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CATALYTIC CYCLOPHANES: A HIGHLY EFFICIENT MODEL FOR PYRUVATE OXIDASE

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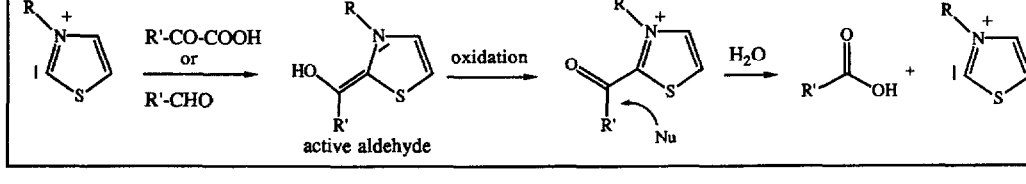
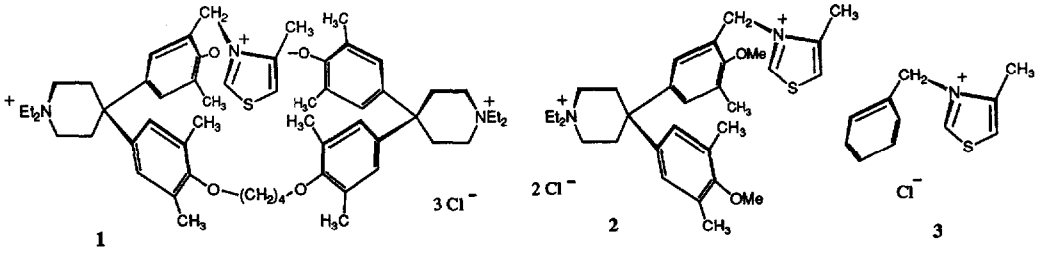
Abstract: The thiazolium macrocycle **1** is prepared by a novel synthetic route to monofunctionalized cyclophanes. Host **1** is a very efficient catalyst for the oxidation of aromatic aldehydes to carboxylic acids in the presence of potassium ferricyanide.

Thiamine pyrophosphate (TPP) serves as the prosthetic group in a variety of enzymes that catalyze, among other functions, the formation and cleavage of carbon-carbon bonds as well as oxidation reactions.[1] The catalytic unit of TPP is the thiazolium ring, and various simple thiazolium salts effect these transformations even in the absence of enzyme.[2] Recently, the preparation of a fully-synthetic thiazolium macrocycle with a cavity large enough to accommodate two benzaldehyde molecules was reported by one of us.[3] It acts as an efficient catalyst of the benzoin condensation.[4] The flavin-dependent enzyme pyruvate oxidase transforms pyruvate into acetate (Scheme 1).[5] The active aldehyde intermediate (Scheme 1, R' = methyl) is oxidized, followed by rapid solvolysis, resulting in the production of acetate and the regeneration of the thiazolium ylide. In a similar sequence, aldehydes are oxidized to carboxylic acids. This conversion has been catalyzed by simple thiazolium ions,[6] thiazolium micelles,[7] and thiazolium-cyclodextrin derivatives[4] in the presence of a variety of oxidation agents, e.g. ferricyanide.The cyclophane **1** consists of a cavity complementary in size to one benzene or naphthalene molecule. A thiazolium ring is attached to the binding site via a benzylic linkage. We describe here the synthesis of **1** and its catalytic activity in the oxidation of aromatic aldehydes to carboxylic acids.

