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Metal-Catalyzed Racemization of an α-Amino Lactam

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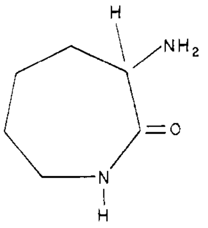
Chelation of α-amino acids or their alkyl esters with a variety of metal ions results in the labilization of the methylene protons on the γ-carbon atom. This has been convincingly demonstrated by pmr deuterium-exchange studies,[1] mutarotation through the action of strong bases,[2] and the condensation of the corresponding carbanions with aldehydes.[3]

Chelates derived from α-amino acid derivatives capable of (a) tautomerism and (b) transamination with excess unchelated amino acid have been shown to racemize in a reaction which is *catalytic* with respect to metal ion. Such derivatives include Schiff bases from salicylaldehyde,[4] pyridoxal,[5] nitro-substituted salicylaldehydes,[6] aurintricarboxylic acids,[7] or azo compounds derived from nitrosophenols.[8]

Formation and mutarotation of chelates derived from optically active α-amino lactams has not been studied so far. Since lactam–lactim tautomerism can be formulated in principle, it appeared interesting to investigate whether ligand lability, just as the transamination reaction in the case of Schiff bases, would allow the racemization to become catalytic with respect to metal ion.

We have studied the racemization of chelated L-α-amino-ε-caprolactam (L-3-aminohexahydro-2H-azepin-2-one, **1**) in the presence of uncoordinated ligand and our findings are reported in this note.



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Experimental Section

Preparation of the Ligand.—α-Amino-ε-caprolactam (**1**, abbreviated ACL) was prepared from ε-caprolactam and resolved *via* salt formation with L-2-pyrrolidone-5-carboxylic acid.[9] $[\alpha]^{25}\mathrm{D}$ −33.0° (*c* 2.3, 1 *N* HCl);[10] ir (KBr) (cm^{-1}): 1660 (C═O), 3260 (NH), 3390 and 1600 (amine NH).

Tris(DL-α-amino-ε-caprolactam)nickel(II) Chloride.—A solution of 40 g (0.31 mol) of DL-ACL in 100 ml of absolute ethanol was slurried with 13.0 g (0.1 mol) of anhydrous $NiCl_2$ for 1 hr at reflux temperature; 400 ml of dry ethyl ether was added and the crystal slurry was filtered. The filter cake was washed with 50 ml of ethyl ether and the solid was dried overnight at 40°. The yield of the complex was 97.5% (50.1 g). *Anal.* Calcd for $C_{18}H_{36}N_6O_3NiCl_2$: C, 41.90; H, 7.03; N, 16.67; Ni, 11.38; Cl, 13.74. Found: C, 41.24; H, 7.40; N, 16.26; Ni, 11.6; Cl, 13.8. Ir (KBr) (cm^{-1}): 3250 (NH), 1627 (C═O), 1600 (NH_2); visible and uv (CH_3OH) (mμ): 605 (ε 4.5), 355 (ε 11.8); nmr (CD_3OD) signals were very broad indicating paramagnetic structure. No melting was observed below 300°.

Tris(L-α-amino-ε-caprolactam)nickel(II) Chloride.—A solution of 0.576 g (0.0045 mol) of L-ACL in 10 ml of absolute ethanol was stirred for 30 min with 0.195 g (0.0015 mol) of anhydrous $NiCl_2$ at reflux temperature. After cooling the blue precipitate was filtered and dried under vacuum yielding 0.50 g of complex. No melting was observed up to 290°. *Anal.* Calcd for $C_{18}H_{36}N_6O_3NiCl_2$: C, 41.90; H, 7.03; N, 16.67; Ni, 11.38; Cl, 13.74. Found: C, 41.40; H, 7.26; N, 15.05; Ni, 11.1; Cl, 13.8. The ir spectrum was identical with that of the corresponding DL Ni(II) complex; CD (*c* 0.34, H_2O) (mμ): 240 (Θ 800), 208 (Θ 68,500).

