

Metal Ion Catalysis in the Hydrolysis of Imines

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A hidrólise das bases de Schiff 1-3 em etanol aquoso 88% é sujeita a catálise por percloratos de metais alcalinos (Li^+) e alcalinos-terrosos (Mg^{+2} , Ca^{+2} e Sr^{+2}). Os cátions divalentes são catalizadores mais eficazes do que o Li^+ . A efetividade catalítica para um dado metal aumenta na ordem 3. Esta ordem é racionalizada em termos de um efeito templato devido à cadeia lateral de 1, a qual ajuda a estabilizar o estado de transição associado ao íon metálico.

The hydrolysis of Schiff's bases 1 - 3 in 88% aqueous ethanol was found to be subject to metal-ion catalysis by alkali (Li^+) and alkaline-earth (Mg^{+2} , Ca^{+2} and Sr^{+2}) perchlorates. The divalent cations were more effective catalysts than Li^+ . The catalytic effectiveness for a given metal ion increased in the order 3. This was rationalized in terms of a template effect of the polyether side chain of 1, which helped stabilize the metal-ion-associated transition state.

Key words: catalysis; imine hydrolysis; Schiff's bases.

Introduction

The influence of metal ions in biochemical processes is a subject of ever-growing interest. In the past decade, quite a few interesting papers have appeared on this subject. Such, for example, is the case of metal-ion-controlled systems, which mimic the enzymatic allosteric regulation in biochemical processes^{1,2}. Molecules have been designed, which are capable of exhibiting substantial changes in their visible spectra, according to the nature and/or concentration of an added cation^{3,4}. An exciting area of research, the role of metal ions in supramolecular processes, is being actively investigated by different groups⁵⁻⁸.

Attempts to mimic biochemical processes have yielded remarkable examples of rate accelerations by metal ion catalysis in model compounds⁹⁻¹⁰. Specific metal ion catalysis has been demonstrated in a variety of organic processes that include nucleophilic substitutions¹¹, transesterifications^{10a,12} and ester hydrolysis^{10d}. These reports constitute an alternative approach to the classic studies of salt effects, in so far as they concentrate on the specific interactions between a substrate and the metal ion, which acts as an electrophilic catalyst.

An attractive candidate for model studies on metal ion catalysis is the hydrolysis of Schiff's bases. The reaction plays an important role in many biochemical processes. The chemistry of vitamin B₆ offers many examples of enzymatic and nonenzymatic processes that revolve around the forma-

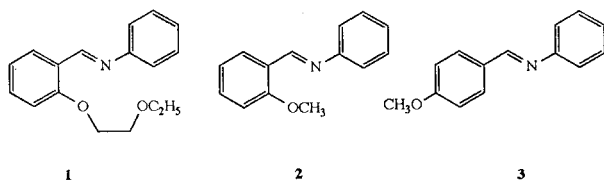
tion and the hydrolysis of the C=N bond. Pyridoxal 5'-phosphate, via the formation of Schiff's bases, function as a coenzyme in the deamination, transamination, racemization and decarboxylation of amino acids and peptides¹³. These processes are frequently catalyzed by transition metals, which help stabilize Schiff's base chelates¹⁴.

The mechanism of hydrolysis of Schiff's bases has been thoroughly investigated and the occurrence of general acid catalysis in this process has been well established¹⁵. This reaction should in principle be accelerated by the addition of any electrophilic catalyst such as a metal ion. We therefore decided to investigate the influence of alkali and alkaline-earth cations on the rates of hydrolysis of Schiff's bases. We were concerned with specific interactions between reactants and the metal ion catalyst. As in other example of classic organic processes¹⁶, the formation of transient chelates should provide the basis for noticeable rate enhancements. The results presented here confirm these expectations and constitute the subject of this report.

Results and Discussion

The hydrolysis of imines **1-3** in aqueous ethanol (88% v/v) was studied at a constant ionic strength of 0.0312 M.

