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Lewis-Acid Catalyzed Organic Reactions in Water. The Case of $AlCl_3$, $TiCl_4$, and $SnCl_4$ Believed To Be Unusable in Aqueous Medium[†]

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Classical Lewis acids such as $AlCl_3$, $TiCl_4$, and $SnCl_4$, believed to be unusable as catalysts in aqueous medium, efficiently catalyzed regio- and stereoselective azidolysis and iodolysis of α,β-epoxycarboxylic acids in water at pH 4.0 and 1.5, respectively. The concept of *water-tolerant* metal−salt is reexamined in direct relationship to the aqua ion hydrolysis constant.

Introduction

Lewis-acid catalyzed organic reactions in water are currently one of the most challenging topics in organic synthesis because they allow environmentally friendly processes under mild conditions.[1] Kobayashi and coworkers recently screened the catalytic activity of many metal chlorides, perchlorates, and triflates using the model reaction of benzaldehyde with the acid-sensitive (*Z*)-1-phenyl-1-(trimethylsilyloxy)propene (the Mukaiyama aldol reaction) to compare their catalytic effectiveness.[2a,c] The reactions were mostly carried out in H_2O/THF 1:9 and, in some cases, in H_2O/EtOH/PhMe 1:7:3, in the presence of 20% catalyst. $Ln(OTf)_3$ [Ln = lanthanides], ScX_3 (X = Cl, ClO_4), $Cu(ClO_4)_2$, YX_3 (X = Cl, ClO_4), $Cd(ClO_4)_2$, $InCl_3$, YbX_3 (X = Cl, ClO_4), and $Pb(ClO_4)_2$ were the catalysts that gave the best results (yield 65−92%), and the Japanese authors infer that perchlorates and triflates are more efficient Lewis acids than metal chlorides.[2a]

$M(NO_3)_2$ [M = Cu, Co, Ni, Zn],[3,4] $Sc(OTf)_3$,[5] $Bi(OTf)_3$,[6] and $MeReO_3$[7] have also been used to catalyze reactions in aqueous media in the aldol reaction,[2,8] Michael reaction,[9] Diels−Alder reaction,[1d,e,10] allylation reaction,[5c,11] and azidolysis reaction.[4]

All these catalysts are called *water-tolerant* Lewis acids and are regarded as stable in water.[2] In contrast, $AlCl_3$, $TiCl_4$, and $SnCl_4$ are described by synthetic organic chemists as moisture-sensitive Lewis acids that react with water and, consequently, must be used under strictly anhydrous conditions.

We here report evidence that confutes this last statement.

Results and Discussion

The azidolysis and iodolysis[12] reactions of α,β-epoxycarboxylic acids were chosen as probe reactions. α,β-Epoxycyclohexanecarboxylic acid **1** and *trans*-α,β-epoxyhexanoic acid **4** were used as models because they are stable in acid water; the former is stable at pH of 3−3.5 and the latter to even lower pH values.[14]

The azidolysis of α,β-epoxycyclohexanecarboxylic acid **1** with NaN_3 (5 mol/equiv) in pure water at pH 4.0, held

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(12) For the ring-opening reaction of epoxides to give iodohydrins, the term iodination has been used.[13] In the context of this paper, we prefer the term iodolysis in analogy with azidolysis.

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(14) Azidolyses of the methyl ester of **1** and **4** in pure water, catalyzed by $InCl_3$, were also carried out but with disappointing results. Low reaction conversion, poor selectivity, and no significant catalytic effect were observed even in the presence of a large amount of catalyst. Thus, the methyl ester of **1** at 30 °C and at pH 4.0 in the absence of the Lewis acid after 24 h gave the esters of **2** and **3** in a 10:90 ratio with 37% conversion; in the presence of $InCl_3$ (30 mol %), the conversion was 58% and the ratio of the products was unchanged. The methyl ester of **4** at 65 °C and at pH 4.0 in the absence of the Lewis acid gave the ester of **5** and **6** in a 37:63 ratio with 29% conversion after 24 h; in the presence of $InCl_3$ (30 mol %) after 24 h, the conversion and the ratio of the products were the same.

