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Activation and Orientation by Receptor-Substrate Binding. The Case of Acyl Transfer from O-Acetylhydroxylamine[≠]

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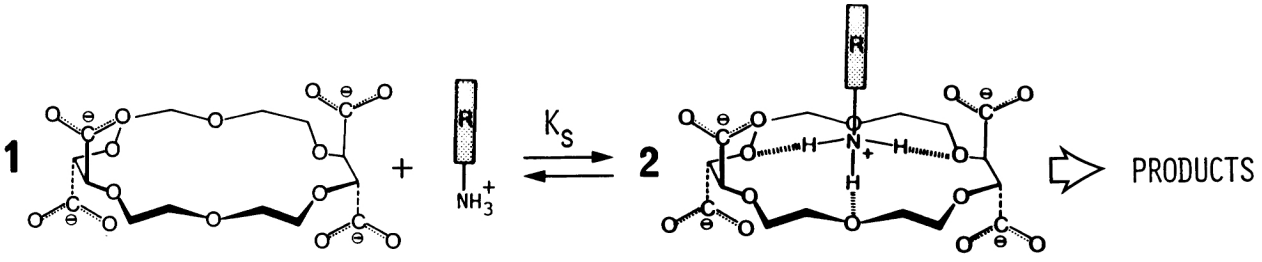
The strong binding ability of the receptor molecule 1 induces complexation of O-acetylhydroxylamine and of hydroxylamine in their protonated forms ; as a result, subsequent reaction of bound $CH_3COONH_3^+$ becomes fast and selective, giving only acetic acid with a rate enhancement by a factor of about 30.

Substrate binding and subsequent transformation by functionalized receptor molecules have been actively studied for designing selective chemical processes, supramolecular reagents and catalysts, and mimics of enzymatic reactions.[2,3)] Thus, macrocyclic polyethers bearing functional groups react with bound substrates, anchored to the macrocyclic cavity by a primary ammonium site, displaying substrate specificity, rate enhancement and chiral discrimination.[2-5)] However, binding itself may markedly affect the reactivity of the receptor-substrate supermolecule by modifying the properties of the species in the complex with respect to the free state, or by favouring or hindering a given reaction path. For instance, if a suitable receptor molecule binds more strongly the protonated state of substrates than their unprotonated one, it may induce : 1) substrate <u>protonation</u> through binding, 2) <u>activation</u> and 3) <u>orientation</u> if the bound protonated species have a higher and/or different reactivity compared to the unprotonated ones.

We describe here such effects for the deacylation of O-acetylhydroxylamine CH_3COONH_2 in presence of the macrocyclic polyether 1 bearing four carboxyl groups derived from tartaric acid.[6)] 1 is a receptor for primary ammonium substrates which are bound by the $-NH_3^+$ group to the macrocyclic cavity.[7)]. The complexes 2 formed are the most stable ones known to date for macrocyclic polyethers, due mainly to strong electrostatic interactions between the $-COO^-$ and $-NH_3^+$ groups.[8)]



≠ Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

pH-metric determination of the equilibrium constants between $CH_3COO-NH_2$,[9] $HO-NH_2$, $H_2NCOO-NH_2$[10] or $CH_3CONH-NH_2$,[11] and the macrocyclic receptor 1 in its different ionization states gave distributions curves like those shown in Fig. 1.

