# ALKALI METAL CHELATION BY DIACETAMIDE[1a]

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Abstract: Proton NMR spectroscopy indicates that diacetamide exists as an equilibrium mixture of Z,Z and E,Z diastereomers in methanol solution. Addition of LiI, NaI or KI (configurational titration) shifts the equilibrium because of bidentate complexation (chelation) by the amide carbonyl oxygens.

The interaction of alkali metals with amide or ester carbonyl functions is important in the mode of action of ionophoric cyclic peptide and depsipeptide antibiotics and affects the biological properties of naturally occuring proteins as well.[2] The effect of lithium ion on the dynamic nuclear magnetic resonance behavior of dimethyl formamide was described recently.[3] It was suggested that lithium ion coordination increased the amount of $\pi$-bonding in the amide bond although the free energy of activation for torsion about the C-N partial double bond was essentially unchanged by introduction of lithium ion. Ground state effects can, in any case, provide a more direct way of evaluating the importance of the coordination of alkali metals with the amide functional group. We report here on the effect of polar solvents and alkali metal ions on the configurational equilibrium of diacetamide and suggest that "configurational titration" experiments developed in the study of chelation of alkali metal ions by acetylacetonate[4] can be useful in studying the interaction of alkali metals with imides.

The interchange between imide isomers which differ in configuration at amide partial double bonds can be slowed at low temperatures and the configurational distribution determined using nmr spectroscopy. In nonpolar solvents the imides of n-alkanoic acids exhibit an overwhelming preference for the E,Z configuration.[5] This preference was attributed to a combination of steric factors, which destabilize the E,E form, and coulombic repulsion, which destabilizes the Z,Z configuration since it has the highest calculated dipole moment of the
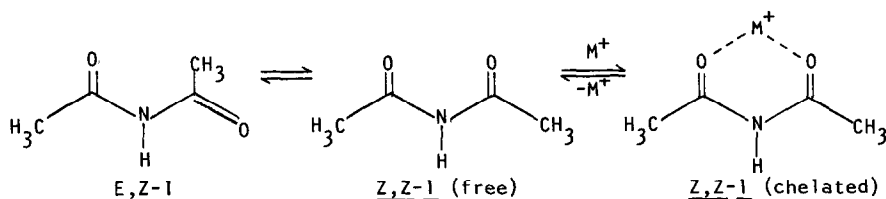


three possible configurational isomers.[5] Since the latter factor can be affected by a change in medium, it was of interest to examine the effect of solvent polarity on the configurational equilibrium. In addition, the configurational equilibrium of the isoelectronic

acetylacetonate anion can be shifted toward the Z,Z form by chelation of alkali metal ions[4] and such effect might be observed for imides as well.

The low temperature (-98°C) spectrum of diacetamide in methanol-$d_4$ features two unequally intense resonances in the acetyl methyl region at $\delta 2.13$ and $\delta 2.42$ in a ratio of 1:2. By contrast in $CH_2Cl_2$, the two singlets observed at $\delta 2.17$ and $\delta 2.46$ are of equal intensity, within experimental error, indicating a preponderance of the E,Z isomer. We interpret the behavior in methanol as indicative of the presence of the E,Z isomer with resonances of $\delta 2.13$ and $\delta 2.42$, and a second isomer whose resonance overlaps the upfield resonance due to the E,Z isomer. We assign the Z,Z configuration to this second isomer, which is present to an extent of about 34%, since the more polar Z,Z isomer should be favored by the charge to the more polar solvent, methanol.[6]

Chelation of an alkali metal ion can effect a further shift to the Z,Z configuration. The possibility of chelation was tested by "configurational titration" of a methanol solution by LiI, NaI and KI.[7] Addition of all three salts effected an increase in the intensity of the resonance at $\delta 2.13$ which is due to the methyl groups in Z,Z-1, as well as one of the methyl groups in E,Z-1. The exchange of metal ions between the free and chelated forms of Z,Z-1 is apparently fast enough that the Z,Z-1 (free) and Z,Z-1 (chelated) do not give rise to separate signals. However, the effect of chelation in changing the equilibrium ratio of the E,Z and Z,Z configurations is clearly evident. The magnitude of the effect is dependent upon the alkali metal cation (Figure 1). Thus the addition of one equivalent of NaI or KI raises the mole fraction of the Z,Z configuration from 0.34 to 0.62 or 0.61 respectively while the addition of LiI causes an increase to only 0.48.

The added potassium iodide could be back-titrated with dibenzo-18-crown-6 indicating that the effect is due to chelation by the free metal ion rather than solely an effect on the ionic strength of the solution. Thus the addition of 0.48 equiv. of KI raises the mole fraction of the Z,Z form to 0.56. If 0.26 moles of crown ether is added, the mole fraction of the Z,Z form drops to 0.49 nearly the same as the ratio obtained if 0.22 equivalents (=0.48-0.26) of KI is added, viz. 0.46.