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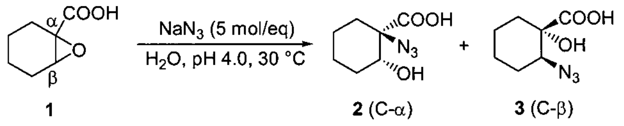
Table 1. Lewis Acid Catalyzed Azidolysis of α,β-Epoxycyclohexancarboxylic Acid 1 in Water at pH 4.0



entry	catalyst (1 mol %)	t (h)	C^a (%)	C-α (%)	C-β (%)	diol (%)
1	none	0.3	4	<1	>99	0
2	none	1.5	28	<1	>99	0
3	none	75	>99	<1	>99	0
4	$Cu(NO_3)_2$	1.5	93	<1	>99	0
5	$InCl_3$	1.5	>99	<1	>99	0
6	$AlCl_3$	0.3	>99	<1	>99	0
7	$Al(NO_3)_3$	0.3	>99	<1	>99	0
8	AlF_3	1	98	0	96	4

[a] Reaction conversion and C_β/C_α ratios were determined by GC analyses. The regioisomer **3** was isolated in pure form in 95% yield, and its structure was proven as reported.[4b]

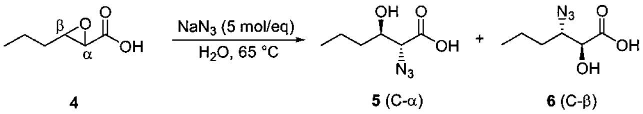
constant for the entire reaction time, quantitatively gave the azido alcohol **3** in 75 h (Table 1, entry 3).

Under the same conditions, 1 mol % of $Cu(NO_3)_2$ and $InCl_3$ greatly accelerated[15] the reaction (Table 1, entries 4 and 5). $AlCl_3$ (1 mol %) was even more effective, and the same beneficial effect was observed using $Al(NO_3)_3$ and AlF_3 (Table 1, entries 6−8). Interestingly, the catalysis by Al^{3+} did not seem to be strictly dependent on the metal counteranion. The longer reaction time for AlF_3 (Table 1, entry 8) with respect to those of $AlCl_3$ and $Al(NO_3)_3$ is due to its low solubility in water that reduces the percentage of catalyst in the reaction medium. The comparisons between metal-catalyzed reactions (Table 1, entries 4−8) and those carried out at the same pH values, but without metal catalyst (Table 1, entries 1 and 2), indicate that the Brønsted acid catalysis did not significantly occur.[16]

The azidolysis in water of the less reactive α,β-epoxyhexanoic acid **4** at 65 °C and at constant pH 4.0 was also greatly accelerated by using 1 mol % of $Cu(NO_3)_2$, $AlCl_3$, and $InCl_3$ (Table 2, entries 7−10 and 12). The azido alcohol **6**, again derived from the *anti* nucleophilic attack at the β-carbon of the oxirane ring, was practically the sole reaction product. $SnCl_4$ showed little activity, and $TiCl_4$ slowed the reaction rate; both gave a mixture of **5**, **6**, and a large amount of diol (Table 2, entries 11 and 13). At pH 7.0, the regioselectivity was reversed and *anti*-α-azido-β-hydroxycarboxylic acid **5** was the main reaction product. $Cu(NO_3)_2$ was only moderately active; $AlCl_3$, $TiCl_4$, $InCl_3$, and $SnCl_4$ were inoperative and gave the same results as those obtained when the reaction was carried out without catalyst.[17]

Given the results reported in Tables 1 and 2, some comments can be made.