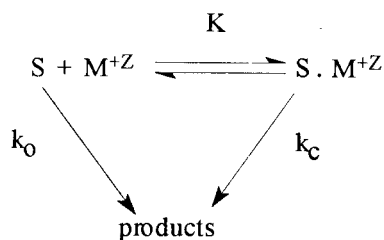
The ionic strength of the medium was adjusted by the addition of tetrabutylammonium tetrafluoroborate to the perchlorate salt solutions. Electrophilic catalysis by this large organic cation can be ruled out on the basis of its negligible



association with the substrates¹⁶. Furthermore, problems of incomplete dissociation of the metal perchlorates were minimized by working with reasonably dilute electrolyte solutions, and by employing the ClO_4^- and BF_4^- counteranions, both of which exhibit low tendency to associate with cations.

The observed rate constants for the hydrolysis of compounds 1-3 at 25°C, in the presence of increasing concentrations of alkali and alkaline-earth perchlorates, are given in the Experimental Section.

The generally accepted mechanism for the hydrolysis of Schiff's bases^{15,17} postulates an initial nucleophilic addition to the C=N double bond, followed by an elimination step of the resulting carbinolamine. At neutral pH the first step is rate-determining. Addition of a metal ion to the medium may catalyze the reaction through a substrate-cation association. This process is depicted in the scheme below,



where the imine substrate S can form the carbinolamine intermediate via an uncatalyzed and a metal-ion-catalyzed pathway. K is the association constant between the substrate and the metal ion,

$$K = [\text{S} \cdot \text{M}^{+Z}] / [\text{S}] \cdot [\text{M}^{+Z}] \quad (1)$$

The rate of the reaction is proportional to the total concentration of the substrate,

$$v = k_{\text{obs}} ([\text{S}] + [\text{S} \cdot \text{M}^{+Z}]) \quad (2)$$

and may be also expressed in terms of the microscopic rate constants k_0 and k_c as

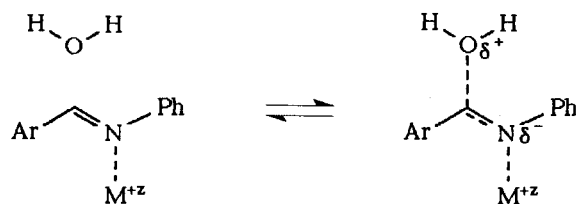
$$v = k_0 [\text{S}] + [\text{S} \cdot \text{M}^{+Z}] k_c \quad (3)$$

From equations (1), (2) and (3) we arrive at expression (4), which relates the ratio k_{obs}/k_0 to the concentration of the added metal ion $[\text{M}^{+Z}]$.

$$k_{\text{obs}}/k_0 = (1 + K \cdot (k_c/k_0) \cdot [\text{M}^{+Z}]) / (1 + K \cdot [\text{M}^{+Z}]) \quad (4)$$

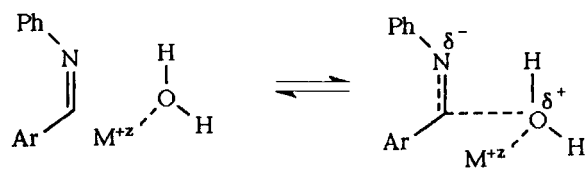
Catalysis by a given metal ion clearly depends on the relative values of k_c and k_0 . Estimates of the ratio k_c/k_0 and of the association constant K were obtained by a non linear least-square fit of equation (4) to the experimental k_{obs}/k_0 values, and are given in Table 1. It is seen that the addition of an alkaline-earth perchlorate always accelerated the rates of hydrolysis of the substrate ($k_c/k_0 > 1$). LiClO_4 catalyzed the process for imines 1 and 2, but inhibited ($k_c/k_0 < 1$) the hydrolysis of compound 3.

These observations can be rationalized in terms of an enhancement of the substrate reactivity after association with a metal ion, as shown below.



The harder alkaline-earth cations are in general more effective catalysts than the monovalent Li^+ species. The ratios k_c/k_0 in Table 1 are larger for those divalent species, decreasing in general in the order $\text{Sr}^{+2} > \text{Ca}^{+2} > \text{Mg}^{+2}$. These trends had been observed before¹⁶ in the metal-ion-catalyzed reaction of aryl acetates with MeO^- , a process that bears some analogy with our system.

