Cavitand templated catalysis of acetylcholine†

Felix H. Zelder and Julius Rebek, Jr.*

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A Zn–salen-modified cavitand templates the catalytic formation of acetylcholine from choline and acetic anhydride.

The catalytic esterification of alcohols by enzymes or chemocatalysts plays a key role in biological systems, organic synthesis and industry. Despite the long history of this reaction, progress in the kinetic resolution of racemic alcohols with chiral, non-enzymatic acylation catalysts has only recently attracted attention.[1] Moreover, little is known about substrate-selective acylation involving alcohols differing in size and shape.[2]

Cavitands derived from resorcinarenes are supramolecular hosts that selectively bind suitable guests.[3] Specifically, guests bearing a trimethylammonium "knob" are well positioned deep within the cavity. Recently, we demonstrated how the Zn–salen monofunctionalised complex cavitand **Zn–1** (Fig. 1) can accelerate the hydrolysis of the bound guest *para*-nitro phenyl choline carbonate (PNPCC).[4] Other examples of catalyst-modified calixarenes or cavitands have been applied in this context, but all of these examples report the catalytic cleavage of activated choline derivatives.[4,5]

Acetylcholine (**ACh**) is a neurotransmitter generated from choline (**Ch**) and acetyl coenzyme A. Since cavitands bind choline derivatives[3,4,5b] and Zn complexes catalyze the acylation of alcohols,[1e,2] it was expected that **Zn–1** may template the catalytic formation of **ACh** from **Ch** and acetic anhydride (**4**) (Scheme 1, left). Herein, we report the esterification of **Ch** with anhydrides in the presence of **Zn–1**.

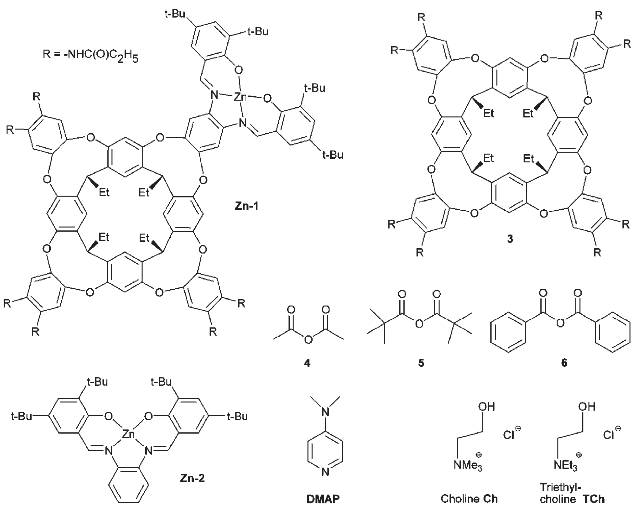


Fig. 1 Compounds used in the esterification reactions.

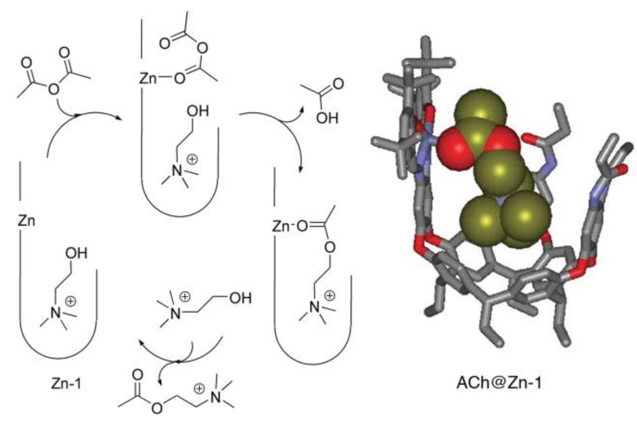
An energy-minimized structure of the host–guest complex **ACh@Zn–1** indicates that binding through cation–π-interactions and Zn^{2+}–carbonyl coordination can take place simultaneously (Scheme 1, right). To ensure the solubility of all components and enable weak binding for the desired catalytic turnover, the acylation of choline was carried out in DMSO-d_6 and monitored by ^{1}H-NMR spectroscopy (Table 1).

In the absence of catalyst, the acylation with **4** is very slow (Table 1, entry 1), whereas the reaction is significantly accelerated in the presence of **Zn–1** (Table 1, entries 2–5).‡

In the presence of 0.4 mol% of **Zn–1**, the acylation is accelerated 320 times, and when 2 mol% of **Zn–1** is added, the reaction takes place 1900 times faster than the background reaction (Table 1, entries 2 and 5). Compared to the reaction catalyzed by **Zn–1** (Table 1, entry 5), the reaction is up to 23 times slower when the metal complex **Zn–2** is not covalently attached to the cavitand **3** (Table 1, entry 10) or used without any additional binding pocket (Table 1, entry 6).

No reaction is observed with **3** alone (Table 1, entry 9). It is puzzling that a catalytic amount of the non-functionalized cavitand **3** slows down the reaction (Table 1, entry 9 *vs.* 1), and we observed this effect in almost all other control experiments (Table 1, entries 10, 14 and 15).