Table 2. Lewis Acid Catalyzed Azidolysis in Water of *trans*-α,β-Epoxyhexanoic Acid 4 at pH 7.0 and 4.0



entry	catalyst (1 mol %)	pH	*t* (h)	C^a (%)	C-α (%)	C-β (%)	diol (%)
1	none	7.0	22	98	78	22	0
2	$Cu(NO_3)_2$	7.0	14	98	65	35	0
3	$AlCl_3$	7.0	22	98	69	31	0
4	$TiCl_4$	7.0	22	97	76	24	0
5	$InCl_3$	7.0	22	97	75	25	0
6	$SnCl_4$	7.0	22	98	77	23	0
7	none	4.0	1.5	28	52	48	0
8	none	4.0	24	82	54	46	0
9	$Cu(NO_3)_2$	4.0	4	90	6	94	0
10	$AlCl_3$	4.0	1.5	>99	<1	>99	0
11	$TiCl_4$	4.0	70	75	22	35	43
12	$InCl_3$	4.0	2	>99	<1	>99	0
13	$SnCl_4$	4.0	8	87	11	32	57

[a] Reaction conversion and C_β/C_α ratios were determined by GC analyses. The regioisomer **5** was isolated with 68% total yield (entries 1, 4, 6); the regioisomer **6** was isolated with 95% total yield (entries 10 and 12). The structures of **5** and **6** agree with those reported in the literature.[29]

Scheme 1. Dissociation Equilibria of a Metal Salt, Aqua Ion Hydrolysis Constant, and Prevailing Species in Water[18]

$$M_qA_x \rightleftharpoons qM^{x+} + xA^{q-} \qquad \text{(eq. 1a)}$$

$$M^{x+} + n(H_2O) \rightleftharpoons M(H_2O)_n^{\ x+} \qquad \text{(eq. 1b)}$$

$$M(H_2O)_n^{\ x+} \rightleftharpoons M(H_2O)_{n-1}(OH)^{(x-1)+} + H^+ \qquad \text{(eq. 1c)}$$

$$M(H_2O)_{n-1}(OH)^{(x-1)+} \rightleftharpoons M(H_2O)_{n-2}(OH)_2^{\ (x-2)+} + H^+ \qquad \text{(eq. 1d)}$$

$$K_{1,1} = \frac{[M(OH)^{(x-1)+}]\,[H^+]}{[M^{x+}]} \qquad \text{(eq. 1e)}$$

$$\underset{\mathbf{7}}{M_2(OH)^{(2x-1)+}} \quad \underset{\mathbf{8}}{M_2(OH)_2^{\ (2x-2)+}} \quad \underset{\mathbf{9}}{M_3(OH)_3^{\ (3x-3)+}}$$

$$\underset{\mathbf{10}}{M(H_2O)_{n-1}N^{(x-1)+}} \quad \underset{\mathbf{11}}{M(H_2O)_{n-2}N_2^{\ (x-2)+}}$$

It is well-known that the metal salt, M_qA_x, dissociates in water followed immediately by hydration (Scheme 1, eqs 1a and 1b). The aqua ion hydrolysis generates numerous possible mononuclear (Scheme 1, eqs 1c and 1d) and polynuclear species **7**−**9** (Scheme 1).[18] Species **10** and **11**, derived from the substitution of the water ligand with the nucleophile N^-, can also occur (Scheme 1), especially when there is a high concentration of nucleophile such as that used in the preparatory conditions.[18] The distribution of aqua ion and mononuclear and polynuclear species is a function of pH and metal concentration. The range of pH values in which soluble hydrolysis products are present is limited by the precipitation of the hydroxide or oxide of the metal cation. The chemical behavior of the metal, in a given oxidation state, is a complicated function of the pH and concentration.[18]

Among the species in solution, the aqua ion $M(H_2O)_n^{\ x+}$ has the most Lewis acid character and the hydrolysis constant, $K_{1,1}$, (Scheme 1, eq 1e) can be used to estimate the pH value below which the aqua ion is the prevailing cationic species.

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(15) We were not able to carry out significant kinetic experiments. None of the techniques used (IR, UV, NMR), achieved the purpose, and therefore, we used reaction conversion after a certain reaction time to get an impression of the catalytic efficiency.

