Tetrahedron Letters Vol. 22, pp 807 - 810
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0040-4039/81/0222-0807$02.00/0

STEREOCHEMISTRY IN TRIVALENT NITROGEN COMPOUNDS. 37. EFFECT OF ALKALI METAL COORDINATION ON AMIDE CONFIGURATIONAL EQUILIBRIA[1a,b]

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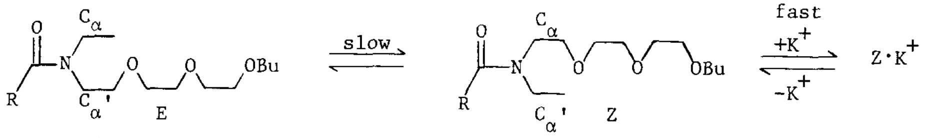
Abstract: Carbon-13 NMR spectroscopy indicates that amides bearing a triethyleneoxide substituent at nitrogen exist as a mixture of E and Z isomers; the change in isomer ratio upon addition of KSCN can be used to determine the association constant for chelation.

The interaction of alkali metal cations with amide and ether oxygen atoms is a well accepted phenomenon. Such interactions are responsible for the mode of action of ionophoric cyclic peptides and the synthetic ionophores, the crown ethers, and can affect the biological properties of naturally occurring proteins as well.[2,3] However, direct experimental demonstrations of alkali metal coordination by amide carbonyl oxygen using NMR spectroscopy are rare.[4-6] One possible consequence of ionic interactions is the change of conformation or configuration. Since the configuration at the amide partial double bond can be easily determined using NMR spectroscopy, monitoring of amide configuration could provide a useful approach toward the quantitative study of alkali metal coordination.

Previous work[6] using this approach to complexation by imides has demonstrated that alkali metal chelation by the bidentate ligand diacetamide can affect the configurational equilibrium of the imide, increasing the mole fraction Z,Z, form (which can chelate) at the expense of the non-chelating E,Z form. We now report the perturbation of amide configuration by chelation in two compounds, 1 and 2, which possess simple amide and ether functions. Further, we have developed a useful method which allows the association constant of the complex to be determined from the change in the configurational ratio.

Amides 1 and 2 were prepared by condensation of ethyl-(3,6,9-trioxatridecyl)amine with the acid chloride of the corresponding acid.[7] The ambient temperature ^{13}C NMR spectrum of 1 in deuterichloroform revealed the presence of two isomers which differ in configuration at the amide configurational unit. Thus two resonances at δ41.9 and δ43.6 were observed for the ethyl methylene attached to nitrogen (C_α) and two resonances at δ45.4 and δ46.4 were observed for the



1 $R=BuO(CH_2CH_2O)_2CH_2$
2 $R=CH_3$

N-methylene carbon of the polyether (C_α'). In each pair we have assigned the upfield resonance to the methylene group syn to the carbonyl oxygen (C_α in E-1 and C_α' in Z-1) in accord with previous assignments in simple amides.[8,9] The same order of resonances was observed in methanol solution and in mixtures of chloroform and methanol. The intensity of C_α was used as a measure of the isomer ratio[10] in methanol since the downfield resonance from C_α' (in E-1) lies close to the methanol resonance.

In methanol solution a configurational ratio E-1/Z-1 of 2.19 is observed. Addition of KSCN decreases the E/Z ratio: 0.5 eq KSCN, E/Z ratio 1.01, 1.0 eq KSCN, E/Z ratio 0.59. We interpret these observations as indicating that the equilibrium constant between E-1 and Z-1 is not changed by the addition of KSCN, but that a new species, $Z\text{-}1\cdot K^+$, is formed, which is characterized by complexation of potassium by the ether and/or carbonyl oxygen atoms. The resonance observed for the Z configuration derives from two species Z-1 and $Z\text{-}1\cdot K^+$ which are in rapid equilibrium on the NMR time scale. In contrast to a previous study[5] which appeared in the course of this work, amides 1 and 2 bear complexing ether oxygens at the nitrogen terminus of the amide bond, and this accounts for the fact that 1 and 2 exhibit configurational shifts not previously observed.

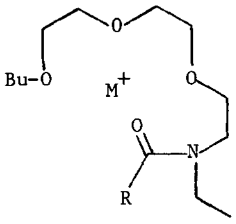
The changes in carbon chemical shifts observed upon addition of KSCN are in accord with this interpretation (Table 1). Thus the resonance assigned to the non-chelating E isomer is essentially unchanged upon addition of KSCN while that for the Z isomer exhibits a significant change since it corresponds to a weighted average of the chemical shifts of two species, Z-1 and $Z\text{-}1\cdot K^+$, whose relative concentrations change upon the addition of salt.

