WARWICK

Chemical catalytic properties and photophysical properties of a coordination cage host

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Octanuclear cubic cage is a stable, nicely-sized host

Window diameter $\approx 4 \text{ \AA}$

Anions located around surface

Water-solubility makes for excellent guest binding

MeCN soluble Co_8L_{12} host cage

Water soluble Co_8L_{12} host cage

Hydrophobic effect ensures strong binding of guests in water

Binding constants $10^3 - 10^6 \text{ M}^{-1}$ in water depending on hydrophobic surface area / goodness of fit

1:1 binding from many luminescence / NMR titrations and crystal structures

‘Crystalline sponge’ experiments allow guest sorption

Binding of guests in water related to hydrophobic surface area

- Perfectly linear increase in ΔG with hydrophobic surface area (5 kJ/mol per CH_2 group)
- Matches results from protein folding (Alan Fersht)
- Decrease in ΔG above 'Rebek limit' (55% of cavity volume) as guests get too large
- Best guest (C_{11} ketone) has $K = 1.2 \times 10^6 \text{ M}^{-1}$ in water

Can predict binding constants using molecular docking software (GOLD) and custom scoring function.

Scoring function:

$$\log K_{\text{calc}} = -4.48 f(\text{ligand_clash}) + 0.20 f(\text{part_buried}) - 0.10 f(\text{non-polar}) + 0.90 f(\text{ligand_torsion}) - 0.93 f(\text{ligand_flexibility})$$

Use this improved scoring function to predict binding of new guests from a 'virtual library' of 3000 molecules....

- Excellent agreement between prediction and calculation
- Several new strongly-binding guest types identified *quickly*

Windows on surface provide anion binding pockets

Remember these ?!

Windows in cyclic helicates bind anions / exert templating effects

Nobel Lectures

P. J. Crutzen
M. J. Molina
F. S. Rowland

Lehn, 1996

Dunbar, 2005

Orthogonal interactions bring together cavity-bound and surface-bound species

Two components can be varied independently of one another

Catalysis in the cage cavity

Kemp elimination

Reaction can easily be followed by ^1H NMR:

Clear acceleration in presence of cage

Catalysed reaction pH independent as all cage windows contain $[\text{HO}^-]$ even at pD 8.5

Background reaction first order in $[\text{HO}^-]$

Maximum acceleration 2×10^5 at pD ≈ 8.5

1 HO^- in each window of cage makes local $[\text{DO}^-] \approx 1\text{M}$ around substrate

Cage catalysis – essential control experiments

1. Cycloundecanone displaces substrate:
reaction now at uncatalysed rate

2. XS Chloride ions bind more strongly to cage surface and displace hydroxides:
reaction now at uncatalysed rate

- **Two orthogonal interactions:** hydrophobic cavity binds guest; cationic surface binds anions
- Multiple turnovers because anionic product is released (hydrophilic)

Changing the anion... onset of autocatalysis

Addition of Cl^- not only inhibits reaction, it also changes its nature...

Rebek and co-workers, PNAS 2010, 107, 541

2-cyanophenolate (product) acts as base to deprotonate benzisoxazole

'Soft' anion, easily desolvated, high affinity for hydrophobic but cationic cage surface

phenolate > Cl⁻ > HO⁻

- Cl⁻ displaces HO⁻ from cage surface and shuts down Kemp elimination
- As 2-cyanophenolate forms it displaces Cl⁻ from cage surface *and acts as a base to catalyse its own formation*

What about other substrates in the cavity?

Dichlorvos – toxic organophosphate insecticide – destroyed by hydroxide

Binds weakly in cage cavity

$K = 16 \text{ M}^{-1}$ in water

Catalysed hydrolysis: pD 7.5, 298K, observed by ^{31}P NMR

$$k_{\text{cat}} / k_{\text{uncat}} \approx 1000$$

Other phosphotriesters behave similarly with 10^3 -fold acceleration of hydrolysis

unpublished

One control experiment too far!

Blocking cavity with strongly binding cycloundecanone *makes no difference* to rate of disappearance of dichlorvos!

Conclusion: catalysed hydrolysis on cage exterior surface

More control experiments!

(i) Use substrate that does not fit inside cage cavity at all

‘Para-oxon’: another insecticide

... still seeing catalysis

(ii) Use a smaller cage with no significant cavity

Smaller M_4L_6 cage with cavity that only binds $[BF_4]^-$ acts as comparably good catalyst for phospho-ester hydrolysis!

Crystal structure shows both starting material and 4-nitrophenolate product in contact with cage exterior surface

Same proximity of reactants – but not dependent on good match for cavity

Contact of hydrophobic surfaces on cage exterior

accumulation of anions driven by ion-pairing

Surface that is both **hydrophobic** and **cationic**

“In this work, the authors illustrate a (sort of) novel property of self-assembled cage-based catalysis, in that solvolysis can be catalyzed at the exterior surface of highly cationic cages, rather than in the cavity. The conclusion is pretty obvious, really, and the kind of thing we will look back at in 10 years and say “well, of course that happens”. Surface scientists and physical organic chemists would also probably say that this is obvious. However, I agree with the authors - this type of mechanism is definitely not considered when catalysis applications of cage hosts are studied.”

Another external-surface catalysed reaction

Indane-1,3-dione
Colourless
 $\text{pK}_a \approx 7$

'Bindone' (purple) *via*
aldol condensation

Neutral guests inside cavity...

... and enolate forms interacting with
exterior surface (short $\text{CH}\cdots\text{O}$ bonds)

Weak acid ($\text{pH} \approx 4$) – no detectable aldol reaction in absence of cage

Catalysed reaction very slow (few % conversion after 12h): but happening!

Competing cavity-blocker (CUD) makes little difference to rate profile

Co-location of neutral indane-dione and enolate anion around cage surface promotes catalysis

Stabilisation of enolate anions: valuable / general catalytic utility?

Synthesis / host guest chemistry / photophysics / catalysis

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