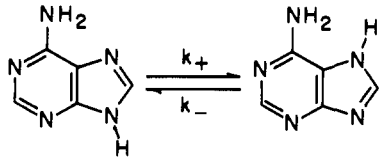

(8)

$= 50\ s^{-1}$, $k_- = 160\ s^{-1}$. These rate constants, which may include reaction without water participation, are very much smaller again than that obtained for imidazole.

Returning to the reaction mechanism for UH^-, it seems clear that the presence of the C=O groups brings about a marked enhancement of the rate of bifunctional proton transfer with water participation, which supports the reaction mechanism shown in eq 1.

References and Notes

(1) Work supported by the National Science Foundation.
(2) For a review of experimental techniques and interpretation of results, see E. Grunwald and E. K. Ralph in "Dynamic Nuclear Magnetic Resonance", L. M. Jackman and F. A. Cotton, Ed., Academic Press, New York, N.Y., 1975, Chapter 15.
(3) Proton exchange catalyzed by H_3O^+ is negligible under these conditions. Compare (a) S. Meiboom, *J. Chem. Phys.*, **34**, 375 (1961); (b) Z. Luz and S. Meiboom, *J. Am. Chem. Soc.*, **86**, 4768 (1964).
(4) H. G. Busse and G. Maass, *Z. Phys. Chem.*, (*Frankfurt am Main*), **66**, 92 (1969) $k_f = 3 \times 10^5\ s^{-1}$ at 20°.
(5) J. R. De Member and F. A. Wallace, *J. Am. Chem. Soc.*, **97**, 6240 (1975). For UH_2, $pK_{a1} = 9.7$; $pK_{a2} = 14.2$.
(6) J. P. Kokko, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.*, **83**, 2909 (1961).
(7) E. K. Ralph and E. Grunwald, *J. Am. Chem. Soc.*, **90**, 517 (1968), have previously studied proton exchange between imidazole and water. They worked under conditions of relatively low pH and thus missed the kinetic term, 1.5×10^6 [Im]. The rate constant they obtained for the kinetic term in [Im][ImH$^+$] was about 10% greater than ours, possibly due to neglect of the term in Im.
(8) The rate constant for OH^--catalyzed reaction is listed as $2.1 \times 10^9\ s^{-1}\ M^{-1}$ in eq 2, differing by 10% from that in eq 6. The discrepancy provides an index of the good consistency with which rate constants can be measured, in spite of the complicated kinetics.
(9) M. Eigen, G. G. Hammes, and K. Kustin, *J. Am. Chem. Soc.*, **82**, 3482 (1960).
(10) M. Dreyfus, G. Dodin, O. Bensaude, and J. E. Dubois, *J. Am. Chem. Soc.*, **97**, 2369 (1975).

Kuang-Chou Chang, Ernest Grunwald*
Department of Chemistry, Brandeis University
Waltham, Massachusetts 02154

Received March 15, 1976

Synthesis of L-Lysine. Simultaneous Resolution/Racemization of α-Amino-ε-caprolactam[1]

Sir:

In recent years there has been some activity[2] concerned with the resolution of α-amino-ε-caprolactam (ACL), an important precursor in the chemical synthesis of L-lysine. Of particular interest are the resolution methods relying on kinetically controlled crystallization[3] of one enantiomer on seed crystals of the same enantiomer. Generally this type of resolution can be carried out only if the racemic modification exists as a true racemic mixture, rather than a racemic compound or racemic solid solution, in the solid phase.[3] In the case of ACL, several salts, such as the hydrochloride,[2b] hydrobromide,[2g] β-naphthalenesulfonate,[2e] and α-amino-β-naphthalenesulfonate,[2e] meet this requirement and have been resolved in this manner. Earlier work in this laboratory[2c] had shown that the coordination complex of ACL with nickel(II) chloride of empirical formula **1** can also be resolved by kinetically controlled crystallization from ethanol solution induced by seed crystals of formula **2** or **3**. It had also been shown[4] that optically active ACL can be racemized by heating in alcohol solution with catalytic amounts of nickel(II) chloride. These facts encouraged us to attempt the resolution of DL-ACL by preferential crystallization of **2** under conditions of simultaneous racemization of D-ACL in solution. Such a process would theoretically transform all of the DL-ACL to **2**[5] and could be of practical interest if carried out at a reasonably high rate.[9]

