To check for a possible anion effect, the calorimetric reaction of 18-crown-6 with $La^{3+}$ and $Ce^{3+}$ was repeated using the nitrate salts of both cations and the perchlorate salt of the latter. The nitrates both produced precipitated complex, while the reaction results (both log $K$ and $\Delta H$) of 18-crown-6 with $Ce(ClO_4)_3$ were well within the range of values found for that with $CeCl_3$.

Although the lighter lanthanides are similar in size to $Na^+$, and although the stability constant of $Ce^{3+}$ (log $K$ = 3.57, radius = 1.03[10]) approaches that of $Na^+$ (log $K$ = 4.36,[11] radius = 1.02[10]), entirely different thermodynamic factors are responsible for the stabilities of the complexes of these two cations. While alkali and alkaline earth metal ion complexes of 18-crown-6 are enthalpy stabilized and entropy destabilized,[12] the opposite is true of the rare earth complexes. In addition, the stability decrease along the series of lanthanides is enthalpic in origin for the cations up to $Nd^{3+}$ and then entropic in origin for those from $Sm^{3+}$ to $Gd^{3+}$. This fact reflects the delicate balance among ligand–cation binding, solvation, and ligand conformation which exists in these systems,[12] each of which will be discussed briefly in the following paragraphs.

Stability sequences of cyclic polyether complexes with nonpolarizable cations have been related to the relative sizes of cation and ligand cavity.[4,12] Like $Na^+$, the lanthanide(III) cations are too small for an ideal fit into the cavity of the 18-crown-6 ring. For this reason it is not surprising that complex stability decreases as cation size diminishes while proceeding across the series. This stability trend is opposite to that found for most ligands, whose complexes are generally more stable with the lanthanides of higher atomic number.[5]

Evidence exists that solvation number of the rare earth cations decreases with higher atomic number and that a sudden drop in solvation number occurs around $Gd^{3+}$.[6] It is possible, therefore, that the entropy contribution from loss of solvent ($CH_3OH$ and/or $H_2O$) molecules which favors complexation is smaller for the lanthanides of higher atomic number. This factor may contribute significantly to the lack of formation of complexes with any of the rare earth cations beyond $Gd^{3+}$.

An x-ray crystal structure of the dicyclohexo-18-crown-6 complex of $La(NO_3)_3$ has been reported[13] showing $La^{3+}$ to be situated in the crown ring cavity, and further coordinated to six oxygen atoms of three bidentate nitrate ions. The crown oxygens are not quite coplanar, two opposite atoms being displaced below the plane of the other four. This distortion from planarity is reminiscent of the bent ligand conformation of the 18-crown-6 complex of $Na^+$.[12] Further ordering of the ligand may also be responsible for a loss of entropic stabilization with the higher lanthanides.

Since 18-crown-6 exhibits unusual and potentially useful complexation characteristics with the lanthanides and since there is considerable interest in developing methods of separating actinides, we have investigated the possibility of interaction of this ligand with $UO_2Cl_2$ and $Th(NO_3)_4$ in methanol. Previous reports of the synthesis of solid uranyl complexes with 18-crown-6 have since been discounted as an example of cocrystallization.[14-16] Likewise no interaction has been reported between the uranyl cation and dibenzo-18-crown-6 or benzo-15-crown-5 in the solid phase[17] or with the cis-syn-cis isomer of dicyclohexo-18-crown-6 in aqueous solution.[4] We find no measurable heat of interaction of $UO_2^{2+}$ or $Th^{4+}$ with 18-crown-6 in methanol. This observation in the case of uranyl ion for which other data are available is supportive not only of the hypothesis that there is no complex formation between these two species under these conditions, but also of the usefulness of titration calorimetry in detecting the presence or absence of complexation in general.