Making the reasonable assumptions of a 1:1 stochiometry for complexation in $Z\text{-}1\cdot K^+$ and negligible complexation by E-1, the equilibrium constant for association K_a is expressed by eq (1) where K is the E/Z ratio in the absence of added metal ion, R is the observed E/Z ratio in the presence of added metal ion, and M and A are the nominal concentrations of metal salt and amide respectively. Application of this equation to experiments in which 0.5 eq and 1.0 eq of salt were added gave values of K_a of 17.0 and 18.1 respectively indicating the validity of this treatment.

$$K_a = \frac{K(K-R)(1+R)}{R[MK(1+R)-A(K-R)]} \qquad (1)$$

Calculated values of the relative amounts of Z-1 and $Z\text{-}1\cdot K^+$ could also be used to obtain the chemical shift at C_α of $Z\text{-}1\cdot K^+$ at both values of added salt. Again the two values were in good agreement. The chelated form $Z\text{-}1\cdot K^+$ exhibits an upfield shift of 0.8 ppm at the C_α carbon of the N-ethyl group as the result of complexation.

In order to probe the role of the polyether side chain attached to the carbonyl carbon we have also examined 2, in which the substituent is a methyl group. Similar trends were observed for this compound.[11] Here the Z-form is slightly favored in the absence of added salt. Addition of KSCN effects a further increase in the mole fraction of the Z-configuration which must result from chelation involving the amide carbonyl and one or more ether oxygens, (e.g. 3).



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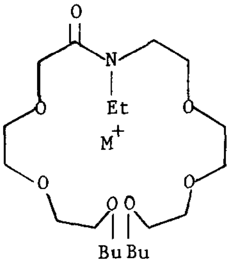

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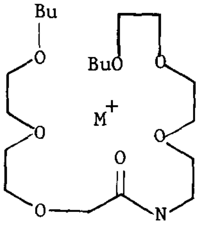

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However, the association constant for 2 is much lower than that for 1, indicating that the polyether side chain at the carbonyl carbon plays a major role. One possibility is that one or more oxygens from both polyether chains and the carbonyl oxygen are simultaneously involved in complexation. A possible structure of this type, 4, could involve the carbonyl and up to five ether oxygens. A second possibility is that the chelation by 1 involves the two polyether chains but not the amide carbonyl carbon. If this is the case, complexation by the two polyether chains must be greatly facilitated by the geometry produced by a trans amide linkage. Structure 5 represents a possible structure of this kind. Some non-planarity at the amide nitrogen could permit coordination by up to five or six ether oxygens in a geometry which resembles that in crown ethers.

While this method based upon the use of configurational ratios does not provide direct information about the detailed structures of complexes, it does provide a simple but powerful method for determining association constants. It is noteworthy that the method provides the equilibrium constant for the "hidden" equilibrium between Z and Z-K^+, although only a single resonance is observed for the two species. Further work employing this method is underway in our laboratory.

Table 1 - Stability Constants and ^{13}C Chemical Shifts of the N-Ethyl Methylene Carbons of the Potassium Complexes of 1 and 2 in Methanol at 35°C.

Compound	KSCN Molar Concentration	R	K_a	δ_E	δ_{Z+MZ}(obs)	δ_{MZ}(calc)[b]
1[a]	0	2.19	-	42.0	43.7	-
	0.138	1.01	17.0	41.9	43.3	42.9
	0.270	0.59	18.1	41.9	43.0	42.8
2[a]	0	0.84	-	41.8	45.5	-
	0.276	0.73	0.59	41.9	45.2	43.0
	6.541	0.59	0.88	41.9	44.9	43.6

[a] The concentrations of 1 and 2 were 0.257 M and 0.276 M, respectively.

[b] The calculated chemical shifts of the complexed form δ_{MZ}(calc) were obtained using the expression $\delta_{Z+MZ}(\text{obs}) = \chi_Z\delta_Z + \chi_{MZ}\delta_{MZ}(\text{calc})$, where δ_Z was the chemical shift in the absence of added metal and the mole fractions χ_Z and χ_{MZ} were obtained using the calculated values of K_a.

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10. In chloroform, where both resonances could be used to measure the isomer ratio, good agreement was obtained indicating that relaxation and NOE effects are essentially the same for both configuraitons and that the ratio of intensities gives a good measure of the isomer ratio.
11. In compound 2 the signal from the Z form lies closer to that of the solvent methanol and some overlap occurs. As a result, the determination of the isomer ratio was less accurate accounting for the poorer agreement in the determination of K_a and δ_{MZ}(calc).

(Received in USA 22 October 1980)