Qi-Qiang Wang*[a,b]

**Abstract:** The tight host-guest binding enabled by functional macrocycles can be utilized to tune catalysis. While the strong crown ether-cation complexation has been widely applied on enhancing the reactivity of the paired-anion, the complementary strategy by applying a macrocyclic anion receptor to trap a *counteranion* to improve the cation catalytic activity remains unexplored. To realize this strategy, a macrocycle incorporating multiple cooperative H-bonding sites was synthesized and shown to tightly trap ethanedisulfonate anion in crystals and in acetonitrile solution ($K > 10^6$ $M^{-1}$). With the strong binding tendency, the presence of as low as 0.25 mol% of the macrocycle can significantly improve the ethanedisulfonic acid-catalyzed Povarov reaction efficiency, while the acyclic analogues had diminished effect. Catalysis outcomes and binding studies taken together suggested the macrocycle promotion was through favoring the substrate protonation by trapping the counteranion of the acid catalyst.

In the past decades the tremendous development of supramolecular chemistry has provided abundant supramolecular scaffolds and noncovalent tools to boost catalysis process, and has led to the emergence of supramolecular catalysis.[1] Among which various macrocyclic compounds have been widely used and played a vital role. On one hand, many cavity-containing macrocycle and cage compounds including cyclodextrin,[2] cucurbiturils,[3] cavitands,[4] calixarenes[5] and hemicryptophanes[6] can serve as a catalysis vessel to accommodate reaction substrates within their confined cavitties and facilitate otherwise unfavored transformations in bulk solutions. On the other hand, the macrocycle-enabled high binding affinity towards certain guests can be utilized to mediate a catalysis process through tightly binding an “indirect” catalytic species, *e.g.* counterions. In this context, the strong crown ether-cation complexation has been widely used not only on phase-transfer catalysis[7] by bringing the insloluble alkali metal salts across the phase interface, but also to yield activated anions (*e.g.* “naked” $F^-$) with increased nucleophilicity,[8] and even to realize stereoselectivity control[9,10] (Scheme 1a). Surprisingly, the complementary strategy, for example, applying a macrocyclic anion receptor to trap a *counteranion* and accordingly to tune the cation-directed catalysis process, as far as we know remains unexplored probably due to the complexity on anion binding and catalysis intergration (Scheme 1b, the cation can be simply a proton). Stimulated by the recent progress on anion coordination chemistry,[11] we envisioned that if we can design and incorporate a macrocyclic anion receptor with high binding affinity in a catalysis system to realize this strategy, and specifically to improve catalytic efficiency through trapping an indirect counteranion. Herein we reported the synthesis, binding studies and significant promotion effect of a bi-thiourea macrocycle on acid-catalyzed Povarov reactions. With a strong binding (up to $10^6$ $M^{-1}$) towards ethanedisulfonate counteranion, the presence of as low as 0.25 mol% of the macrocycle can improve the reaction yields from <10% to over 90% in most cases, while the acyclic mono-thiourea analogue has little effect.




**Scheme 1.** Macrocycle-enabled counterion trapping strategies for tuning (catalytic) reactivity.

As containing two mini-chelating H-bonding donors, thioureas are good anion binding groups and usually have a greater binding ability than ureas due to the increased acidity.[12] We chose to incorporate two diarylthiourea units into a macrocyclic motif to take advantage of the macrocyclic cooperativity (Scheme 2). The introduction of electron-withdrawing $CF_3$ groups can further increase the N-H acidity and also the structural rigidity for better preorganization (via facilitating intramolecular phenyl C-H···S H-bonding formation).[13] The resorcinol connection could provide additional C-H H-bonding sites. The synthesis of the macrocycle **5** was straightforward and gram-scale preparation can be easily realized (Scheme 2). By reacting resorcinol with two equivalents of 3-nitro-5-trifluoromethylbenzyl bromide **1** followed by nitro reduction, the diamine **3** was obtained and can be further converted to diisothiocyanate **4** in high yields. The macrocyclization between **3** and **4** in pyridine readily provided the macrocycle product **5** in 59% yield. The crystal structure showed the macrocycle possesses an overall planar conformation (Figure 1a). The two thiourea groups align in parallel and each forms a pair of bifurcated H-bonds with a solvent acetone molecule. This alignment permits only one thiourea group pointing inward the macrocyclic cavity while the other flipping out. The resorcinol connections are nonsymmetric as well by inward/outward -$OCH_2$- orientation on each side. However, the macrocycle should enjoy the conformation flexibility as in solution only one simple set of $^1H$ and $^{13}C$ NMR signals exist.

