Cu^{2+}-promoted Hydrolysis of Cyanomethyl-substituted Tetra-azamacrocycles

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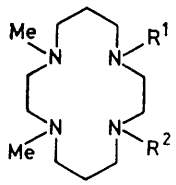
Summary The fast Cu^{2+}-promoted hydrolysis of the two macrocyclic nitriles (**3**) and (**4**) is due to the proximity of the reactants allowing an intramolecular nucleophilic attack of the co-ordinated OH^- on the cyano-group to take place.

THERE are many examples of metal ion-promoted or -catalysed reactions in which esters,[1] amides,[1] or nitriles[2] are hydrolysed. In many cases the mechanism of such reactions is difficult to ascertain except for those of Co^{3+}-complexes, which are kinetically inert and thus allow differentiation between several mechanistic pathways.

During our studies on functionalized tetra-azamacrocycles[3] we prepared compounds (**3**) and (**4**) by cyanomethylation[4] of (**2**) and (**1**), respectively. Our attempts to prepare the Cu^{2+}-complex of (**3**) in water gave a crystalline product, whose i.r. spectrum (ν_{max} 1645 cm^{-1}) and elemental analysis showed that the nitrile had undergone hydrolysis to give the amide (**5**). However, it is possible to prepare the



(**1**); $R^1 = R^2 = H$
(**2**); $R^1 = H$, $R^2 = Me$
(**3**); $R^1 = CH_2CN$, $R^2 = Me$
(**4**); $R^1 = R^2 = CH_2CN$
(**5**); $R^1 = CH_2CONH_2$, $R^2 = Me$
(**6**); $R^1 = CH_2CONH_2$, $R^2 = CH_2CN$

Ni^{2+}, Cu^{2+}, and Zn^{2+} complexes of (**3**) and (**4**) in non-aqueous solvents such as dimethylformamide (DMF). On mixing a DMF solution of one of these metal complexes with 0·1 M NaOH the cyano-group is hydrolysed more or less rapidly depending on the metal ion, the Cu^{2+}-complex being the most reactive. In neutral or slightly acidic solutions the complexes are stable. Hydrolysis of the free ligands (**3**) or (**4**) does not give the pure amides (**5**) or (**6**) but a mixture of other products. This result is similar to the observation of Wainwright,[5] who obtained the tetracarbamoyl derivative of 1,4,8,11-tetra-azacyclotetradecane only when the tetracyano-product was hydrolysed as its Ni^{2+} complex, but not as the free ligand.

The Cu^{2+}-promoted reaction was studied in more detail. The stopped-flow kinetics experiments[6] performed by mixing a neutral solution of the Cu^{2+}-complex of (**3**) with 10^{-3} to 10^{-1} M NaOH could only be interpreted by assuming two consecutive pseudo-first-order steps. The first shows only a small amplitude at 643 nm; its rate depends on $[OH^-]$ and can be inhibited by SCN^-. The rate law is given by equation (1), where $C_{complex}$ is the total concentration of the

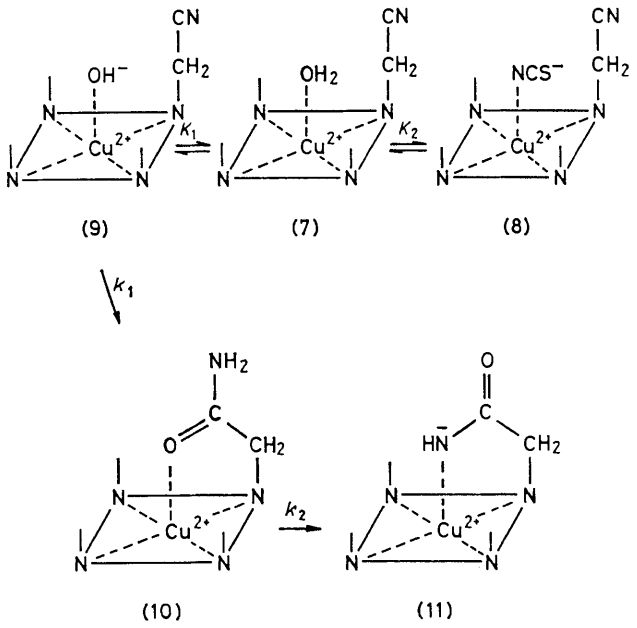
$$v_1 = k_1 \cdot K_2 \cdot C_{complex} \cdot [OH^-]/(K_1K_2 + K_2 \cdot [OH^-] + K_1 \cdot [SCN^-]) \quad (1)$$