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## Asymmetric Hydrogenation of α,β-Dehydroamino Acid Residue in Cyclic Dipeptides

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AM-Toxin I is a host specific phytotoxin, its structure being determined as c(L-Amp[1]-Dha[2]-L-Ala[3]-L-Hmb[4]) (c = cyclo, Amp = 2-amino-5-(*p*-methoxyphenyl)pentanoic acid, Dha = dehydroalanine, Hmb = 2-hydroxy-3-methylbutanoic acid).[1] To elucidate the role of a double bond in Dha[2] residue, we planned to prepare [L-Ala[2]]- and [D-Ala[2]]-AM-toxin I by hydrogenation of natural or synthetic[2] AM-toxin I. As a preliminary study we hydrogenated c(L-Leu-Dha) and observed unexpectedly high asymmetric induction affording pure c(L-Leu-L-Ala). This paper reports asymmetric hydrogenation of Dha residue in several cyclic dipeptides, preparation of pure L-alanine from c(L-Lys(ε-Ac)-Dha), preparation and hydrogenation of c(L-Leu-Dhb) (Dhb = dehydrobutyrine), and preparation of c(NMe-L-Trp-Dhb) (NMe = *N*-methyl) corresponding to natural cyclic dipeptide.[3] Poisel and Schmidt reported the efficient asymmetric induction forming L-Phe residue in some 90% on hydrogenation of c(L-Pro-NH-C(=$CHC_6H_5$)-CO) or c(L-Pro-$NCOCH_3$-C(=$CHC_6H_5$)-CO); there was however, almost no asymmetric induction isolating DL-phenylalanine in the case of c(L-Leu-$NCOCH_3$-C(=$CHC_6H_5$)-CO).[4] Akabori et al. observed low asymmetric induction isolating phenylalanine with 15% L form

**Table I.** Asymmetric Hydrogenation of Cyclic Dehydrodipeptides

| Entry | Cyclic dehydrodipeptide | Cyclic dipeptide by hydrogenation[a] | Chiral induction, %,[b] in the cyclic dipeptides |
|---|---|---|---|
| 1 | c(L-Ala-Dha)[c] | c(L-Ala-Ala) | 94.6 |
| 2 | c(L-Val-Dha)[c] | c(L-Val-Ala) | 98.4 |
| 3 | c(L-Leu-Dha)[c] | c(L-Leu-Ala) | 95.8 |
| 4 | c(L-Leu-Dha)[d] | c(L-Leu-Ala) | 94.6 |
| 5 | c(L-Leu-Dha)[d] | c(L-Leu-Ala)[e] | 92.2 |
| 6 | c(L-Phe-Dha)[c] | c(L-Phe-Ala) | 94.6 |
| 7 | c(L-Pro-Dha)[f] | c(L-Pro-Ala) | 84.8 |
| 8 | c(L-Lys(ε-Ac)-Dha)[c] | c(L-Lys(ε-Ac)-Ala) | 91.8 |
| 9 | c(L-Lys(ε-Ac)-Dha)[d] | c(L-Lys(ε-Ac)-Ala) | 91.8 |
| 10 | c(L-Leu-*Z*-Dhb)[d] | c(L-Leu-Aba) | 95.6 |

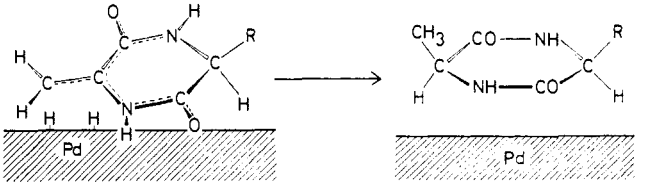
[a] MeOH was used as a solvent except *e*. [b] Defined as % L-Ala or L-Aba (Aba = 2-aminobutanoic acid) minus % D-Ala or D-Aba in c(L-aminoacyl-Ala or -Aba). [c] Nitecki's method. [d] Fischer's method. [e] AcOH was used instead of MeOH. [f] Since action of $NH_3$–MeOH on H-L-Pro-L-Ser-OMe afforded a by-product in addition to c(L-Pro-L-Ser) (**12**), **12** was synthesized by spontaneous cyclization of H-L-Ser-L-Pro-OMe.

on hydrogenation of c(L-isovalyl-NH-C(=$CHC_6H_5$)-CO).[5] Bycroft and Lee reported the efficient asymmetric hydrogenation forming L-Ala residue >90% from c(L-Pro-Dha).[6] From these results, two groups[4,6] emphasized that an optically active proline in cyclic dehydrodipeptides is an important factor causing high asymmetric induction on hydrogenation.