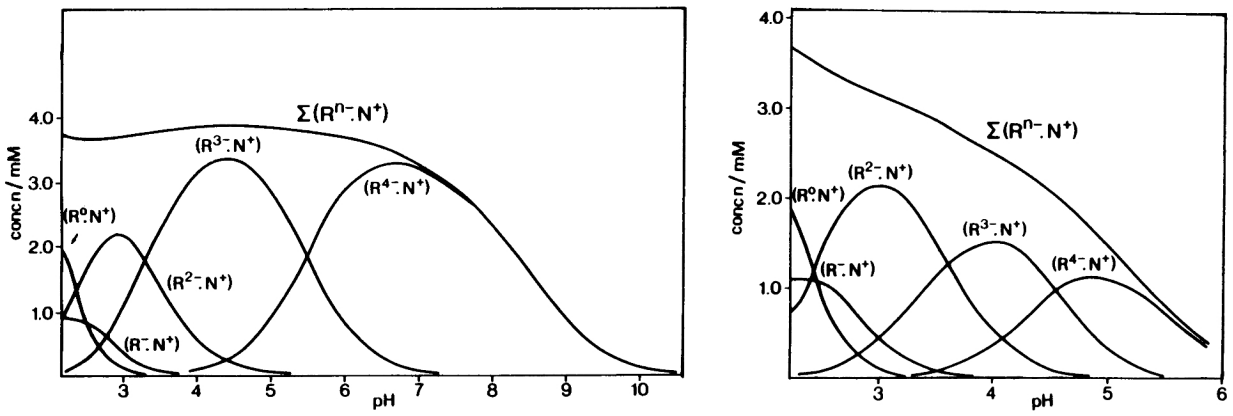


Fig. 1. Distribution curves of the complexes formed by $N^+ = HO-NH_3^+$ (left) and $CH_3COO-NH_3^+$ (right) with the non-, mono-, di-, tri-, and tetra-ionized forms, R^0, R^-, R^{2-}, R^{3-}, and R^{4-} of the tetracarboxylic receptor molecule 1; 5.0 mM 1 and N^+; 0.1 M NMe_4Cl in H_2O/dioxane 95/5 v/v at 20 °C. The curves were calculated from the equilibrium constants (K_s and pK_a's) for the various species, obtained by computer analysis of the pH-metric curves determined by titration with 0.1 M NMe_4OH; NMe_4^+ counterions are not bound.[8]

The following pK_a values for free and bound substrates $R-NH_2$ and the stability constants log K_s for the complexes with tetracarboxylate 1 (R^{4-}) were obtained :

R =	CH_3-	H_2N-	CH_3CONH-	HO-	H_2NCOO-	CH_3COO-
pK_a (free)	10.60	8.20	3.30	6.00	2.45	2.15
pK_a (bound)	(13.5)	11.80	7.70	11.00	7.55	7.70
log K_s	2.90[8]	3.60[12]	4.40	5.00	5.10	5.55

The stability increases and becomes very large as the pK_a of the free $R-NH_2$ decreases and the electronegativity of R increases. The comparatively stronger binding of hydroxylamine may be due to additional effects, like lower steric hindrance and hydrogen bonding. The effective pK_a's of the bound species are much higher than those of the free ones, so that complexes of $R-NH_3^+$ will form at pH values for which the free species are entirely unprotonated. In particular, a significant amount of O-acetylhydroxylamine will be bound in the protonated form as ($R^{4-}.N^+$), ca. 20% at pH = 5 (Fig. 1) and ca. 50% at pH = 5.5 (recalculated from data for 53 mM). Such large pK_a shifts due to strong receptor-substrate binding have been observed for complexation of NH_4^+ by a receptor possessing a tetrahedral recognition site.[13]

In conclusion, strong binding is a prerequisite for the existence of $CH_3COONH_3^+$ as a complex with 1 (R^{4-}). One may expect the bound protonated species to have different reactivities from the unbound, unprotonated ones.

Hydrolysis of CH_3COONH_2 in aqueous solution yields CH_3COOH and NH_2OH as well as the rearranged acetohydroxamic acid $CH_3CONHOH$, which results from reaction of the NH_2OH produced with CH_3COONH_2.[9,11] Protonation and binding of substrate and product brought about by 1 (see above) should generate a better leaving group and hinder N-acylation. The half-life and products of the reaction of CH_3COONH_2 in presence of 1 are given in the Table 1, with either NMe_4^+ or K^+ counterions.