[a] Mr. R. Ning, Dr. Y.-F. Ao, Prof. Dr. D.-X. Wang, Prof. Dr. Q.-Q. Wang
Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function
Institute of Chemistry, Chinese Academy of Sciences
Beijing 100190, China
E-mail: qiqiangw@iccas.ac.cn
[b] Mr. R. Ning, Prof. Dr. D.-X. Wang, Prof. Dr. Q.-Q. Wang
University of Chinese Academy of Sciences
Beijing 100049, China

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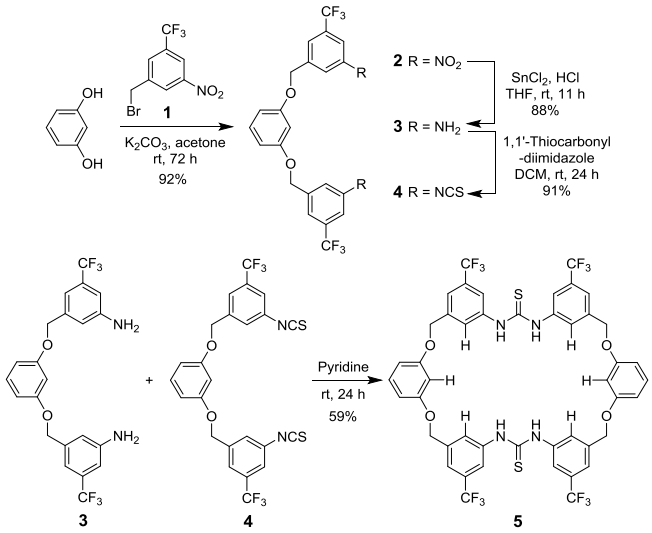



**Scheme 2.** Synthesis of the macrocycle **5**.

With the multiple H-bonding sites existed, the macrocycle would be suitable to bind polydentate sulfonates, which represent an important class of anions and serve as counteranions in many protonic and Lewis acid catalysts.[14] To our delight a complex crystal structure of [**5**•$^{-}O_3SCH_2CH_2SO_3^{-}$][$Et_4N^{+}$]$_2$ was obtained (Figure 1 b,c). The ethanedisulfonate anion is tightly trapped within the nearly-planar macrocyclic cavity. It enjoys mulitiple interactions including two pairs of strong bifurcated H-bonds with the two now inwardly-orientated thioureas (N-H···O distances of about 2.87 Å) and six weak H-bonds with the phenyl and methylene protons. This convergent interaction motif highlights the importance of macrocyclic cooperativity on binding.

