Reactions of Co-ordinated Ligands. Hydrolysis of Tetramethyl Ethylenediaminetetra-acetate and its Copper(II) Complexes

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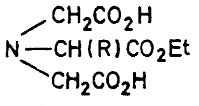
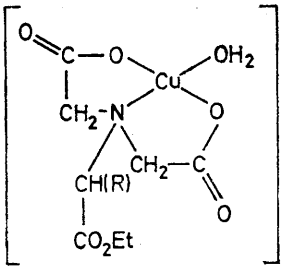
Tetramethyl ethylenediaminetetra-acetate, Me$_4$edta, interacts with copper(II) ions to give the complex [Cu(Me$_4$edta)]$^{2+}$ in which probably two ester groups of the ligand are bonded to the metal ion in conjunction with the two nitrogen donors. Base hydrolysis of two ester groups occurs in the pH range 4·1—5·4 with k_{OH} = 3·23 × 10^5 and 7·02 × 10^4 l mol^{-1} s^{-1} at 25 °C and I = 0·1M. These constants apply to the hydrolysis of [Cu(Me$_4$edta)]$^{2+}$ and [Cu(Me$_3$edta)]$^+$, respectively. Hydrolysis by water also occurs in this pH range. Hydrolysis of the second pair of ester groups takes place in the pH range 7·2—9·0 with k_{OH} = 1·54 × 10^3 and 7·47 × 10 l mol^{-1} s^{-1} at 25 °C. Base hydrolysis of the first ester groups of [Cu(Me$_4$edta)]$^{2+}$ is *ca.* 10^5 times faster than in the free ligand. The observed rate acceleration, and the results of solution i.r. studies, are consistent with a weak interaction between the metal ion and the carbonyl group of the ester. Base hydrolysis involves nucleophilic attack by ' external ' hydroxide rather than attack by a hydroxide ion co-ordinated to Cu^{II}. The preparation of sodium salts of the partial esters Me$_3$edta$^-$, Me$_2$edta^{2-}, and Meedta^{3-} is described.

ANGELICI and his co-workers [1-3] have studied the effect of metal ions on the base-hydrolysis rates of a number of polyfunctional ester ligands. Typical ligands were the derivatives of iminodiacetic acid (I; R = H,[1] Pr^i,[2] or Bu^i [2]). In complexes with copper(II) a vacant co-ordination site, presumably in the equatorial plane, is occupied by a water molecule as in (II). Ionisation of the water molecule to give the hydroxo-complex occurs in the pH range 6—7 and it has been suggested that metal-ion-promoted hydrolysis could involve nucleophilic attack by co-ordinated rather than ' external ' hydroxide ion. We have therefore studied the effect of Cu^{II} ions on the hydrolysis of the tetramethyl ester of ethylenediaminetetra-acetic acid.† On the basis of solution n.m.r. measurements, Rossotti and Sunshine [4] suggested that in [Cu(edta)(OH$_2$)]$^{2-}$ the ligand is quinquedentate with the water molecule equatorial. The potentiometric and polarographic data of Bennett and Schmidt [5] suggests that the pK_a of the water molecule in [Cu(edta)(OH$_2$)]$^{2-}$ is 11·35. