Effect of Complexation by Crown Ethers on Anisochrony of Diastereotopic Groups in NMR Spectra

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Anisochrony of geminal methyls in alkylamines bearing a chiral center in the molecule is affected by complexation with crown ethers, which amplify the chemical shift non-equivalence in NMR. The resolved signal of *gem*-methyls in valine methyl ester were unequivocally assigned to *pro-R* and *pro-S* methyl groups respectively.

In principle, different NMR chemical shifts are to be expected for diastereotopic groups, since they experience different molecular environments. However, these groups, particularly in acyclic compounds, are often accidentally isochronous because of the practically close similarity of individual surroundings. This situation can often be circumvented by such techniques as to ensure improvement of resolving ability or a change in magnetic environments, probably resulting in manifestation of the latent anisochrony. For example, the application of a higher magnetic field,[1] a change in the solvent medium, and use of NMR shift reagents[2] have generally been employed for this purpose.

Crown ethers have recently been introduced to organic chemistry and proved to be versatile from the viewpoint of both synthetic and mechanistic utilities.[3] Complexation with primary ammonium salt is one of the most important properties of crown ethers.

We now describe the notable effect of crown ethers on anisochrony of diastereotopic groups in amino compounds owing to complexation. Crown ethers were found to realize the potential anisochrony and amplify the chemical shift non-equivalence of paired ligands in alkylamines.

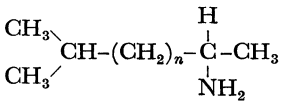
In alkylamines **1** and **2**, the signals for *gem*-methyls were unresolved in the form of free amine, but non-equivalence was observed in the hydrochloride; the chemical shift difference, 0.01 ppm for **1** and 0.02 ppm for **2**. Complexation by 18-crown-6 enhanced the difference up to 0.06 ppm, which probably arised from decrease in conformational mobility and/or the shielding effect of the crown ether. In complexes with dibenzo-18-crown-6, the $\Delta\delta$ value varied in a characteristic way depending on the length of the methylene chain, which may be ascribed to the benzene ring-currents. The chemical shift differences between *gem*-methyls were no longer observed for **3** at any state.

Amino acid esters were also of our great concern from the viewpoint of anisochrony of diastereotopic groups. In contrast to alkylamines, methyl doublets of valine methyl ester (**4**) were unresolved in the hydrochloride, whereas those of the free amine were resolved with $\Delta\delta$ of 0.07 ppm. Here again, a significant difference was caused by complexation with 18-crown-6; 0.14 ppm. The chemical shift difference was furthermore magnified in the case of dibenzo-18-crown-6, 0.22 ppm.

Non-equivalence was not observed in the spectra of leucine methyl ester in any form except for the dibenzo-18-crown-6 complex, for which a significant but rather small $\Delta\delta$ of 0.04 ppm was observed. In ^{13}C-NMR measurements, chemical shift differences of leucine methyl ester were enhanced in the order of the hydrochloride, the free amine, and the complex with 18-crown-6; 0.5, 1.2, and 1.4 ppm, respectively, which was also the case in ^{1}H-NMR of **4**.

In order to assign the resolved signals of *gem*-methyls in **4** ^{1}H-NMR spectra were investigated in every form of isoleucine (**5**) and alloisoleucine (**6**) methyl esters, whose configurations were unambiguously established. For the hydrochloride, the spectral feature of **5** and **6** very much resembled each other, and both of them can not be distinguished by ^{1}H-NMR. Liberation from the hydrochloric salt caused a slight variation in spectra and the complexes with the crown ether showed quite a remarkable difference over the methyl region between the two isomeric amino acid esters. The chemical shift differences of the methyl groups of **5** and **6**, corresponding to R^2 and R^1 respectively, were enhanced as one

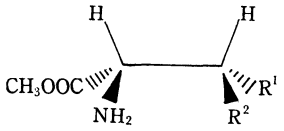
TABLE 1. CHEMICAL SHIFTS,[a,b] δ OF METHYL DOUBLETS IN ALKYLAMINE



Compound	n	Free amine	Hydrochloride	18-Crown-6 complex[c]	Dibenzo-18-crown-6 complex[c]
1[d]	0	0.89(0.00)	$\frac{0.98}{0.97}$(0.01)	$\frac{1.01}{0.95}$(0.06)	$\frac{0.63}{0.59}$(0.04)
2	1	0.88(0.00)	$\frac{0.92}{0.90}$(0.02)	$\frac{0.97}{0.91}$(0.06)	$\frac{0.70}{0.56}$(0.14)
3	2	0.89(0.00)	0.88(0.00)	0.89(0.00)	0.80(0.00)

a) The coupling constant has a value of about 6—7 Hz.
b) The value in parentheses represents the chemical shift difference ($\Delta\delta$, ppm).
c) The ratio of substrate/crown ether in $CDCl_3$ is 1.0 ± 0.1 (except for **3**; 4.0).
d) For "hydrochloride in $CDCl_3$," the chemical shift difference was 0.01 ppm.