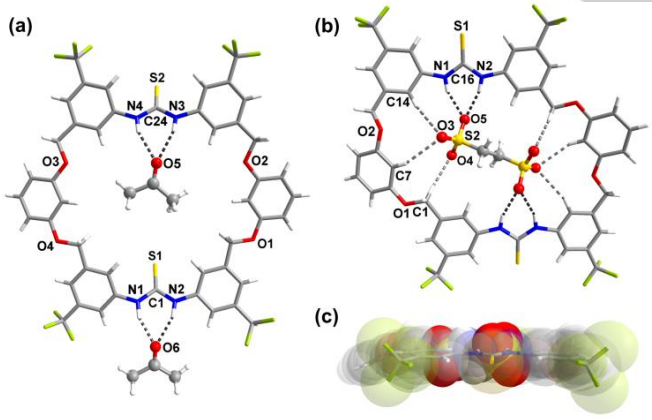



**Figure 1.** Crystal structures of (a) **5**•2$CH_3COCH_3$ and (b, c) [**5**•$^{-}O_3SCH_2CH_2SO_3^{-}$][$Et_4N^{+}$]$_2$. In (b, c) $Et_4N^{+}$ counterions are omitted for clarity. H-bonding distances: in (a) N1-H···O6, 2.842; N2-H···O6, 2.902; N3-H···O5, 2.960; N4-H···O5, 2.968 Å; in (b) N1-H···O5, 2.875; N2-H···O5, 2.867; C14-H···O3, 3.553; C7-H···O3, 3.524; C1-H···O4, 3.401 Å.

The binding affinities of the macrocycle **5** towards different sulfonates were then investigated in solution (Table 1). As shown by $^1$H NMR titrations in $CD_3CN$ (Figure S1), upon addition of ethanedisulfonate (as $TBA^{+}$ salt), the thiourea proton signal underwent large downfield shift ($\Delta\delta_{max}$ = 2.1 ppm), consistent with strong H-bonding interactions. The signals for the inner resorcinol protons and one set $CF_3$-phenyl protons also showed significant downfield shifts, suggesting cooperative or concurrent H-bonding. Upon complexation a large downfield shift (1.3 ppm) for ethanedisulfonate C*H*$_2$ signal was also observed. As the binding affinity is too large to be measured by NMR, it was then determined by isothermal titration calorimetry (ITC) with an apparent binding constant of 2.1 × $10^6$ $M^{-1}$. The affinity is extremely high especially considering the competitive polar solvent acetonitrile was used.[12] The macrocycle shows much weaker binding towards methylenedisulfonate (26 times weaker) and methanesulfonate (270 times weaker) (Table 1), once again showcasing the power of complementary binding enabled by macrocyclic motif with multiple functionality intergration.

**Table 1.** Binding constants *K* [$M^{-1}$] [a] of **5**-**8** with different sulfonate anions.

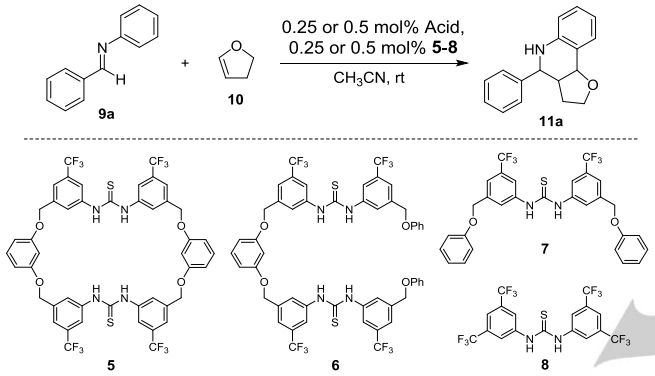
| | $CH_3SO_3^{-}$ | $^{-}O_3SCH_2SO_3^{-}$ | $^{-}O_3SCH_2CH_2SO_3^{-}$ |
|---|---|---|---|
| **5** | 7.8 × $10^3$ | 7.9 × $10^4$ [b, c] | 2.1 × $10^6$ [b, c] |
| **6** | 2.4 × $10^3$ | 3.0 × $10^5$ [b] | 9.6 × $10^4$ [b] |
| **7** | 1.8 × $10^3$ | 3.0 × $10^4$ | 4.8 × $10^3$ |
| **8** | 7.7 × $10^3$ | 8.1 × $10^4$ | 2.9 × $10^4$ |

[a] Determined by $^1$H NMR titrations in $CD_3CN$ at 298 K (errors <10 %). Anions were used as $TBA^{+}$ salts. [b] Determined by ITC in $CH_3CN$ as beyond NMR detectability. [c] Apparent stepwise binding constant for the 2:1 L:A binding.