$(DL\text{-ACL})_3NiCl_2$ $(L\text{-ACL})_3NiCl_2 \cdot EtOH$
1 **2**

$(D\text{-ACL})_3NiCl_2 \cdot EtOH$
3

We wish to report that the nickel(II) chloride catalyzed racemization of optically active ACL in alcohol solution is greatly accelerated by alkoxide ions, provided that the molar ratio of ACL to nickel(II) is maintained above ~3.5:1.[10] Moreover, resolution of DL-ACL from supersaturated ethanol solutions by means of kinetically controlled crystallization induced by seed crystals of **2** can take place under these racemization conditions. The process is carried out most conveniently at the boiling point of the solution (~80°). This mode of operation allows continuous removal of solvent and results in relatively high conversion of DL-ACL to crystalline **2**. In a typical experiment DL-ACL, 5.40 g (42 mmol), was dissolved in 25 ml (10.5 mmol) of 0.42 M ethanolic nickel(II) chloride at reflux and 0.72 ml (1.58 mmol) of 2.19 M ethanolic sodium ethoxide was added to the resulting dark blue solution. A small amount of sodium chloride that formed was removed by filtration. Seed crystals of **2**, $[\alpha]^{25}D$ −23.3° (*c* 4, 1 N hydrochloric acid[11]), average diameter 3.6 μm, 1.50 g (26.8 mmol), were added to the filtrate, and the mixture was boiled gently under nitrogen atmosphere with slow mechanical stirring. An ethanol solution (30 ml) containing 4.60 g (36 mmol) of DL-ACL and 11.6 mmol of nickel(II) chloride was added dropwise to the reaction mixture during 1.5 h while the overall level of the mixture was maintained at 30 ml by simultaneous evaporation of ethanol. The reaction mixture was then filtered, and the crystals were washed with cold ethanol and dried in vacuo at 70°, yield 7.70 g (50% conversion[12]). The product had equivalent weight (Cl^-, Ni^{2+}) and elemental analysis (C, H, N) consistent with the formula $(ACL)_3NiCl_2 \cdot EtOH$; $[\alpha]^{25}D$ −22.3° (*c* 4, 1 N hydrochloric acid[11]), i.e., 96% enantiomeric excess. The crystals had an average diameter of 5.3 μm. The mother liquor, when acidified with hydrochloric acid, had a slightly positive rotation corresponding to approximately 5% enantiomeric excess of D-ACL.

Still higher conversions of DL-ACL to **2** are possible if a continuous mode of operation is adopted. We were able to obtain up to 92% conversion[12] by charging an ethanol solution containing DL-ACL, nickel(II) ion, chloride ion, and ethoxide ion[13] in respective molar ratios 4.50:1.00:1.85:0.15 together with seed crystals of **2**. Ethanol was removed continuously by evaporation while a feed ethanol solution containing the same reagents in ratios 3.12:1.00:1.97:0.03 was added. Approximately 20% of the grown crystals were removed every hour and fresh seed crystals, corresponding to 25 wt % of the crystals removed, were added. The enantiomeric excess of the product was about 97%.

The resolved complex is decomposed instantly by reaction with hydrogen chloride in methanol solution. The hydrochloride of L-ACL crystallizes in ~95% yield, with respect to the enantiomeric excess of L-ACL in the complex, and is 100% enantiomerically pure. The enantiomeric enrichment taking place during the crystallization is due to the fact that DL-ACL hydrochloride is a true racemic mixture in the solid phase[2b] and so remains in solution.

$$(L\text{-ACL})_3NiCl_2 + 3HCl \rightarrow NiCl_2 + 3L\text{-ACL} \cdot HCl$$

The current simultaneous resolution/racemization process has several unique features worth emphasizing.

(1) The racemic modification resolved is an octahedral transition metal ion complex which can theoretically exist in as many as 12 diastereoisomeric pairs of enantiomers.[14] Equilibration of the ligands around the metal ions is very fast, however, compared to the rate of racemization of the ligands, as evidenced by the following facts. (a) Addition of 3 mol of L-ACL ($[\alpha]^{25}D$ −34°) to a solution of 1 mol of **3** ($[\alpha]^{25}D$ −59°) results in complete loss of optical activity in less than 10 s after mixing. (b) No mutarotation is observed in solutions containing 1 mol of nickel(II) and 3 mol of L-ACL, although the corresponding complex can exist in as many as four diastereoisomers.[14] It is obvious, therefore, that the rate determining step in the current process is not the interconversion of diastereoisomers involving the metal ion but the racemization of ACL.