Bis(DL-α-amino-ε-caprolactam)nickel(II) Chloride.—A solution of 5.0 g of DL-ACL (0.0375 mol) and 1.69 g (0.0131 mol) of anhydrous $NiCl_2$ in 160 ml of ethanol was stirred for 3 hr at 50–60°. An additional 0.84 g (0.0065 mol) of anhydrous $NiCl_2$ was added and stirring resumed for 20 min at reflux temperature. On cooling the solution became cloudy. After standing overnight the green crystals were collected, washed twice with ethanol, and dried under vacuum at 80°. *Anal.* Calcd for $C_{23}H_{24}N_4O_2NiCl_2$: C, 37.34; H, 6.27; N, 14.51; Ni, 15.21; Cl, 18.37. Found: C, 37.26; H, 6.39; N, 14.70; Ni, 14.9; Cl, 18.2. Ir (KBr) (cm^{-1}): 3200 (NH), 1625 (C═O), 1600 (NH_2); visible and uv, maxima (CH_3OH) (mμ): 620 (ε 5.1), 365 (ε 21.1), 273 (ε 148); nmr (CD_3OD) signals were in general agreement with structure. No melting was observed below 320°.

Bis(DL-α-amino-ε-caprolactam)copper(II) Chloride.—Racemic ACL and $CuCl_2$ in anhydrous acetone in a 2:1 mole ratio gave the above compound; mp 185.5°. *Anal.* Calcd for $C_{23}H_{24}N_4O_2CuCl_2$: C, 36.88; H, 6.19; N, 14.34; Cu, 16.26; Cl, 18.14. Found: C, 37.21; H, 6.26; N, 14.56; Cu, 15.8; Cl, 18.31. Ir (KBr) (cm^{-1}): 3150 (NH), 1625 (C═O), 1600 (NH_2); visible and uv, maxima (CH_3OH) (mμ): 600 (ε 58.7), 330–340 and 230–240 (shoulders); the nmr spectrum (D_2O) gave one extremely broad band indicating the compound was paramagnetic.

Kinetic Studies.—L-α-Amino-ε-caprolactam was purified by sublimation at 47° (0.02 mm), $[\alpha]^{25}\mathrm{D}$ −33.0° (*c* 2.3, 1 *N* HCl), and handled in a glove bag in nitrogen atmosphere. It was dissolved in 25 ml of methanol at various concentrations ranging from 0.112 to 0.166 *M* in five different runs. Anhydrous $NiCl_2$ was added to give the desired ligand to metal ion ratio. The solution was divided into five portions which were transferred into aerosol pressure tubes and immersed and stirred in an oil bath, maintained at 85 ± 0.1°. After 3 min of thermal equilibration, one tube was cooled in an ice bath, 2 ml of 1 *N* HCl was added, the solution was brought to set volume, and the rotation was determined. This value was taken as the optical rotation at time zero. The rotations of the four remaining solutions were then measured at convenient time intervals, as described above. From these data, the pseudo-first-order and the second-order rate constants, k' and k, respectively, were calculated (Table II). The ratio k'/ka was then determined for each run and plotted against R.

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[10] Optical rotations were measured with an O. C. Rudolph Model 70 polarimeter.

Results and Discussion

It was noted that upon heating a methanol solution of L-α-amino-ε-caprolactam and nickel chloride in the mole ratio 2:1 in a sealed tube at 95° for 4 hr, no racemization occurred. The addition of a base, even weaker than the ligand itself,[11] caused total racemization under the same conditions. This observation prompted us to study the configurational stability of optically active α-amino-ε-caprolactam in the presence of less than stoichiometric amounts of metal ion, that is, a solution where unchelated ligand was present. Indeed, racemization was found at ligand to metal ratios as high as 60. Besides nickel, a series of other metal ions were active as racemization catalysts (Table I).

TABLE I

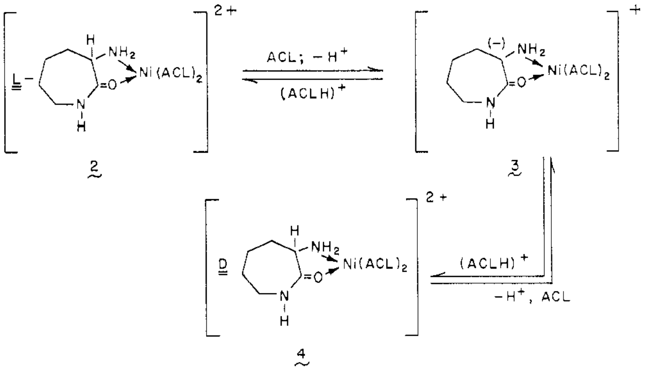
RACEMIZATION OF **1** IN THE PRESENCE OF METAL ION[a]