With the very strong binding of ethanedisulfonate enabled by the macrocycle **5**, we envisioned this system can be incorporated with acid-catalyzed reactions, for example, to trap the counteranion of a acid catalyst and hence improve the "proton" catalytic efficiency. The acid-catalyzed Povarov reaction between benzylidene aniline **9a** and 2,3-dihydrofuran **10**, which represents one of the most convenient synthetic routes to various tetrahydroquinolines,[15] was then investigated. Polar solvent acetonitrile was used as on one hand to ensure the strong binding as above evaluated, and on the other hand to inhibit ion-pair formation which may complicate the situation.[15c] As shown in Table 2, the presence of 0.25 mol% ethanedisulfonic acid (**EDSA**) catalyzed the reaction with only 7% yield in 40 min (entry 1). Strikingly, the co-existence of as low as 0.25 mol% macrocycle **5** dramatically increased the yield to 94% on the same duration (Table 2, entry 2). The macrocycle itself, however, didn't show any catalytic activity within 48 h. To elucidate the macrocycle effect, acyclic analogues **6** and **7** (for synthesis, see Supporting Information), and the privileged Schreiner's thoiurea **8**[16] were also applied in the reactions. While **7** had little effect, **8** and **6** showed some extent of promotion but all significantly less than the macrocycle **5** (Table 2, entries 3-5). The reaction kinetics clearly showed the promotion effect follows the order of **5** > **6** > **8** > **7** (Figure 2), in line with their binding affinity sequence towards the ethanedisulfonate counteranion (Table 1). When methylenedisulfonic acid (**MDSA**) was used as acid catalyst, the macrocycle still showed the most pronounced promotion, albeit

a longer period required to complete the reactions (Table 2, entries 6-10). As from the binding studies the macrocycle showed some weaker binding towards methylenedisulfonate than the acyclic bi-thiourea **6** (Table 1), the outstanding promotion effect could be due to the macrocyclic motif can provide a tighter surrounding to accommodate the counteranion to minimize its interference on the catalytic process. For methanesulfonic acid (**MSA**) catalyzed reactions, both the macrocycle **5** and acyclic analogues **6**-**8** showed little promotion effects (Table 2, entries 11-15). This was not difficult to understand as all of them displayed significantly weaker and no much difference of binding towards the counteranion methanesulfonate (Table 1).

**Table 2.** Macrocycle promotion on acid-catalyzed Povarov reactions comparing with acyclic analogues.[a]




| Entry | Acid[b] | Thiourea | Time | Yield [%][c] |
|---|---|---|---|---|
| 1 | **EDSA** | - | 40 min | 7 |
| **2** | **EDSA** | **5 (0.25 mol%)** | **40 min** | **94** |
| 3 | **EDSA** | **6** (0.25 mol%) | 40 min | 53 |
| 4 | **EDSA** | **7** (0.5 mol%) | 40 min | 9 |
| 5 | **EDSA** | **8** (0.5 mol%) | 40 min | 20 |
| 6 | **MDSA** | - | 1.5 h | 9 |
| **7** | **MDSA** | **5 (0.25 mol%)** | **1.5 h** | **87** |
| 8 | **MDSA** | **6** (0.25 mol%) | 1.5 h | 45 |
| 9 | **MDSA** | **7** (0.5 mol%) | 1.5 h | 13 |
| 10 | **MDSA** | **8** (0.5 mol%) | 1.5 h | 49 |
| 11 | **MSA** | - | 1 h | 77 |
| 12 | **MSA** | **5** (0.25 mol%) | 1 h | 86 |
| 13 | **MSA** | **6** (0.25 mol%) | 1 h | 85 |
| 14 | **MSA** | **7** (0.5 mol%) | 1 h | 81 |
| 15 | **MSA** | **8** (0.5 mol%) | 1 h | 88 |

[a] All the reactions were carried out at rt with **9a** (0.2 mmol) and **10** (0.4 mmol). [b] Acid loading: **EDSA** (0.25 mol%), **MDSA** (0.25 mol%), **MSA** (0.5 mol%). [c] Determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard. *Endo*- and *exo*-forms of products were obtained in *ca.* 1:1 ratios.