We synthesized c(L-Leu-L-Ser) (**1**) from Boc-L-Leu-L-Ser-OMe (**2**)[7] by a procedure of Nitecki et al.;[8] the Boc group in **2** was removed by formic acid and subsequent treatment of a dipeptide ester with *sec*-BuOH and toluene afforded **1**, 60% yield from **2**, mp 237–239 °C dec, $[\alpha]^{20}_D$ −41.0° (MeOH).[9] c(L-Leu-Dha) (**3**) was synthesized according to a procedure of Photaki;[10] the action of Tos chloride (3 equiv) on **1** in pyridine yielded c(L-Leu-L-Ser(Tos)) (**4**), and treatment of $Et_2NH$ (2 equiv) for 5 h on **4** in DMF afforded **3**, 64% yield from **1**, mp >290 °C dec, $[\alpha]^{20}_D$ −93.6° (DMF). Hydrogenation of **3** (50 μmol) at 1-atm pressure of $H_2$ with Pd black (1–2 mg) in MeOH (2 mL) yielded c(L-Leu-Ala) (**5**) quantitatively. The filtrate was evaporated and hydrolyzed with 6 M HCl at 110 °C for 24 h. Amount of D-alanine in the hydrolysate was determined as follows.[11] After evaporation the residue was treated with Cbz-L-Leu-ONSu and $Et_3N$, and whole reaction mixture was hydrogenated and subjected to an amino acid analyzer. The ratio of LL and LD isomers in H-Leu-Ala-OH was determined as 96.4:3.6 and the real ratio of L- and D-alanine in **5** was calculated as 97.9:2.1, after correction of 1.5% D-alanine which is caused from pure L-alanine under the same hydrolytic condition. The chiral induction (percent) was calculated as 97.9–2.1 = 95.8 (entry 3 in Table I). Alternately the presence of c(L-Leu-L-Ala) as a major product in **5** was observed visually on TLC; when **5** was subjected to TLC, there was a main spot with $R_f$ 0.46, whereas there was a very faint spot with $R_f$ 0.54.[12]

Although a cyclic dipeptide has been synthesized easily by a procedure of Fischer,[13] Nitecki et al. claimed that a cyclic dipeptide obtained by Fischer's method contains partially racemized amino acid residues.[8] We found that almost optically pure cyclic dipeptide is obtained when a reaction time with $NH_3$–MeOH on a dipeptide ester is shortened to 4 h at room temperature. Thus, c(L-Leu-L-Ser) (**1**) with mp 236–238 °C dec and $[\alpha]^{20}_D$ −40.2° (MeOH) was obtained in 73% yield from Cbz-L-Leu-L-Ser-OMe via hydrogenation and subsequent treatment with $NH_3$–MeOH. Reaction with Tos chloride and $Et_2NH$ on **1** afforded c(L-Leu-Dha) (**3**), mp >290 °C dec, $[\alpha]^{20}_D$ −91.7° (DMF). Although the chiral induction (entry 4 in Table I) with **3** was slightly lower than entry 3, the same chiral induction was obtained in the case of c(L-Lys(ε-Ac)-Dha) (entries 8 and 9). After hydrogenation of **3** (5 mmol) with $[\alpha]_D$ −91.7°, pure c(L-Leu-L-Ala) showing no spot for c(L-Leu-D-Ala) on TLC was obtained by recrystallization with MeOH–ether, 64% yield, mp 240–241 °C dec, $[\alpha]^{20}_D$ −49.8° (DMF).

Scheme I




We carried out the hydrogenation of a series of c(L-aminoacyl-Dha) wherein L-amino acid residues were Ala, Val, Phe, Lys(ε-Ac), and Pro. Table I shows that isopropyl side chain of L-Val causes extremely high asymmetric induction, but even the small methyl group in L-Ala is highly efficient. It would be of interest to note that L-Pro residue causes lower asymmetric induction than other L-amino acids tested. We examined whether L-amino acid residues in linear peptide or macrocyclic peptide containing a Dha causes chiral induction. On hydrogenation of Boc-L-Leu-Dha-OMe, the ratio of LL and LD isomers in Boc-Leu-Ala-OMe was 49:51. Furthermore, hydrogenation of AM-toxin I yielded [$Ala^2$]-AM-toxin I in which the ratio of [L-$Ala^2$] and [D-$Ala^2$] isomers was 41:59.[14] Thus, we propose Scheme I indicating a mechanism of asymmetric hydrogenation,[15] in which dotted line represents the maximum π conjugation as proposed by Corey et al.[16]