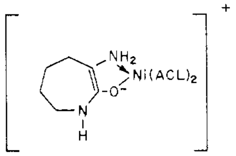
Metal salt	[**1**]/[metal]	Time, hr	Extent of racemization, %
$NiCl_2$	2	4	0
$NiCl_2$	4	4	100
$NiCl_2$	10	2	100
$NiCl_2$	60	2	56
$NiCl_2\cdot 6H_2O$	10	2	37[b]
$CrCl_3\cdot 5H_2O$	10	2	100
$PdCl_2\cdot 2H_2O$	10	2	100
$ZnCl_2$	10	5	100
$CoCl_2\cdot 6H_2O$	10	5	73
$AlCl_3\cdot 6H_2O$	10	5	69
$InCl_3$	10	5	58
$CuCl_2$	10	5	33
No metal	. . .	4	0

[a] Solvent is methanol and the temperature is 95°. [b] Water solution at 95°.

In the case of nickel, the nature of the complexes was investigated in some detail. At mole ratios of ligand to Ni(II) of 2:1 good yields of (DL-ACL)$_2$NiCl$_2$ could be isolated. At mole ratio of 3:1 or higher, practically quantitative yields of (DL- or L-ACL)$_3$NiCl$_2$ were obtained. Chelation of the amino lactam to the metal ion occurs through the amino and the carbonyl group as indicated by ir where the frequency for the carbonyl absorption was shifted from 1660 to 1627 cm^{-1}. The absence of racemization at ligand to Ni(II) ratios of 2:1 suggests high stability for this complex.

For ligand to nickel ratios above 3:1 we suggest the following mechanism. The proton on the α-carbon atom is labilized through coordination of the keto and the amino group to the metal ion. The mobility of this proton in complex **2** is further enhanced by the possibility of enolate ion formation, **5** and **6**. It was observed that nonenolizable amino compounds such as methylbenzylamines did not racemize under the same conditions. Uncoordinated α-amino lactam acts as a base for proton abstraction and gives the coordinated carbanion, **3**. The latter may abstract a proton from the protonated α-amino lactam, ACLH$^+$, to yield a racemized ligand, shown in **4**.





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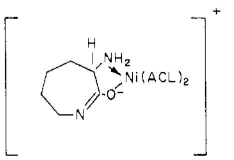

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Fast exchange between coordinated and free ligand allows the reaction to become catalytic with respect to metal ion

$$(\text{D-ACL})\text{Ni}(\text{ACL})_2{}^{2+} + \text{L-ACL} \overset{\text{fast}}{\rightleftharpoons} (\text{L-ACL})\text{Ni}(\text{ACL})_2{}^{2+} + \text{D-ACL}$$

In the absence of free, uncoordinated ligand, no racemization is observed.

By considering the racemization as a pseudo-first-order reversible reaction (first order in chelated substrate with concentration of free ligand constant in a given run), the following expression can be derived

$$dx/dt = ka\left[1 - \frac{3}{R}\right]\left[\frac{3(a-x)}{R} - \frac{3x}{R}\right] = k[\text{free ACL}]([\text{chelated L}] - [\text{chelated D}])$$

which gives

$$t = \frac{2.3}{2k'} \log\left[\frac{a}{a-2x}\right]$$

where x is the concentration of D-α-amino-ε-lactam (free and chelated) at time t, a is the total concentration of ligand (D- and L-ACL), $R = a/[\text{Ni(II)}]$, k is the second-order rate constant for the racemization, k' is the pseudo-first-order rate constant defined as: $k' = [3ka(1/R - 3/R^2)$.

TABLE II

KINETIC PARAMETERS FOR RACEMIZATION OF **1** WITH NICKEL ION

[**1**], M	R {= [**1**]/[Ni(II)]}	$10^4k'$,[a] sec^{-1}	10^3k, M^{-1} sec^{-1}	k'/ka
0.156	4.3	1.03	3.19	0.205
0.124	5.8	0.992	3.21	0.250
0.166	7.6	1.29	3.25	0.240
0.112	9.2	0.763	3.10	0.220
0.152	14.6	0.759	3.06	0.165

[a] Rate constants were calculated by least-squares analysis. Their standard deviation is less than 1%.