Scheme 1

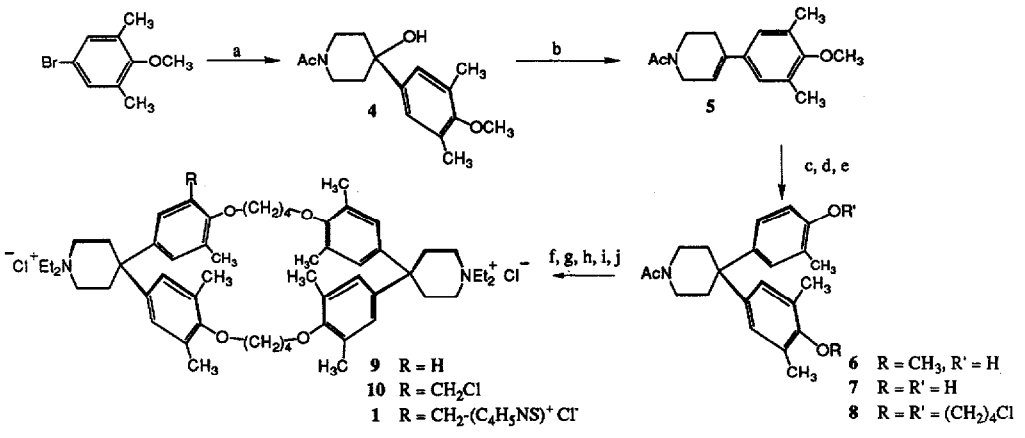




1 2 3

The novel synthetic sequence to regioselectively monofunctionalized cyclophanes is shown in Scheme 2.[8] The Grignard reagent of 4-bromo-2,6-dimethyl-anisole reacted with 1-acetyl-4-piperidone to form the alcohol **4** which, upon dehydration, yielded the olefin **5**. Treatment of **5** with $BF_3{\cdot}OEt_2$ and *o*-cresol afforded **6** which was demethylated with BBr_3 to give the asymmetrically substituted bisphenol **7**.[9] The cyclization component **8** was converted into the quaternized macrocycle **9** following established procedures.[10] Chloromethylation of **9** with HCl/CH_2O in acetic acid gave the benzyl chloride **10**. Refluxing **10** in acetonitrile with an excess of 4-methylthiazole afforded the water-soluble thiazolium cyclophane **1**. The non-macrocyclic comparison compound **2** was obtained by a similar sequence.

Scheme 2



(a) Mg, THF; then 1-acetyl-4-piperidone, 65%. (b) TsOH, toluene, reflux, 53%. (c) 2.7 eq. $BF_3{\cdot}OEt_2$, 3 eq. *o*-cresol, 85° C, 2.5h, 95%. (d) 1.5 eq. BBr_3, $CHCl_3$, 0°C, 15h, 84%. (e) $Cl(CH_2)_4Cl$, NaOH, K_2CO_3, n-BuOH, 66%. (f) 1-Acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine, Cs_2CO_3, DMF, 13%. (g) $LiAlH_4$, THF, 88%. (h) EtI, $CHCl_3$, ion-exchange (Cl^-), 97%. (i) CH_2O, HCl, CH_3COOH, 80%. (j) 4-Methylthiazole, CH_3CN, reflux, 68%.

The ^1H NMR spectrum of **1** in D_2O revealed that its thiazolium moiety is located within the cavity. Considerable upfield shifts of all thiazolium protons are observed as compared to the same resonances in **3** (2-H: +0.70 ppm, 5-H: +0.39 ppm, 4-CH_3: +0.27 ppm). Therefore, ^1H NMR (500 MHz, T = 293K) binding studies[11] were performed in 60:40 (v/v) D_2O:CD_3OD to analyze how the thiazolium ion influences the binding of aromatic substrates. A comparison of the calculated free energies of complexation for various aromatic guests with hosts **1** and **9** revealed that the binding to **1** is weaker by 0.4 - 0.7 kcal·mol^{-1} (Table 1). We propose that a large part of this energy is needed to displace the thiazolium ring from the cavity by an incoming guest.

The oxidation of 2-naphthaldehyde (2.0 mM - 36.0 mM) is catalyzed by **1** (0.5 mM) in the presence of potassium ferricyanide (5.0 mM) in 60:40 (v/v) Me_2SO: aqueous phosphate buffer (pH = 7.5) at 303K.[4] For comparison, this oxidation was also studied under similar conditions with the non-macrocyclic derivatives **2** and **3**. The course of the reaction was followed by monitoring the decrease in absorbance of the Fe (III) chromophore at λ = 420 nm. The reaction is zero order in ferricyanide. Initial velocities were obtained using the initial linear portion of the absorbance vs. time plots.[12] These rates were corrected by

subtracting background rates for slow thiazolium catalyst oxidation.[13] The background rate of oxidation of **1** is 5-15% of the total rate measured in the presence of 2-naphthaldehyde. A comparison of initial rates demonstrates that the oxidation of 2-naphthaldehyde by **2** and **3** is considerably slower (Table 2). The background oxidation rate of these catalysts is 25-95% of the total rate. No reduction of ferricyanide was observed in the absence of a thiazolium catalyst.