Since a bulky side chain such as in L-Leu was recognized as sufficient to cause asymmetric induction, we planned preparing pure L-alanine from c(L-Lys(ε-Ac)-Dha) (**6**). c(L-Lys(ε-Ac)-L-Ser) was converted to **6** in 70% yield, $[\alpha]^{20}_D$ −55.0° (DMF), which was subjected to hydrogenation. The product, c(L-Lys(ε-Ac)-L-Ala) (**7**), was recrystallized from MeOH, 82% yield, mp 244–245 °C dec, $[\alpha]^{20}_D$ −34.8° (AcOH), and hydrolyzed with 6 M HCl at 110 °C for 12 h. The hydrolysate was treated with Dowex 50 ($H^+$ form) and eluted with 1 M pyridine, and pure L-alanine was obtained by recrystallization from water–EtOH, 78% yield, $[\alpha]^{20}_D$ +14.3° (5 M HCl).

We examined whether the Dhb residue in a cyclic dipeptide is hydrogenated asymmetrically. Cbz-L-Thr-L-Leu-OEt was converted to c(L-Leu-L-Thr) (**8**), mp 264–265 °C dec, by Fischer's method. c(L-Leu-*Z*-Dhb) (**9**) was obtained from **8** by treatments of Tos chloride (6 equiv) and successively $Et_2NH$ (2 equiv) for 24 h, mp 275–276 °C dec. High asymmetric induction (entry 10) was observed on hydrogenation of **9**. Thus, we established a synthetic procedure for Dhb-diketopiperazine, and then achieved synthesizing a cyclic dipeptide corresponding to a natural Dhb-diketopiperazine

isolated from *Streptomyces spectabilis*.[3] Cbz-L-Thr-NMe-L-Trp-OMe (**10**) was converted to c(NMe-L-Trp-Dhb) (**11**) by tosylation and action of $Et_2NH$, mp 122–124 °C dec, mass spectrum $M^+$ 283, UV max (95% EtOH) 219 nm ($\epsilon$ 36 200) (lit.[3] mp 121–123 °C, UV max 220 nm ($\epsilon$ 34 900)).[17]

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(12) We synthesized authentic c(L-Leu-L-Ala) and c(L-Leu-D-Ala) by Fischer's method, $R_f$ 0.46 and 0.54 (with 5:1 $CHCl_3$–MeOH), mp 240–242 °C and 244–246 °C (both dec), $[\alpha]^{20}_D$ −49.2 and +12.3° (DMF), respectively.
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(15) Meyer et al., *Biochem. Biophys. Res. Commun.*, **56**, 234 (1974), hydrogenated tentoxin, c(NMe-L-Ala[1]-L-Leu[2]-NMe-dehydroPhe[3]-Gly[4]) and isolated [NMe-D-Phe[3]]-tentoxin as the sole product. Thus, it should be possible that dehydroamino acid residue in a certain peptide other than a type of dehydrodiketopiperazine is asymmetrically hydrogenated.
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## Structure of the *tert*-Butyl Radical

*Sir:*

The structure of the *tert*-butyl radical is still a controversial topic. One of us[1] has suggested that the equilibrium conformation of this radical is planar and that deviations from planarity in a solid matrix might arise from steric hindrance. A stable pyramidal structure was inferred by Wood et al.[2] from the negative temperature dependence of the $^{13}C$ coupling of the radical trapped in an adamantane matrix. Symons[3] gave another interpretation of our spectra and claimed to have given evidence for planarity of the *tert*-butyl radical. The problem is again discussed in two recent papers [4,5]in which the authors support the view of nonplanarity of the radical on the basis of a temperature dependence calculation of $^{13}C$ and H couplings. Since, as has already been suggested by Symons,[6] the negative temperature coefficient of H coupling may be caused by a medium effect, we have investigated the H coupling variation as a function of temperature in four different trapping matrices. We have irradiated at 77 K polycrystalline matrices of *tert*-butyl chloride, neopentane, and isobutane coming from quick freezing of the corresponding liquids, and neopentane in a xenon matrix containing 2% neopentane. Figure 1 shows that the variations of the H coupling $a^H$ as a function of temperature are different in the four matrices. Neither the slopes of the curves nor the position of the plateaus are the same. Our