(16) The pH values of 5×10^{-3} M aqueous solutions of $Cu(NO_3)_2$, $AlCl_3$, $Al(NO_3)_3$, $TiCl_4$, $InCl_3$, and $SnCl_4$ (corresponding to 0.01 mol/equiv) are 5.2, 3.8, 4.0, 1.7, 3.5, and 1.8, respectively; the pH values of 5×10^{-2} M aqueous solutions of $Cu(NO_3)_2$, $AlCl_3$, $TiCl_4$, $InCl_3$, and $SnCl_4$ (corresponding to 0.1 mol/eq) are 4.6, 3.5, 1.0, 3.2, and 1.0, respectively.

(17) The same results were obtained for $Cu(NO_3)_2$-, $AlCl_3$-, and $InCl_3$-catalyzed azidolyses of α,β-epoxycyclohexancarboxylic acid **1** at pH 7.0.

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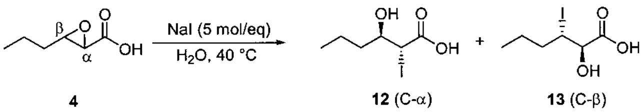
Table 3. Lewis Acid Catalyzed Iodolysis in Water of *trans*-α,β-Epoxyhexanoic Acid 4 at pH 4.0 and 1.5



entry	catalyst (10 mol %)	pH	*t* (h)	C^a (%)	C-α (%)	C-β (%)	diol (%)
1	none	4.0	6	20	99	1	0
2	none	4.0	64	99	99	1	0
3	$AlCl_3$	4.0	8	98	20	38	42
4	$TiCl_4$	4.0	56	95	96	4	0
5	$InCl_3$	4.0	2.5	>99	2	78	20
6	$SnCl_4$	4.0	44	97	96	4	0
7	none	1.5	4	91	64	36	0
8	none	1.5	0.5	18	64	36	0
9	$AlCl_3$	1.5	0.5	93	2	98	0
10	$TiCl_4$	1.5	0.5	44	32	68	0
11	$TiCl_4$	1.5	2	92	33	67	0
12	$InCl_3$	1.5	0.5	>99	2	98	0
13	$SnCl_4$	1.5	0.5	92	11	89	0

[a] Reaction conversion and C_β/C_α ratios were determined by GC analyses. The regioisomers **12** and **13** were isolated with 85−95% total yield from entries 9, 11, 12, and 13, respectively. The structures of **12** and **13** agree with those reported in the literature.[23]

The p$K_{1,1}$ values of Cu^{2+}, Al^{3+}, Ti^{4+}, In^{3+}, and Sn^{4+} are 8.0,[18] 4.97−5.5,[18,19] −0.3,[18,20] 3.0−4.0,[18] and −0.57,[18] respectively. Therefore, at pH < 3−4, copper, aluminum, and indium ions are mostly unhydrolyzed, while the mononuclear and polynuclear hydrolysis products of titanium and tin ions are largely present. At pH 4.0, Cu^{2+}, In^{3+}, and Al^{3+} catalyze the azidolyses of **1** and **4**, while Ti^{4+} and Sn^{4+} are not good catalysts for the azidolysis of **4**. At pH 7.0, all the catalysts were inactive for the azidolysis of **4** (Table 2), with the exception of $Cu(NO_3)_2$ (p$K_{1,1}$ of Cu^{2+} = 8.0), and the azido ion preferentially attacked the more electrophilic α-carbon of α,β-epoxycarboxylate.[21]

On the basis of $K_{1,1}$ hydrolysis constant values, $SnCl_4$ and $TiCl_4$ should be active catalysts at very low pH values, but the very low concentration of azide ion at pH 0−2 (pK_a of HN_3 = 4.7) precludes the azidolysis reaction from being carried out under these conditions. To check this hypothesis, we chose the iodolysis reaction[12] of **4** in water with NaI. The results of catalyzed (10 mol % of metal chloride) and uncatalyzed reactions at 40 °C and at pH values 4.0 and 1.5 (hold constant for all reaction time) are reported in Table 3.