Table 1: Association Constants, K_a, and the Free Energies of Complexation (ΔG^o) at 293 K in 60:40 (v/v) D_2O:CD_3OD

	K_a L·mol^{-1}	ΔG^o kcal·mol^{-1}	$\Delta(\Delta G^o)$ kcal·mol^{-1}
Complexes of **1**			
p-dicyanobenzene	$3.49 \cdot 10^2$	-3.41	
6-methoxy-2-naphthonitrile	$4.81 \cdot 10^3$	-4.94	
2-naphthaldehyde	$1.97 \cdot 10^3$	-4.42	
benzaldehyde	$1.20 \cdot 10^2$	-2.79	
Complexes of **9**			
p-dicyanobenzene	$1.14 \cdot 10^3$	-4.10	0.69
6-methoxy-2-naphthonitrile	$1.50 \cdot 10^4$	-5.60	0.66
2-naphthaldehyde	$6.34 \cdot 10^3$	-5.10	0.68
benzaldehyde	$2.39 \cdot 10^2$	-3.19	0.40

Table 2: Kinetic Data for the catalyzed oxidation of 2-naphthaldehyde to 2-naphthoic acid (T = 303K).

Catalyst	Initial Velocities ($M \cdot s^{-1}$) [a]	Second Order Rate Constants ($M^{-1} \cdot s^{-1}$)
1	$4.18 \cdot 10^{-6}$	$k_{cat}/K_M = 2.8$
2	$1.17 \cdot 10^{-7}$	$k_2 = 0.037$
3	$3.90 \cdot 10^{-8}$	$k_2 = 0.0061$

[a] at [naphthaldehyde] = 6.0 mM, [catalyst] = 0.5 mM; corrected for background rate of catalyst oxidation.

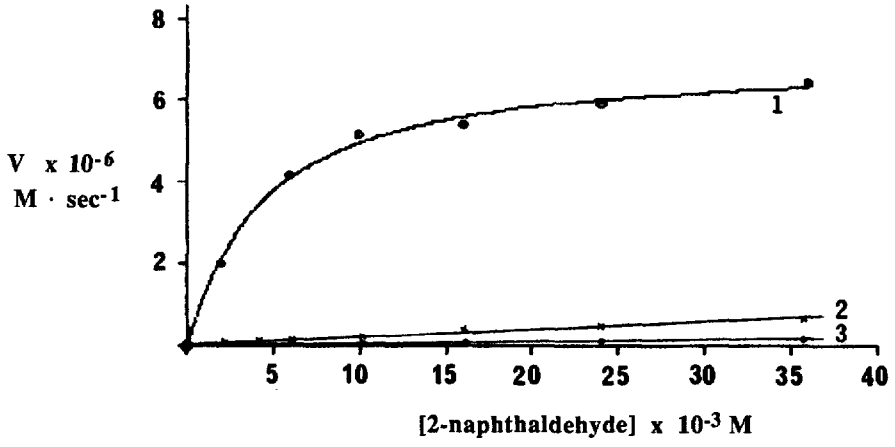


Figure 1: Plot of initial rates vs substrate concentration for the oxidation of 2-naphthaldehyde catalyzed by the thiazolium derivatives **1**, **2**, and **3** (T= 303K, [catalyst] = 0.5 mM).

Saturation kinetics were observed with the cyclophane **1** (Figure 1). A Lineweaver-Burke plot {1/V vs. 1/[S]} gave $K_M = 5.4$ mM and $V_{MAX} = 7.5 \cdot 10^{-6}$ M · s^{-1}. The turnover number, k_{cat}, was calculated to be 0.015 s^{-1}. In contrast, rates in the presence of **2** and **3** increased in a linear fashion with increasing

substrate concentration. A comparison of the apparent bimolecular rate constant, k_{cat}/K_M, of **1** with the calculated second-order rate constants of the simple thiazolium salts **2** and **3** reveals that the rate acceleration is 75-fold between **1** and **2** and 460-fold between **1** and **3** (Table 2). The formation of 2-naphthoic acid was confirmed by ^{1}H NMR spectroscopy. Comparison with authentic samples of 2-naphthaldehyde and 2-naphthoic acid showed that no other by-product was formed. The naphthoin condensation was studied by ^{1}H NMR (500 MHz) at 50°C in 60:40 (v/v) Me_2SO-d_6:D_2O (initial concentrations of: [**1**] = 0.5 mM, [2-naphthaldehyde] = 26 mM, [NEt_3] = 40 mM; under Ar). Even after 4 h, no sign of naphthoin formation could be detected. The association constant and the free energy of formation of the 1:1 complex between **1** and 2-naphthaldehyde were determined from a ^{1}H NMR titration performed in 60:40 (v/v) Me_2SO-d_6:D_2O at 303K as K_a =115 L·mol^{-1} and ΔG^o = -2.86 kcal·mol^{-1}. This data is in good agreement with the kinetic K_M value.