An alternative arrangement may also be suggested, where the role of the metal ion is to activate an attacking water molecule, by bringing it into closer proximity to the electrophilic C=N bond.



As regards the substrate, the catalytic effectiveness of a given metal ion increases in the order $3 < 2 < 1$. This order reveals the important role of an ortho-alkoxy side chain in stabilizing the metal-ion association with the substrate. This template effect^{16,18} is larger for compound 1, because of the additional stabilization provided by a second oxygen atom in the side chain. Here again two alternative structures can be drawn for the transition state. The metal cation may bind directly to the C=N nitrogen, or simply activate the water nucleophile towards attack on the imine bond.

In both cases, the polyether side chain amplifies the catalytic role of the metal ion¹⁶, an effect which is apparent from the values of the ratio k_c/k_0 in Table 1.

In conclusion, the hydrolysis of Schiff's bases in 88% aqueous ethanol was found to be subject to metal-ion-cataly-

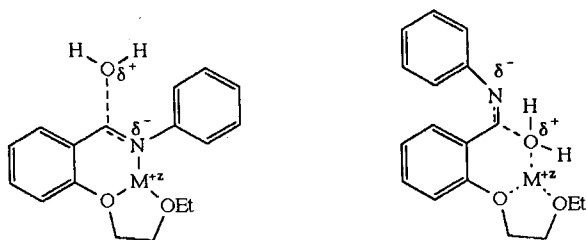


Table 1. Estimated association constants K and ratios K_c/K_o for the hydrolysis of compounds 1-3 at 25°C in the presence of different perchlorate salts

Substrate	Perchlorate Salt	K_c/K_o , l/mol	K , l/mol	K_c/K_o
1	LiClO ₄	420	55	7.6
1	Mg(ClO ₄) ₂	4360	150	29.1
1	Ca(ClO ₄) ₂	8290	390	21.3
1	Sr(ClO ₄) ₂	14780	850	17.4
2	LiClO ₄	120	50	2.4
2	Mg(ClO ₄) ₂	1010	120	8.4
2	Ca(ClO ₄) ₂	2810	310	9.1
2	Sr(ClO ₄) ₂	2680	300	8.9
3	LiClO ₄	25	65	0.4
3	Mg(ClO ₄) ₂	90	20	4.5
3	Ca(ClO ₄) ₂	140	20	7.0
3	Sr(ClO ₄) ₂	450	60	7.5

sis by alkali and alkaline-earth perchlorates. The latter were more effective catalysts than the Li⁺ cation. The catalytic effectiveness was greatest for compound 1, where the ortho-side chain provided a means of stabilizing the metal-ion-associated transition state via a template effect.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer, ¹H NMR spectra were taken with a Varian EM 360 instrument, employing tetramethylsilane as internal reference. UV spectra were obtained with a Beckman DU-065 spectrometer.

Melting points were recorded with a digital hot-plate instrument (Microquímica APF-301) and were not corrected.

The reagents were all analytically pure. Lithium perchlorate was purchased from Fluka, tetrabutylammonium tetrafluoroborate from Sigma. The other perchlorates were prepared from the corresponding metal carbonates and 70% perchloric acid solution (Merck). The salts were recrystallized from water and thoroughly dried under vacuum (1-2 Torr) at 100°C in an Abderhalden apparatus for 2-3 h.

The following compounds were prepared following reported procedures: 1-Bromo-2-ethoxyethane¹⁹, b.p. (125-126)°C, lit. (125-237)°C; N-(2-methoxybenzylidene)aniline, mp (44-45)°C, lit.²⁰ 44°C; N-(4-methoxy-benzylidene)aniline, m.p. (62-63)°C, lit.²¹ (63-64)°C.