(2) Although the exact structure of the crystals of formula **2** is not known,[15] it is certain that they are enantiomeric to the crystals of formula **3**. (In fact the current process can be carried out with equal success using **3** as seed crystals.) When spontaneous crystallization is allowed to take place from a solution of **1** containing 50% enantiomeric excess of L-ACL, the first crystals formed are **2**, although statistically the most abundant species is $(L\text{-ACL})_2(D\text{-ACL})NiCl_2$; correspondingly, **3** is obtained when D-ACL is in excess. Clearly, crystalline **2** and **3** (two enantiomers) are the stable solid phases in equilibrium with a solution of **1**. In view of the foregoing discussion, it is clear that the current process is a simultaneous resolution/racemization of enantiomers, although not the same pair of enantiomers are involved in each half of the process: with respect to the resolution the relevant enantiomers are crystalline **2** and **3**; with respect to racemization, these are L-ACL and D-ACL. The possible presence of 24 diastereoisomers in solution and four in each solid phase is kinetically irrelevant to the process.

Acknowledgment. We thank Mr. W. J. Lukasavage for technical assistance in the course of this work.

References and Notes

(1) Presented in part at the First Chemical Congress of the North American Continent, Mexico City, Mexico, Dec 5, 1975, No. ORGA-178.

(2) (a) M. Brenner and H. R. Rickenbacker, *Helv. Chim. Acta*, **41**, 181 (1958); (b) H. Watase, Y. Ohno, T. Okada, and T. Takeshita, U.S. Patent 3 879 382 (1975); (c) A-M. Kubanek, S. Sifniades, and R. Furhmann, U.S. Patent 3 824 231 (1974); (d) I. Tanaka, Y. Ohno, and T. Okada, U.S. Patent 3 658 811 (1972); (e) Y. Shibahara, M. Suzuki, Y. Hayashi, and T. Fukuda, U.S. Patent 3 591 579 (1971); (f) Tanabe Seiyaku Co., Ltd., French Patent 1 559 885 (1969); *Chem. Abstr.*, **72**, 55890 (1970); (g) M. Shibasaki and J. Onogi, Japanese Patent 673 489 (1967); *Chem. Abstr.*, **68**, 13394*k* (1968); (h) J. E. Nelemans, A. H. Pecasse, W. Pesch, and V. Verstrijden, U.S. Patent 3 105 067 (1963).

(3) R. M. Secor, *Chem. Rev.*, **63**, 297–309 (1963).

(4) A-M. Weidler-Kubanek, Y. C. Kim, and R. Fuhrmann, *Inorg. Chem.*, **9**, 1282 (1970).

(5) Preferential crystallization of a chiral species under conditions of simultaneous epimerization of the other optical isomer in the liquid phase is known as an asymmetric transformation of the second order.[6] The process, although common in the case of diastereoisomers,[7] has been reported in only a few cases of enantiomers.[8]

(6) E. E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 42.

(7) M. M. Harris, *Prog. Stereochem.*, **2**, 157 (1958).

(8) (a) W. Baker, B. Gilbert, and W. D. Ollis, *J. Chem. Soc.*, 1443 (1952); (b) H. M. Powell, *Nature (London)*, **170**, 155 (1952); (c) E. Havinga, *Biochim. Biophys. Acta*, **13**, 171 (1954); (d) R. E. Pincock and K. K. Wilson, *J. Am. Chem. Soc.*, **93**, 1291 (1971).

(9) In a continuously operated asymmetric transformation the steady-state rate of resolution must equal the steady-state rate of racemization. If pseudo-first-order kinetics are obeyed, it can be shown that at steady state $R = 0.0069CD_{ee}/(t_{1/2})_r$, where R is the rate of crystallization of the L-enantiomer expressed in g $l.^{-1}$ h^{-1}, C is the total concentration of the two enantiomers in g $l.^{-1}$, D_{ee} is the percentage steady-state enantiomeric excess of the D enantiomer in solution and $(t_{1/2})_r$ is the half-life of racemization in h. For typical concentrations of 250 g $l.^{-1}$ and D_{ee} of 10%, $(t_{1/2})_r$ must be on the order of 1 h or less for the process to have a practical output.

(10) Kinetic studies and a discussion of the mechanism of racemization will be published in a forthcoming paper.