At pH 4.0, $TiCl_4$ and $SnCl_4$ are practically inactive and the regioisomer **12**, which results from the attack at the more electrophilic α-carbon, is the main reaction product (Table 3, entries 2, 4, and 6). $AlCl_3$ and $InCl_3$ catalyze both the iodolysis and hydrolysis[22] of **4** (Table 3, entries 3 and 5). At pH 1.5, all the metal chlorides are active catalysts and the expected[23] regioisomer **13** is obtained in excellent yield.

Lewis acids such as $AlCl_3$, $TiCl_4$, and $SnCl_4$, believed unusable as catalysts in organic reactions in water, are, on the contrary, efficacious catalysts in aqueous medium provided that they are used at suitable pH values, which are related to their $K_{1,1}$ hydrolysis constant. $AlCl_3$, $TiCl_4$, and $SnCl_4$ are active catalysts at 1 mol %, and this is the least amount of catalyst used to catalyze azidolysis of α,β-epoxycarboxylic acids and their esters reported in the literature. The reaction of **4** with NaI reported in this study is the first example of iodolysis of α,β-epoxycarboxylic acids. Generally, much more catalyst is used for aqueous-catalyzed organic reactions, but when more than 10−20 mol % of catalyst is used, one must consider that, in water, the chemical behavior of metal ion depends on the ion concentration.

This study also shows that a single model reaction cannot be used to test the Lewis acid catalytic ability of all metal salts in water[2a] because the pH of the reaction medium suitable for carrying out such a reaction may not be proper for the catalyst. For a successful Lewis acid catalyzed organic reaction in water, it is necessary to consider the pH at which the reagents and/or reaction products are stable, the pH at which the catalyst is active, and the concentration of the catalyst.

The rationalization of the mechanism of Lewis acid catalyzed azidolysis and iodolysis of α,β-epoxycarboxylic acids in water requires further studies. It can tentatively be explained by thinking that the aqua ion coordinates[24] the epoxycarboxylic acid (the complex formation is dominated by the water exchange rate[19]) after which the activated epoxide undergoes nucleophilic ion attack. Another possibility is that the metal simultaneously coordinates the epoxycarboxylic acid and the nucleophile (the latter probably via water−nucleophile exchange) and then the nucleophile is intramolecularly transferred to the epoxide ring.[22] The β-azido derivative is the main or sole regioisomer observed when the reaction is Lewis-acid catalyzed,[28] while, when the catalyst is inactive, the prevalent nucleophilic attack can also occur at the more electrophilic α-carbon of the oxirane ring.

Conclusions

The results of this study indicate that easily hydrolyzable metal salts such as $AlCl_3$, $Al(NO_3)_3$, AlF_3, $SnCl_4$, and $TiCl_4$ are effective catalysts, even in aqueous medium. Therefore, it is necessary to reexamine the use of the expression *water-tolerant Lewis acid* for metal salts.

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(19) *Coordination Chemistry of Aluminum*; Robinson, H. G., Ed.; VCH: Weinheim, 1993.

(20) The principal aqueous species of Ti(IV), also at low concentration, was supposed to be $Ti(OH)_2^{2+}$ or TiO^{2+}.[18b]

(21) α,β-Epoxycarboxylic acids have a pK_a in the range of 3.5−4.5.

(22) The diol (the *anti*-α,β-dihydroxyhexanoic acid) is produced by a hydrolysis reaction of **4**, which occurs in parallel with iodolysis. When **4** was treated with only $AlCl_3$ (10 mol %) at pH 4.0 and 65 °C in water, 60% of **4** was converted to a 4:1 mixture of diol and chlorohydrin, after 2.5 h. Similarly, by using only $InCl_3$ under the same reaction conditions, 27% of epoxide **4** was converted to a 3:1 mixture of diol and chlorohydrin after 2.5 h. Using more than 5 mol/equiv of NaI, the production of diol was suppressed: after **4** was treated with $AlCl_3$ (10 mol %) and NaI (10 mol/equiv) in water at pH 4.0, total conversion was achieved after 12 h and **12** and **13** were obtained in a 1:1 ratio. This last experiment supports the nucleophile internal delivery.