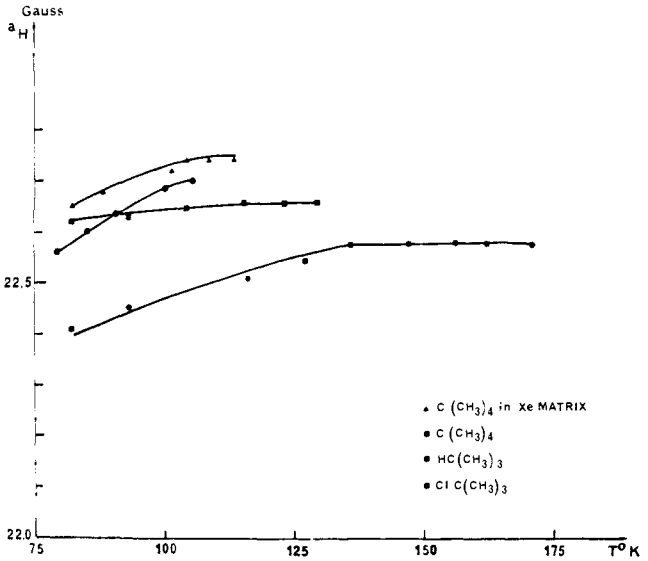


**Figure 1.** $a_{CH_3}{}^H$ coupling of $\dot{C}(CH_3)_3$ radicals as a function of temperature in four different trapping matrices: $ClC(CH_3)_3$, $C(CH_3)_4$, $HC(CH_3)_3$, $C(CH_3)_4$ in xenon.

numerical results agree quite well with the values published by Fessenden et al.[7] for liquid neopentane (22.72 G at 260 K), solid neopentane (22.62 G at 213 K), and liquid isobutane (22.7 G at 128 K).

These results show the influence of the matrix on the structure of the *tert*-butyl radical. This effect is not surprising since the deformation energy of the radical seems to be low.[2] Then, the temperature dependence of $^{13}C$ and H couplings observed by Wood et al. can adequately be interpreted in terms of the influence of the matrix: the radical, the equilibrium geometry of which would be planar, is distorted by the matrix; when the temperature is raised, it reverts toward its equilibrium structure because of the thermal expansion of the matrix. Thus, the $^{13}C$ coupling decreases and the H coupling increases as a function of temperature. Another factor[8] may also contribute to the observed temperature dependence of H couplings: electronic interactions of the unpaired electron with the matrix which slightly alter the observed splittings by perturbing the spin distribution in the radical and are temperature dependent owing to the thermal expansion of the matrix. The contribution of out-of-plane vibrations to the central carbon atom coupling, which certainly exists, is probably low compared to the effect of the matrix. These matrix effects vary with the matrix itself, and Figure 1 reflects the way in which equilibrium is achieved in each case. The present interpretation of the signs of the temperature coefficients of H and $^{13}C$ couplings does not imply a numerical value of the parameter $A_c$ (relating $^{13}C$ couplings to the 2s spin density), which would be in disagreement, as in ref 4 and 5 (407.3 G,[4] 435 G[5]) with the values calculated by different methods (1130 G,[9] 1191 G[10]).

Finally, we would like to point out that a negative temperature coefficient of $^{13}C$ coupling $a_{^{13}C}$ (or a positive temperature coefficient of H coupling $a_H$) is not an automatic consequence of a double minimum potential,[5] but depends on the shape of this potential. The sign of the temperature coefficient of $\langle Q^2 \rangle$ (proportional to the coupling), as calculated from the expression

$$\langle Q^2 \rangle = \frac{\sum_i \langle Q^2 \rangle_i \exp(-E_i/kT)}{\sum_i \exp(-E_i/kT)}$$

where $E_i$ is the vibrational energy of the state $i$, $Q$ the displacement coordinate, and $k$ the Boltzmann constant, depends