(11) The optical activity at the sodium D line measured in 1 N hydrochloric acid is due to the ACL and is not affected by the presence of Ni(II).

(12) The conversion computation was based on the maximum amount of **1** which can form in solution, taken as stoichiometric to the nickel(II) chloride charged.

(13) Ion exchange techniques were utilized in preparing solutions containing Ni^{2+} and ethoxide ion. Details will be presented elsewhere.

(14) F. Basolo, "Chemistry of the Coordination Compounds," J. C. Bailar, Jr., Ed., Reinhold Publishing Corp., New York, N.Y., 1956, p 317.

(15) X-Ray work is currently under way to that purpose.

Stylianos Sifniades,* William J. Boyle, Jr., Jan F. Van Peppen

Chemical Research Center, Allied Chemical Corporation
Morristown, New Jersey 07960

Received January 30, 1976

A Stereoselective Synthesis of the 24(*R*),25-Dihydroxycholesterol Side Chain

Sir:

Introduction of the 24*R*-hydroxy group into a steroid side chain presents a significant challenge. The hydroxy group with this absolute configuration is characteristic of several natural products such as lyofoligenic acid,[1] lyofolic acid,[2] and the vitamin D_3 metabolites 24,25-dihydroxycholecalciferol[3,4] and 1,24,25-trihydroxycholecalciferol.[4,5] We now report a highly stereoselective method for producing this C-24 side chain functionality, which was developed for the vitamin D_3 metabolites but which should also be applicable to the synthesis of other natural products.

Initially, we considered it impractical to generate a specific chiral center on a long and flexible sidechain, but were encouraged by recent reports in the prostaglandin area.[6] Our previous results and those of Ikekawa[7] and Kodicek[8] have shown that no control of stereochemistry was possible in epoxidation and hydroxylation of the $\Delta^{24,25}$-double bond of desmosterol derivatives under a variety of conditions. Near 1:1 mixtures of products always resulted, indicating that this double bond was too far away from the C-17, C-20 chiral environment. Therefore, we decided to explore the chemistry of the (*Z*)- and (*E*)-$\Delta^{23,24}$-allylic alcohols expecting that the closer proximity of the double bond to the C-17 and C-20 chiral centers might have an influence on the stereoselectivity of the hydration reactions.

The two $\Delta^{23,24}$-allylic alcohols **3** and **4** were prepared from the acetylenic ether **1**, which was derived from stigmasterol in five steps (42% overall yield).[9] Compound **1** was cleaved in acidic methanol at 0° to give the acetylenic alcohol **2** ($[\alpha]D$ +50°, 95% yield)[10] which was cleanly hydrogenated to the *Z*-allylic alcohol **3** ($[\alpha]D$ +37°, 90% yield) over Lindlar catalyst in ethyl acetate (Scheme I). Alternatively, the acetylenic alcohol **2** was reduced with lithium aluminum hydride in tetrahydrofuran at reflux to give the *E*-allylic alcohol **4** (mp 126–127°, $[\alpha]D$ +46°, 90% yield).

The *Z*-olefin **3**, when treated with several peracids, yielded a 1:1 mixture of epoxy alcohols **5** and **6**. However, when treated with anhydrous *tert*-butyl hydroperoxide in toluene and a catalytic amount of vanadyl acetoacetate[11] at −78°, followed by warming the mixture to −20° for 6 h, an 85:15 mixture of **6** and the undesired isomer **5** was obtained.[12] The 23*R*,24*R*-epoxy alcohol **6**, $[\alpha]D$ +57°, was isolated by chromatography[13] and was reduced with lithium aluminum hydride (0°, tetrahydrofuran) to give the 24*R*,25-diol **9** contaminated only by 5% of the isomeric 23*R*,25-diol **10.** Pure diol **9**, mp 142–143°, $[\alpha]D$ +63°, was obtained by direct crystallization and was exposed to acidic aqueous dioxane at 60° to yield the desired 24(*R*),25-dihydroxycholesterol (**12,** mp 200–202°, $[\alpha]D$ −11.3° (*c* 1.02, CH_3OH)).

Similarly, when the *E*-allylic alcohol **4** was epoxidized with *tert*-butyl hydroperoxide in toluene at −78° to −20° with vanadyl acetoacetate catalyst, an 85:15 mixture of epoxy alcohols **7** and **8** was obtained. The major epoxy alcohol **7**, mp