2-(2-Ethoxy)ethoxybenzaldehyde. To a mixture of 2-hydroxybenzaldehyde (10g, 0.082 mol) and 1-bromo-2-ethoxyethane (12.5 g, 0.82 mol) in hexamethylphosphoramide (15 ml) was added with stirring sodium hydride (4.2 of a 60% dispersion in mineral oil, 0.1 mol). After the evolution of hydrogen had subsided, the mixture heated in a water-bath at (80-90)°C for 90 minutes. It was then cooled and diethyl ether (200 ml) added to it. The ethereal solution was thoroughly washed with water and then extracted with a saturated solution of sodium bisulfite (3 x 30 ml). The aqueous extracts of the bisulfite complex were then treated with sodium carbonate until there was no more evolution of CO₂ and the resulting solution was distinctly basic. The oil which separated was extracted with diethyl ether, the ethereal extracts dried over MgSO₄ and the ether eliminated in a rotary evaporator to give pure 2-(2-ethoxy)ethoxybenzaldehyde (11.2 g, 70% yield) in the form of a colorless oil. IR (neat, cm⁻¹) 2860, 2760, 1690, 1240, 1120 and 1050; ¹H NMR (CCl₄) δ 1.3 (t, J= 7 Hz, 3H), 3.6 (q, J= 7 Hz, 2H), 3.9 (t, J= 7Hz, 2H), 4.4 (t, J= 7 Hz, 2H), 7.1-7.3 (m, 2H), 7.7 (dd, J= 9 and 2 Hz, 1H), 8.1 (dd, J= 9 and 2 Hz, 1H), 10.7 (s, 1H). Anal. Calcd. for C₁₂H₁₄O₃; C, 68.04%; H, 7.22%; O, 24.74%. Found: C, 67.90%; H, 7.23%.

N-[2-(2-Ethoxy)ethoxybenzylidene]aniline (1). A solution of 2-(2-ethoxy)ethoxybenzaldehyde (2.5 g, 0.013 mol) and aniline (2.4 g, 0.026 mol) in absolute ethanol (20 ml) was refluxed for 5 h. The solvent was then eliminated in a rotary evaporator and the resulting oil was purified in a bulb-to-bulb distillation apparatus. The pure N-[2-(2-ethoxy)ethoxybenzylidene]aniline distilled at (147-150)°C (1 mmHg) as a viscous, pale yellow oil (3.13g, 90% yield), which did not crystallize even after being kept two to three weeks in a desiccator. IR (neat, cm⁻¹) 2850, 1610, 1280, 970 and 870. ¹H NMR (CCl₄) δ 1.3 (t, J=7 Hz, 3H), 3.6 (q, J=7 Hz, 2H), 7.2-7.7 (m, 8H), 8.5 (d, J=8Hz, 1H), 9.2 (s, 1H). UV (ethanol) 264 nm (ε ~ 22900). Anal. Calcd. for C₁₇H₁₉NO₂; C 75.84%; H, 7.06%; N, 5.20%. Found: C, 76.15%; H, 7.20%; N, 5.30%.

Kinetics. All reactions were carried out in aqueous ethanol (88% v/v), prepared by the addition of deionized, freshly boiled water to absolute ethanol (Merck). The ionic strength of all perchlorate solutions was adjusted to the constant value of 0.0312 M by the addition of tetrabutylammonium tetrafluoroborate. In order to check for traces of acid in the employed salts and rule out the possibility of specific acid catalysis, more concentrated ethanolic solutions of all perchlorates were diluted with decarbonated water to a final concentration of about 0.03 M. The pH values of the resulting solutions did not shift from the neutral value of 7.0.

The kinetic runs were carried out by adding 0.2-0.5 μl of a stock ethanolic solution of the Schiff's base to 5 ml of the perchlorate solution in 88% aqueous ethanol so that the final concentration of the substrate in the cell was about 8 x 10⁻⁴ M. The hydrolysis rate constants were determined spectrophotometrically by following the decrease in absorbance of the resulting thermostatted (25.0 ± 0.1)°C solutions at 265 nm. A total of 250 absorbance readings, spanning at least 2-3

half-lives, were acquired and processed by an interfaced microcomputer, yielding rate constants with errors smaller than 2%. Every rate constant was calculated as an average of at least two kinetic runs. Curve fittings to the experimental rate constants were obtained by means of a non-linear least-square program (Marquardt method)²². Values of k and of the ratio k_{obs}/k_0 in Table 1 are estimates from this procedure. Standard deviations from the regressions are as follows: *Substrate 1*: Li^+ , s.d.= 0.055; Mg^{+2} , s.d.=0.15; Ca^{+2} , s.d.=0.17; Sr^{+2} , s.d.=0.2. *Substrate 2*: Li^+ , s.d.= 0.02; Mg^{+2} , s.d.=0.06; Ca^{+2} , s.d.=0.03; Sr^{+2} , s.d.= 0.07. *Substrate 3*: Li^+ , s.d.=0.03; Mg^{+2} , s.d.=0.017; Ca^{+2} , s.d.=0.017; Sr^{+2} , s.d.=0.01.