The above results clearly illustrated the macrocycle **5** had a dramatic promotion effect on the **EDSA**-catalyzed reactions. To demonstrate the generality of this strategy, a series of *N*-aryl imine substrates with versatile electron-demanding properties were applied (Table 3). For each substrate, three parallel reactions in the absence of any thiourea, in the presence of 0.25 mol% macrocyle **5** and 0.5 mol% acyclic mono-thiourea **7** were performed. Although the intrinsic reactivity for each substrate varies (Table S2), in all cases the macrocycle **5** significantly

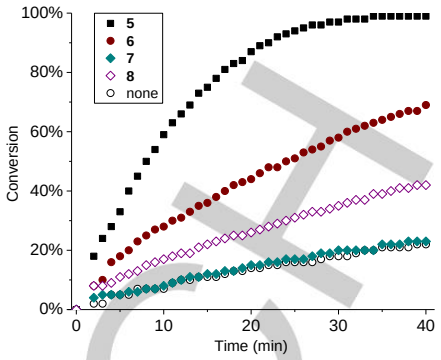
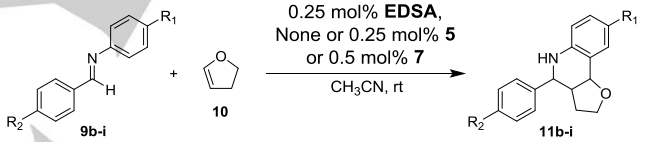



**Figure 2.** Reaction progress for the conversion of **9a** monitored by $^1$H NMR for **EDSA**-catalyzed Povarov reactions in the presence of **5**-**8** in $CD_3CN$. For the reaction conditions, see Table 2 (entries 1–5).

improved the catalytic efficiency, while the acycle **7** had little effects (Table 3). The macrocycle-promoted catalytic reactions can be scaled-up as shown for one case 10-times scaling-up went smoothly without loss of efficiency (Table 3, entry 3). The supramolecular catalysis system can be also applied to three-component Povarov reactions[17] where the macrocycle promotion also stood out (Table S3).

**Table 3.** Macrocycle promotion on **EDSA**-catalyzed Povarov reactions with different imine substrates.[a]




| Entry | 9 | $R_1$, $R_2$ | Time | Yield of **11** [%][b] | | |
|---|---|---|---|---|---|---|
| | | | | None | With **5** | With **7** |
| 1 | **9b** | H, Br | 0.5 h | 6 | 89 | 8 |
| 2 | **9c** | H, $CH_3$ | 3 h | 19 | 95 | 30 |
| 3 | **9d** | H, $NO_2$ | 0.25 h | 2 | 95, 92[c] | 3 |
| 4 | **9e** | H, $OCH_3$ | 8 h | 14 | 75 | 25 |
| 5 | **9f** | Br, H | 0.5 h | 9 | 90 | 11 |
| 6 | **9g** | $CH_3$, H | 2 h | 17 | 90 | 29 |
| 7 | **9h** | $NO_2$, H | 3 h | 15 | 50 | 16 |
| 8 | **9i** | $OCH_3$, H | 5 h | 13 | 81 | 23 |

[a] All the reactions were carried out at rt with **9b-i** (0.2 mmol) and **10** (0.4 mmol) unless otherwise stated. [b] Determined by $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard. *Endo*- and *exo*-forms of products were obtained in *ca.* 1:1 ratios. [c] Isolated yield for 10-times scaling-up reaction.