The relative effectiveness of the alkali metal ions in shifting the configurational distribution of diacetamide is $Na^+ \sim K^+ > Li^+$. A very different order is observed for the tendency toward chelation of alkali metal ions by enolates of acetylacetone,[4a] $\beta$-ketoaldehydes[8a] and $\beta$-ketoesters[8b] viz. $Li^+ > Na^+ > K^+$. We attribute this reversal to the significantly lesser ability of the neutral imides to chelate alkali metal ions as compared with enolate anions. Chelation by enolate or imide requires removal of two methanol molecules from the solvent shell of the alkali metal. Acetylacetonate is such a good ligand for $Li^+$ that removal of two methanol ligands is more than compensated for by the new ionic interactions. However, because the imide is a poorer ligand, removal of solvent methanol becomes more difficult. The removal of ligating methanol molecules from $Na^+$ or $K^+$ is not as difficult since they do not interact with methanol as strongly.[9,10]

Figure 1:  Effect of Added Alkali Metal Ion on the Mole Fraction of Diacetamide in the Z,Z Form



$[M]$ / $[CH_3CONHCOCH_3]$
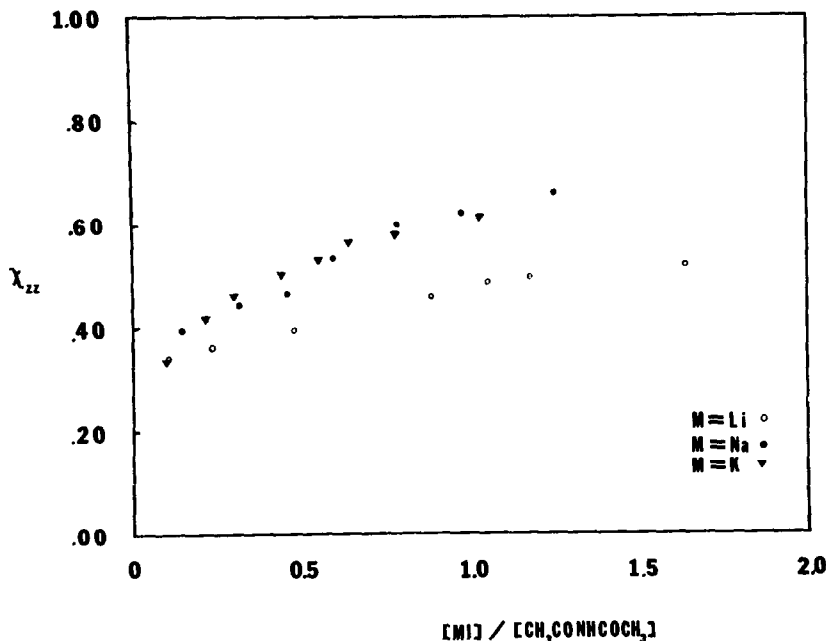
1.  (a)  Stereochemistry in Trivalent Nitrogen Compounds.  34.  Part 33:  M. Raban and E.M. Carlson, Israel J. Chem., 15, 106 (1977).

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6.  (a) The resonances of the Z,Z isomer can be resolved in the cmr spectrum (25 MHz, ca. -90°C, methanol-$d_4$) which features three nearly equally intense carbonyl ($\delta$175.1, 172.1, 171.6) and acetyl methyl ($\delta$26.4, 24.4, 24.1) resonances.

    (b)  We considered the possibility that specific solvation, perhaps involving the hydrogen bonded complex shown, plays a role in stabilizing the Z,Z form, in addition to the general effect of increased dilectric constant.  However, addition of up to two equivalents of

benzoic acid to a methanol solution does not result in a shift in the equilibrium, as might have been expected, were the increased importance of the Z,Z form due to a specific hydrogen bonded complex.  Similarly, addition of up to three equivalents of water failed to affect the configurational ratio.

$$OCH_3$$
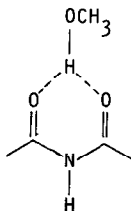
7.  (a)  Evidence for the existence of interactions between imides and alkali metals in the solid state has been adduced from infrared spectra[7b] and x-ray crystallography.[7c]

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9.  (a)  The solubilities[9b] of the three iodides in methanol (in moles/li) can be taken as a reflection of the relative magnitudes of the interactions:  LiI, 23;  NaI, 4.7:  KI, 0.9.

    (b)  W.F. Linke and A. Seidell, "Solubilities," Vol. II, Fourth Edition, American Chemical Society, 1965.

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