Table 2. Chemical shifts,[a,b] δ, of methyl doublets in amino acid ester



Compound	R^1	R^2	Free amine	Hydrochloride	18-Crown-6 complex[c]	Dibenzo-18-crown-6 complex[c]
4	CH_3	CH_3	0.97 0.90 (0.07)	1.04 (0.00)	1.11 0.97 (0.14)	0.77 0.55 (0.22)
5	C_2H_5	CH_3	0.94 0.82 (0.12)	1.00 0.98 (0.02)	0.95 1.09 (0.14)	0.56 0.78 (0.22)
6[d]	CH_3	C_2H_5				
7	OCH_3	CH_3	1.23 1.12 (0.11)	1.32 1.26 (0.06)	1.29 1.33 (0.04)	—
8	CH_3	OCH_3				—
Leucine methyl ester			0.94 (0.00)	0.96 (0.00)	0.98 (0.00)	0.63 0.59 (0.04)
			[23.0 21.8 (1.2)	24.1 23.6 (0.5)	22.8 21.4 (1.4)][e]	

a) The coupling constant has a value of about 6—7 Hz (except for leucine methyl ester, about 5—6 Hz).
b) The value in parentheses represents the chemical shift difference ($\Delta\delta$, ppm).
c) The ratio of substrate/crown ether in $CDCl_3$ is 1.0 ± 0.1.
d) For simplification's sake, the configuration is depicted here for L-alloisoleucine methyl ester, although the actual experiment was carried out on the enantiomer.
e) ^{13}C chemical shifts (δ_C, ppm from TMS).

traversed from the hydrochloride (0.02 ppm), the free amine (0.12 ppm), the 18-crown-6 complex (0.14 ppm) to the dibenzo-18-crown-6 complex (0.22 ppm), which was also in keeping with the the order found for **4**.

Since the chemical shift difference of *gem*-methyls in **4** corresponds correctly to that between methyl doublets in **5** and **6** at any state, it can be safely concluded that the substitution of ethyl for methyl groups did not make any noticeable change in the magnetic environment or the conformation.

In the spectra of free amino acid esters, the methyl doublet of **6** was located in the magnetic field higher than that of **5**. The situation was reversed in the spectra of the complexes with crown ethers. Consequently, in the presence of chirality as depicted in Table 2, R^2-methyl group was shielded more than R^1-methyl in the complexes with crown ethers. It then follows that, in the case of **4**, the methyl doublets in the higher field in the free amines and in the crown ether complexes can be safely ascribed to the *pro-S* methyl (R^1) and the *pro-R* methyl (R^2), respectively.

In order to simplify ^1H-NMR spectra in the methyl region and to ascertain the above conclusion, *O*-methylthreonine (**7**) and *O*-methylallothreonine (**8**) methyl esters were subjected to the same ^1H-NMR tests. In this case, the trend of augmentation in the chemical shift differences between R^1 and R^2 was different from that found for valine series; the 18-crown-6 complex (0.04 ppm), the hydrochloride (0.06 ppm), and the free amine (0.11 ppm). However, the same situation as in the valine series prevailed for the relative positions of signals; the methyl doublet of **8** appears at a field higher than that of **7** for the free amino esters and the reverse for 18-crown-6 complexes.

The causes of the amplified anisochrony observed for diastereotopic groups in crown ether complexes are still obscure. Since dibenzo-18-crown-6 has a well-defined shielding effect, the relative spatial position can

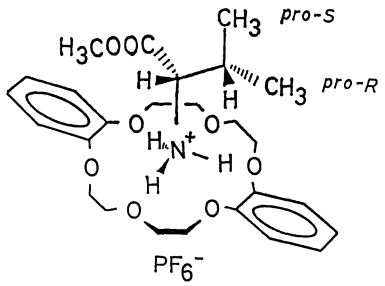


Fig. 1. The relative spatial disposition of *pro-S* and *pro-R* methyls in the valine methyl ester–dibenzo-18-crown-6 complex.

be safely allotted to the methyl groups. That is, *pro-R* methyl of valine methyl ester appearing in a higher magnetic field is disposed closer to the phenyl nuclei than the *pro-S* counterpart, as depicted in Fig. 1, which is consistent with the coupling constant of C_α–H; 4 Hz.