Further experiments were performed to shed more light on the macrocycle promotion effect. Firstly, the effect of the macrocycle binding on the p$K_a$ of ethanedisulfonic acid was investigated. Ethanedisulfonic acid itself showed a moderate acidity (p$K_{a1}$ = 7.6, p$K_{a2}$ = 12.0) as measured in the reaction solvent acetonitrile (Supporting Information). The strong binding tendancy of the counteranionic species specially ethanedisulfonate dianion by the macrocycle caused significant supramolecular complexation-induced p$K_a$ shifts[18] as large as –1.6 ($\Delta$p$K_{a1}$ ) and –3.0 ($\Delta$p$K_{a2}$)

(Supporting Information). Hence the trapping of the counteranion led to an unusual large acidity enhancement. Secondly, the effect of the counteranion trapping-induced acidity enhancement on substrate imine protonation was explored. Based on NMR studies, the protonation of the imine **9a** in $CD_3CN$ is fast but incomplete with equivalent proton source existed (0.5 eq. ethanedisulfonic acid). The presence of the macrocycle promoted the imine protonation to a more significant extent under the same condition while accompanied by the ethanedisulfonate counteranion trapping within the macrocyclic cavity (Supporting Information). On the other hand, however, the presence of acyclic mono-thiourea **7** didn't show any significant influence on the imine protonation. As the protonated imine is the catalytic resting state for the reaction[15c] and hence its enrichment by the supramolecular counteranion trapping would promote the conversion (Figure 3).

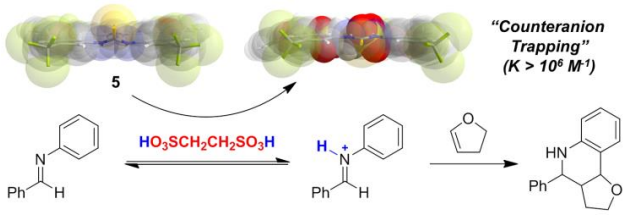



**Figure 3.** Schematic representation of macrocycle-enabled counteranion trapping for promoting the **EDSA**-catalyzed Povarov reaction by favoring the imine protonation.

In conclusion, a macrocycle-enabled counteranion trapping supramolecular catalysis strategy has been demonstrated. Taking advantage of the very strong binding enabled by the designed bi-thiourea macrocycle with multiple and convergent H-bonding sites, the counteranion of ethanedisulfonic acid can be tightly trapped and led to a significant complexation-induced acidity enhancement. When the supramolecular binding system was integrated with the acid-catalyzed Povarov reactions as shown in the current example, the use of as low as 0.25 mol% macrocycle dramatically improved the catalytic efficiency. The acyclic mono-thiourea analogue, however, had little effect, thus showcasing the power of macrocyclic cooperativity on binding and catalysis. In parallel to the largely-explored crown ether-metal ion complexation for anion-directed reactivity control, we believe this macrocycle-enabled counteranion trapping strategy could be also general and can find applications on boosting many cation-directed catalytic transformations. The utilization of this strategy on other types of reactions is undergoing in the laboratory.

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**Keywords:** supramolecular catalysis • macrocyclic compounds • anion binding • counteranion trapping • Povarov reactions

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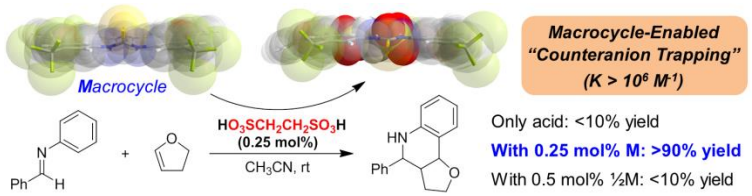
# COMMUNICATION




A macrocycle-enabled counteranion trapping supramolecular catalysis strategy was developed as demonstrated by using as low as 0.25 mol% of a high-binding macrocycle to significantly promote acid-catalyzed Povarov reactions. The macrocycle promotion was through favoring the imine protonation pre-equilibrium by tightly trapping the counteranion of the acid catalyst.

*Rui Ning, Yu-Fei Ao, De-Xian Wang, and Qi-Qiang Wang**

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**Macrocycle-Enabled Counteranion Trapping for Improved Catalytic Efficiency**