(23) Righi, G.; Rumboldt, G.; Bonini, P. *Tetrahedron* **1995**, *48*, 13401−13408.

(24) The metal should coordinate both the oxygen of the epoxide and an oxygen atom of the carboxylic function;[25, 26] the complex probably includes two units of α,β-epoxycarboxylic acid.[27] The complexation of the sole carboxylic functionality should increase the electronegativity of the carboxylic group, and therefore, the α-selectivity should be favored, as observed for the reaction performed in the absence of the Lewis-acid catalyst, while a complete β-selectivity was observed.

(25) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4435−4436.

(26) Azzena, F.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron* **1995**, *48*, 13409−13422.

(27) Doedens, R. J. *Prog. Inorg. Chem.* **1976**, *21*, 209−231.

(28) The prevalent attack at α-carbon, observed in the $Cu(NO_3)_2$-catalyzed reaction of **4** at pH 7.0, is probably due to the accompanying uncatalyzed reaction that per se gives a prevalence of α-adduct (Table 2, entries 1 and 2).

Water-tolerant cannot be used to indicate that the metal salt is stable in water (as a consequence of its slow hydrolysis rate) because its dissociation is fast and the hydration of the metal occurs immediately, and the distribution of species (aqua ion, mononuclear, polynuclear) is a function of pH and metal salt concentration. The term *water-tolerant* for a metal salt should be used to indicate that, in water, it generates a stable aqua ion and it shows the highest effectiveness when the pH of the reaction medium is below its $pK_{1,1}$ hydrolysis constant. From this point of view, $AlCl_3$, $Al(NO_3)_3$, AlF_3, $TiCl_4$, and $SnCl_4$ are *water-tolerant* Lewis acids along with many other metal salts that can be active catalysts in water if used at a suitable pH.

Careful mechanistic studies and more extensive synthetic applications are needed for a more complete knowledge of the chemical behavior of Lewis acid catalysts in water. Further work is in progress in our laboratory.

Experimental Section

The compounds **3**, **5**, **6**, **12**, and **13** are described.[4b,23,29] The conversion reactions were determined by GC analyses of the methyl ester derivatives obtained by treating the reaction mixture with diazomethane after the workup (see below). The pH was measured with an accuracy of ±0.05 units.

Azidolysis of 1 Catalyzed by $AlCl_3$ (1 Mol %) at pH 4.0. In a flask thermostated at 30 °C, equipped with a magnetic stirrer and with pH-stat apparatus, α,β-epoxycyclohexanecarboxylic acid **1** (1.0 mmol) was dissolved in water (2 mL) and powdered NaN_3 (5.0 mmol) was added under stirring. The resulting pH value was 5.0. An aqueous 0.5 M solution of $AlCl_3$ (20 μL) was added, and the pH was adjusted to pH 4.0 with 150 μL of a 50% H_2SO_4 aqueous solution. During the reaction, the pH was kept constant by means of the pH-stat by adding a 50% H_2SO_4 aqueous solution (100 μL). After 20 min, the reaction mixture was cooled to 0 °C, acidified to pH 2.0, and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give pure **3**,[4b] which was isolated in 95% yield.

Iodolysis of 4 Catalyzed by $AlCl_3$ (10 Mol %) at pH 1.5. In a flask thermostated at 40 °C, equipped with a magnetic stirrer and with pH-stat apparatus, *trans*-α,β-epoxyhexanoic acid **4** (1.0 mmol) was dissolved in water (2 mL) and powdered NaI (5.0 mmol) was added under stirring. The resulting pH value was 1.5 and was adjusted to pH 1.8 with 10 μL of 5 M NaOH solution. An aqueous 0.5 M solution of $AlCl_3$ (200 μL) was added, and the resulting pH value was 1.5. During the reaction, the pH was kept constant at 1.5 by means of a pH-stat by adding a 50% H_2SO_4 solution. After 60 min, the reaction mixture was cooled to 0 °C and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give 98% pure **13**,[23] which was isolated in 95% yield.

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