By substituting optical rotations for concentrations, the equation becomes: $t = (2.3/2k') \log (\alpha_0/\alpha_t)$; k'

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[11] Addition of 1 mol of α-hydroxylaminocaprolactam/mol of (L-ACL)$_2$NiCl$_2$ produced 90% racemization in 2 hr at 95° in methanol. Although a weaker base than ACL, α-hydroxylaminocaprolactam is still capable of abstracting the labilized proton in the chelate. Fast exchange between coordinated and free ACL would lead to a catalytic racemization.

can be determined at various R values by measuring the decrease in optical rotation as a function of time (Table II).

If the proposed mechanism is operating, the rate of racemization should vary with R (inversely proportional to concentration of metal ion) according to the function: $k' = 3ka\,(1/R - 3/R^2)$. This function is zero at $R = 3$, has a maximum at $R = 6$, and slowly tapers off at higher R values. A plot of k'/ka against R for the various runs shows excellent agreement with the theoretically constructed curve (Figure 1).

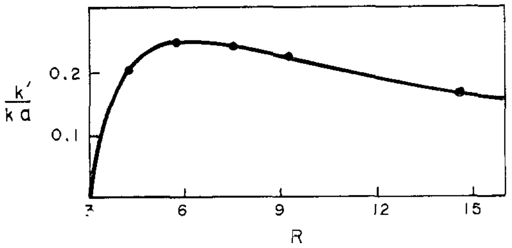

Figure 1.—Effect of ligand to metal ratio, R, on the rate of racemization of 1. The points represent experimental runs, and the curve is constructed theoretically from $k'/ka = 3(1/R - 3/R^2)$.

This strongly supports our proposed mechanism and the reaction is an interesting example of a racemization path, where the action of the metal ion is truly catalytic and where the substrate itself acts as the basic racemization agent.

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Dimethylmercury and Tetraborane(10)

By F. M. Miller and D. M. Ritter[1]

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Dimethylmercury[2] will alkylate tetraborane(10)[3] to give 2-methyltetraborane(10).[4] The best yield (68%) at optimum conversion (27%) was obtained after 5 min at 50° in a volume of 200 ml when the ratio of dimethylmercury to tetraborane was 2.50:0.42 (in mmol).[5] From this was recovered by glpc tetraborane (0.25), 2-methyltetraborane (0.12), methyldiboranes (0.09), and trimethylborane (0.01). Reactants in the ratio 2.38:0.78 underwent a 10% conversion at 25° after 1.6 hr with a 62% yield of 2-methyltetraborane. After 5 hr at 25° reactants in the ratio 3.78:1.37 gave a 42% conversion and a 56% yield. About the same amount of dimethylmercury and larger proportions of tetraborane gave approximately the same conversion, but the yield of methyltetraborane diminished. The reaction appeared to proceed in the dimethylmercury as solvent, and the more dilute the solution, the better was the yield. When all substances were present as vapor only, there was no reaction.

Under similar conditions trimethylbismuth[6] gave 5% conversion to 2-methyltetraborane. Trimethylgallium[7] converted 50% of tetraborane to trimethylborane.

Pentaborane(11) with dimethylmercury after 1 hr gave pentaborane(9), tetraborane(10), and the products expected from the latter. In 12 hr diborane(6) was 16% converted to methyldiboranes.

The results reported here are reminiscent of the cases where trimethylgallium and diborane(6) gave gallium metal and methyldiboranes[8] and where bis(trifluoromethylmercury) and diborane in dimethyl sulfide solvent gave the dimethyl sulfide adduct of trifluoromethylborane.[9]

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[1] Author to whom inquiries should be addressed. Work supported by funds from National Science Foundation Grants GP-3459 and GP-7888.

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Protonic Complexes of Oxo Ligands with Tetrachloroauric Acid

By Richard A. Potts

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At the turn of the century Pickard and Kenyon[1] prepared a series of compounds of tertiary phosphine oxides with acids and salts. Complexes of phosphine oxides with various metal ions[2–4] and nonmetals (halogens)[5] have now been widely studied. Pickard and Kenyon's complexes with acids, however, have received less attention. Collamati[6] studied the compound tetrachloroauric acid–bis(triphenylphosphine oxide), $HAuCl_4\cdot 2(C_6H_5)_3PO$, and found that the phosphine oxide molecules are not coordinated to the gold(III) but are bonded to the hydrogen ion as in the

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