The observed ratios k_{obs}/k_0 for the hydrolysis of imines 1-3 at 25.0°C in the presence of different perchlorates are given below [k_{obs}/k_0 ($10_3 \times$ salt concentration, M)];

Substrate 1. ($k_0 = 1.89 \times 10^{-4} \text{ s}^{-1}$):

LiClO_4 : 3.59 (12.0), 3.62 (12.5), 4.09 (15.0), 4.13 (17.5), 4.21 (20.0), 4.70 (22.5), 4.91 (25.0), 4.98 (27.5), 5.00 (30.0), 5.02 (31.2).

$\text{Mg}(\text{ClO}_4)_2$: 4.0 (0.83), 7.41 (1.70), 7.80 (2.10), 11.30 (3.90), 12.60 (5.20), 14.20 (6.00), 16.50 (7.80), 18.80 (10.4).

$\text{Ca}(\text{ClO}_4)_2$: 5.91 (0.83), 7.76 (1.25), 8.95 (1.70), 10.00 (2.10), 11.39 (2.60), 13.01 (3.90), 14.64 (5.20), 14.90 (6.00), 15.87 (7.80), 17.50 (10.4).

$\text{Sr}(\text{ClO}_4)_2$: 6.32 (0.42), 7.30 (0.83), 9.52 (1.25), 10.90 (2.10), 11.70 (2.60), 14.00 (5.20), 14.70 (6.00), 15.50 (7.80), 16.40 (10.4).

Substrate 2. ($k_0 = 1.73 \times 10^{-4} \text{ s}^{-1}$):

LiClO_4 : 1.15 (2.00), 1.23 (4.00), 1.27 (6.00), 1.35 (8.00), 1.51 (12.0), 1.52 (12.5), 1.56 (15.0), 1.60 (17.5), 1.65 (20.0).

$\text{Mg}(\text{ClO}_4)_2$: 1.92 (1.25), 2.20 (1.70), 2.50 (2.10), 2.70 (2.60), 3.47 (3.90), 3.73 (5.20), 4.23 (6.00), 4.75 (7.80), 4.90 (10.4).

$\text{Ca}(\text{ClO}_4)_2$: 3.40 (1.25), 3.75 (1.70), 4.15 (2.10), 4.57 (2.60), 5.38 (3.90), 6.00 (5.20), 6.20 (6.00), 6.75 (7.80), 7.26 (10.4).

$\text{Sr}(\text{ClO}_4)_2$: 1.74 (0.42), 2.45 (0.83), 3.20 (1.25), 3.75 (1.70), 4.14 (2.10), 4.56 (2.60), 5.80 (5.20), 6.20 (6.00), 6.80 (10.4).

Substrate 3 ($k_0 = 1.40 \times 10^{-4} \text{ s}^{-1}$):

LiClO_4 : 0.96 (2.00), 0.90 (4.00), 0.70 (12.0), 0.64 (20.0), 0.62 (25.0), 0.60 (31.2).

$\text{Mg}(\text{ClO}_4)_2$: 1.20 (2.60), 1.25 (3.90), 1.32 (5.20), 1.38 (6.00), 1.51 (7.80), 1.62 (10.4).

$\text{Ca}(\text{ClO}_4)_2$: 1.26 (2.10), 1.29 (2.60), 1.52 (5.20), 1.59 (6.00), 1.78 (7.80), 1.99 (10.4).

$\text{Sr}(\text{ClO}_4)_2$: 1.60 (1.70), 1.72 (2.10), 1.90 (2.60), 2.25 (3.90), 2.56 (5.20), 2.77 (6.00), 3.10 (7.80), 3.55 (10.4).

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