Enhancement of anisochrony of diastereotopic groups by complexation with crown ethers may possibly be applicable for the establishment of stereochemistry, especially of the *erythro-threo* isomerism, and may substitute partially for shift reagents in resolution of complicated spectra.

Experimental

Melting points were measured on hot plate and uncorrected. NMR chemical shifts were given as δ (ppm from TMS) in deuterochloroform (except for hydrochlorides, from DSS, in deuterium oxide) and were determined at 23 °C on a Varian EM-360 (60.00 MHz, with an error of 0.02 ppm) and/or a JEOL JNM-FX 100 (99.55 MHz for ^1H-NMR, 25.00 MHz for ^{13}C-NMR; 5 mm tube; FT conditions: acquisition time 4.1 s for ^1H-NMR, 0.68 s for ^{13}C-NMR; pulse width 38 μs (90°) for ^1H-NMR, 12 μs (90°) for ^{13}C-NMR; spectral width 1000 Hz for ^1H-NMR, 5000 Hz for ^{13}C-NMR; pulse repetition time 6.0 s for ^1H-NMR, 2.5 s for ^{13}C-NMR; number of data points 8192; number of transients 4 or 8 for ^1H-NMR,

20000 for ^{13}C-NMR; and with an error of 0.003 ppm for ^{1}H-NMR, 0.05 ppm for ^{13}C-NMR).

Material. Valine, isoleucine, alloisoleucine, and leucine methyl ester were supplied from commercial source. Esterification of amino acid was carried out according to Fischer's method. *O*-Methylallothreonine methyl ester (**8**) was prepared by the method of West[4] from crotonic acid. All the compounds were purified in the state of hydrochloride by recrystallization from ethanol–ether and the relevant data were listed in Table 3. The amines were liberated with 2 M aq sodium hydroxide just before use. All products gave satisfactory microanalyses (C=±0.80%, H=±0.27%, N=±0.33%).

Typical Procedure for Preparations of Alkylamines. 2-Amino-4-methylpentane (2): 4-Methyl-2-pentanone (20 g, 0.20 mol), sodium acetate (19.7 g, 0.24 mol) and hydroxylamine (16.7 g, 0.24 mol) were dissolved in ethanol (200 ml). After heating under reflux for 5 h, the mixture was filtered and the filtrate was evaporated and the residue was extracted with chloroform. The chloroform layer was washed with sat. aq sodium carbonate and dried over sodium sulfate. Distillation gave the oxime (bp 85—87 °C/19 Torr, 19.6 g, 85%). The oxime (19.0 g) dissolved in dry ether (50 ml) was added dropwise into lithium aluminum hydride (9.7 g) in dry ether (150 ml) and the mixture was heated under reflux for 13 h. The mixture was treated by dropwise addition of water (9.7 ml), 15% sodium hydroxide (9.7 ml), and water (29 ml) successively. The mixture was filtered and dried over sodium sulfate. The filtrate was distilled to give (**2**) (bp 112—114 °C, 6.8 g, 37%).

O-Methylthreonine Methyl Ester (7).[5] Methyl *erythro*-2-bromo-3-methoxybutyrate[4] (1.25 g, 6 mmol, bp 84—85 °C) prepared from methyl crotonate, sodium azide (0.79 g, 20 mmol), and (2,2,1)-cryptand (50 mg) were dissolved in acetonitrile (10 ml). After heating for 42 h under reflux, the mixture was filtered and the filtrate was evaporated. The residue was hydrogenated over 5% Pd–C (100 mg) in methanol (10 ml). The mixture was filtered, evaporated and then purified by passing through IR 120 B resin (2×50 cm column; About 500 ml of distilled water was passed through the column followed by effluence with 3% aqueous ammonia). The product was esterified by Fischer's method to give an amorphous solid (220 mg, 20%).

Table 3. Physical constants of amino compounds

Compound	Bp(°C)	Mp of hydrochloride (°C)
1	83—84	213
2	112—114	143
3	135—136	117—118.5
4	—	112—113
5	—	95—96.5
6	—	126
7	—	—[a]
8	—	164—165(dec)
Leucine methyl ester	—	154—154.5

a) Amorphous solid.

Method of Complexation with Crown Ether.[6] The mixture of crown ether (0.063 mmol) in deuterochloroform (0.35 ml), hydrochloride of amino compound (0.373 mmol) in deuterium oxide (0.40 ml), and lithium hexafluorophosphate (0.373 mmol) was shaken in ice bath for 5 min. After standing for about 30 min, the deuterochloroform layer was separated for spectral measurement at 60 and/or 100 MHz.

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