Our preliminary studies have shown that **1** is an excellent, selective catalyst for the oxidation of an aromatic aldehyde. It exhibits saturation kinetics and large rate accelerations as compared to simple thiazolium salts. Future studies will focus on the catalyzed formation of other acid derivatives, e.g. of esters in alcohols and of amides in non-nucleophilic solvents that promote complexation. Electrochemical oxidation will also be explored as a means to oxidize the active aldehyde without the concomitant destruction of the thiazolium ring.

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References and Notes

[1] a) Stryer, L. *Biochemistry*, 3rd ed., Freeman: New York, 1988. b) Kluger, R. *Chem. Rev.* **1987**, *87*, 863-876. c) Walsh, C. *Enzymatic Reaction Mechanisms* , Freeman: New York, 1979, pp 690-696.

[2] Breslow, R. *J. Am. Chem Soc.* **1958**, *80*, 3719-3726.

[3] Lutter, H.-D.; Diederich, F. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1125-1127.

[4] a) Hilvert, D.; Breslow, R. *Bioorg. Chem.* **1984**, *12*, 206-220. b) Breslow, R.; Kool, E. *Tetrahedron Lett.* **1988**, *29*, 1635-1638.

[5] a) Hager, L. *J. Biol. Chem.* **1957**, *229*, 251-263. b) Lienhard, G. *J. Am. Chem. Soc.* **1966**, *88*, 5642-5649. c) Bergmann, N.; Schmidtchen, F. P. *Tetrahedron Lett.* **1988**, *29*, 6235 - 6238.

[6] a) Yano,Y.; Tsukagoshi Y. *J. Chem. Research (S)* **1984**, 406-407. b) Castells, J.; Llitjos, H.; Moreno-Manas, M. *Tetrahedron Lett.* **1977**, 205-206. c) Inoue, H.; Higashiura, K. *J. Chem. Soc., Chem. Comm.* **1980**, 549-550. d) Inoue, H.; Tamura, S. *ibid.* **1985**, 141-142.

[7] a) Yano, Y.; Hoshino, Y.; Tagaki, W. *Chem. Lett.* **1980**, 749-752. b) Shinkai, S.; Yamashita, T.; Kusano, Y.; Manabe, O. *Tetrahedron Lett.* **1980**, 2543-2546. c) Shinkai, S.; Yamashita, T.; Kusano, Y.; Manabe, O. *J. Org. Chem.* **1980**, *45*, 4947-4952.

[8] Spectroscopic data (IR, ^{1}H NMR, EI-MS and FAB-MS) and elemental analyses support the structures proposed for new compounds.

[9] Our warmest appreciation goes to Stephen B. Ferguson, UCLA, for working out a general method for producing asymmetric bisphenols such as **7**.

[10] a) Diederich, F.; Dick, K.; Griebel, D. *Chem Ber.* **1985**, *118*, 3588-3619. b) Dharanipragada, R.; Ferguson, S.; Diederich, F. *J. Am. Chem. Soc.* **1988**, *110*, 1679-1690.

[11] Association constants, K_a, free energies of formation, ΔG^o, and complexation shifts at saturation binding, $\Delta\delta_{sat\ calc}$, were determined from non-linear least square fitting of NMR titration curves ($[G]_o = 5 \cdot 10^{-4}$ M and $[H]_o = 5 \cdot 10^{-4}$ - $5.5 \cdot 10^{-3}$ M).

[12] Absorbance measurement times were for 1 s and were taken 12 s apart. Initial velocities were calculated using points during the first 1-2 min when plots of absorbance vs. time were still linear. For thiazolium catalyst **1**, the reaction was typically 7-15% complete during this time period.

[13] El Hage Chahine, J.-M.; Dubois, J.-E. *J. Am.Chem. Soc.* **1983**, *105*, 2335-2340.

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