Cu^{2+}–nitrile complex, $k_1 = 13{\cdot}0 + 0{\cdot}5\ s^{-1}$, K_1 [$(9{\cdot}7 \pm 0{\cdot}8) \times 10^{-3}$ M] is the dissociation constant of the hydroxo-complex (**9**), and K_2 [$(5{\cdot}4 \pm 0{\cdot}5) \times 10^{-3}$ M] is that of the thiocyanato-complex (**8**). The first step is attributed to the hydrolysis of the nitrile to give (**10**) (see Scheme). The dissociation constant of the thiocyanato-complex (**8**) was also measured separately by the spectrophotometric titration of complex (**7**) with KSCN using an automatic titration unit.[7] The value $K_2 = (3{\cdot}9 \pm 0{\cdot}1) \times 10^{-3}$ M obtained in this way is in satisfactory agreement with that determined from the kinetics.

The second step gives a larger amplitude change and its rate is proportional to $[OH^-]$ and is not inhibited by SCN^- up to 10^{-2} M, equation (2). The rate constant k_2 is 89 ± 2 $dm^3\ mol^{-1}\ s^{-1}$.

$$v_2 = k_2 \cdot [(\mathbf{10})] \cdot [OH^-] \quad (2)$$

This reaction is associated with the rearrangement of the amide group from the O- into the N-co-ordinated form after deprotonation. The same reaction, which has previously been observed in many Cu^{2+}–peptide[8] and Cu^{2+}–amide[9] complexes, can of course be measured separately by starting



SCHEME. Cu^{2+}-promoted hydrolysis of complex (**7**).

with the amide complex (**10**) at low pH and by increasing the pH to values at which deprotonation of the amide takes place. The results of such experiments gave $k_2 = 85 \pm 3$ dm^3 mol^{-1} s^{-1}, in good agreement with the value measured for the complete system, and thus support the assignment of the second step.

Before a detailed mechanism can be postulated it is necessary to recall that tetra-azamacrocycles with tertiary amino-groups form complexes in which the metal ion is pentaco-ordinate;[10] we have assumed that the same geometry is also present in our compounds. In accord with this the absorption spectra of the Cu^{2+}-complexes, with maxima at 643 nm for (**7**), 725 nm for (**8**), 640 nm for (**10**), and 735 nm for (**11**), are all typical for pentaco-ordination with axial interaction, since the stronger the axial ligand the larger is the red-shift in the spectra.[11]

The mechanism for the nitrile hydrolysis and the amide rearrangement is shown in the Scheme. The SCN^- inhibition of the hydrolysis and the pH-profile of k_1 [equation (1)], which has a plateau at pH $>12{\cdot}5$, clearly indicate that the hydroxo-complex (**9**) is the reactive species and that co-ordinated OH^- is the nucleophile. Therefore we conclude that the fast hydrolysis in the Cu^{2+}-complex is mainly due to the favourable proximity of the OH^- and the cyano-group so that an intramolecular nucleophilic attack can take place.

We also have studied the reactivity of the Cu^{2+}-complex of (**4**) with OH^-. The product is the Cu^{2+}-complex of (**6**) in which only one cyano-group has been hydrolysed whereas the other has remained unchanged. The selective hydrolysis can be understood by the same mechanism as shown in the Scheme for the mono-nitrile. Once the first cyano-group has reacted the amide will co-ordinate at the axial position with its deprotonated nitrogen, thus blocking this co-ordination site for OH^- addition and inhibiting the further hydrolysis in a similar way to that of SCN^- in the mono-nitrile system.

The very efficient metal-promoted hydrolysis of the two nitriles is an example of how proximity effects can work even though the strength of the nucleophile is weakened by co-ordination to the metal ion.

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