When the bulkier **TCh** is used as a substrate, the **Zn–1**-catalyzed acylation is 6 times slower (Table 1, entry 8), whereas almost no



Scheme 1 Left: Catalytic formation of **ACh** from **Ch** and **4**, triggered by **Zn–1**. Right: Energy-minimized structure (CaChe 4.9©) of the complex between **Zn–1** (stick) and **ACh** (CPK); the front wall and the hydrogens have been omitted for clarity.

The Skaggs Institute for Chemical Biology and The Department of Chemistry, The Scripps Research Institute, MB-26, 10550 North Torrey Pines Road, La Jolla, California, 92037, USA.
E-mail: jrebek@scripps.edu; Fax: (+1) 858-784-2876;
Tel: (+1) 858-784-2250

† Electronic Supplementary Information (ESI) available: Correlation of k_{ob} *vs.* **Zn–1**; representative ^{1}H-NMR spectra; experimental details, binding of **Ch@Zn–1** and **ACh@Zn–1**; preparation of the chloride salt of **TCh**. See DOI: 10.1039/b515558d

Table 1 Acetylation of choline **Ch** and triethylcholine **TCh** in the presence of acetic anhydride[a]

Entry	Catalyst (Quantity)/mol%	Substrate	$k_{ob}/\times\ 10^{-4}\ min^{-1}$	k_{ob}/k_{uncat} [b]
1	—	**Ch**	0.1	1
2	**Zn–1** (0.4)	**Ch**	32	320
3	**Zn–1** (0.6)	**Ch**	46	460
4	**Zn–1** (1.0)	**Ch**	72	720
5	**Zn–1** (2.0)	**Ch**	190	1900
6	**Zn–2** (2.0)	**Ch**	14	140
7	**Zn–2** (2.0)	**TCh**	11	110
8	**Zn–1** (2.0)	**TCh**	32	320
9	**3** (2.0)	**Ch**	—	—
10	**Zn–2/3** (2.0)	**Ch**	8	80
11	**Zn–2/3** (2.0)	**TCh**	11	110
12	**DMAP** (2.0)	**Ch**	180	1800
13	**DMAP** (2.0)	**TCh**	200	2000
14	**DMAP/3** (2.0)	**Ch**	140	1400
15	**DMAP/3** (2.0)	**TCh**	170	1700

[a] Conditions: **Ch**, **TCh** (50 mM), **4** (50 mM); DMSO-d_6, 25 ± 2 °C. Detection method: ^{1}H-NMR. Error limit: 20%. [b] $k_{ob} = \frac{rate}{[Ch]}$; $k_{uncat} = \frac{rate_{(entry\ 1)}}{[Ch]}$

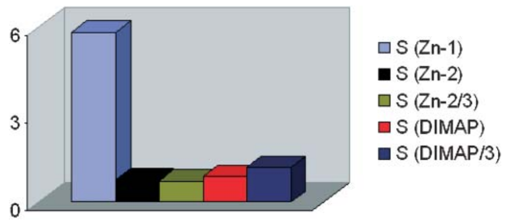


Fig. 2 Selectivity (*S*) of the acylation of **Ch** *vs.* **TCh** ($k_{ob(Ch)}/k_{ob(TCh)}$).

selectivity (*S*) ($k_{ob(Ch)}/k_{ob(TCh)}$) is observed with the metal complex **Zn–2** (Table 1, entries 6 and 7; Fig. 2).

We assume that weak binding of **Ch** and **ACh** within **Zn–1** (K_a = 10 and 20 M^{-1}, respectively)†§ is responsible, since product inhibition has not been observed.‡ In contrast to **Ch**, the bulkier **TCh** showed no inclusion within the cavity.

The **Zn–1**-templated acylation of **Ch** with **4** is in the range of the same reaction catalyzed by dimethylaminopyridine (**DMAP**), one of the best organic acylation catalysts. **DMAP**, or the combination of **DMAP** with cavitand **3**, showed, *as expected*, no selectivity between the electronically equivalent guests **Ch** and **TCh** (Table 1, entries 12–15; Fig. 1). Sterically more demanding anhydrides experienced slower kinetics during the course of the reaction. The relative reactivity of anhydrides **4–6**, tested in the **Zn–1**-catalyzed acylation of **Ch**, were as follows: **4** : **6** : **5** = 15 : 2 : 1.†

In summary, metal complex-modified cavitands are supramolecular catalysts for the synthesis of biologically-relevant **ACh** from **Ch** and **4**. Their ability to discriminate and accelerate the esterification of choline has been demonstrated. Additionally, the activity and selectivity of the metal catalyst is unequivocally enhanced when the metal complex is well positioned at the periphery of the binding pocket.

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Notes and references

‡ As an undesired side reaction, hydrolysis of the anhydride occurred from residual water (6–11% after *ca.* 100 min).

§ The signals of the host are strongly broadened by dynamic effects, probably involving exchange equilibration with the alternative "kite" conformation. Therefore, the binding constant was calculated only from the trimethylammonium "knob" signals of the guests ($\Delta\delta$ = 3.6 ppm). This precludes the accurate determination of the binding constant.

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