Table 1. Half-life of the Reaction of O-Acetylhydroxylamine in Presence of Receptor 1 and Percentage of N-Acetylhydroxylamine Formed[a)]

M^+ b)	K^+				NMe_4^+			
pH	3.0	4.0	4.4	5.5	4.0	4.4	5.5	6.0
Half-life (hours)	18	23	30	56	2.5	2.2	1.8	3.7
% $CH_3CONHOH$	27	55	63	37	2	2	2	2

a) 53 mM 1 and CH_3COONH_2 in dioxane/D_2O 1/1 at 50 °C; pH adjusted with NMe_4OH; half-lifes and % $CH_3CONHOH$ determined by NMR at 200 MHz by observing the formation of CH_3COOH and $CH_3CONHOH$.
b) Counter-cation of the tetracarboxylate 1.

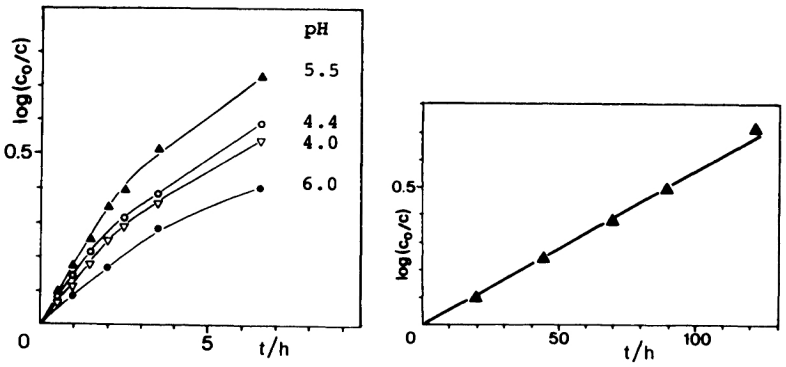


Fig. 2.
Reaction of substrate CH_3COONH_2 in presence of receptor 1; left : NMe_4^+ counterions, at pH indicated; right : K^+ counterions at pH = 5.5; 53 mM CH_3COONH_2 and 1 in water/dioxane 1/1; 40 °C.

With NMe_4^+, at the pH values and in the mixed solvent used, most of the substrate is expected to be in the bound protonated form 2 (R = CH_3COO), as also indicated by the chemical shift of the CH_3 proton NMR signal. The reaction follows first-order kinetics with respect to CH_3COONH_2 for one half-life and then slows down, probably because of competitive complexation of the product NH_2OH (Fig. 2).

K^+ counterions are very strongly bound by 1[8)] and are expected to inhibit binding of the substrate (and of the product) which is therefore in the free, largely unprotonated form. The reaction is first-order for at least two half-lifes (Fig. 2) and yields both acetic and acetohydroxamic acids.

The bound substrate reacts about 30 times faster than the free one and only acetic acid is formed; no $CH_3CONH-OH$ is detected. Protonation increases the leaving group ability of the hydroxylamine unit in the substrate and strong binding of the protonated product $HONH_3^+$ as 2 (R = OH) hinders generation of the N-acetylated compound.[14)]

The reaction is fastest around pH 5.5 where the concentration of complex ($R^{4-}.N^+$) is highest (see above and Fig.1).

In conclusion, strong binding of $CH_3COONH_3^+$ and $HONH_3^+$ by receptor 1 leads to protonation and complexation of the substrate CH_3COONH_2, and results in marked acceleration and complete orientation of the subsequent acyl transfer reaction. The slow and unselective transformation of the free substrate thus becomes fast and selective. Using $NH_2COO\text{-}NH_2$ one might be able to activate carbamyl transfer. Similar effects may also operate when anionic substrates (like for instance acetylsulfate or acetylphosphate) are bound to suitable receptor molecules such as polyammonium macrocycles.[3,15]

Finally the present results stress the key fact that strong substrate binding may already by itself enhance reactivity and selectivity of supramolecular chemical reactions, and for that matter, of enzymatic reactions as well.

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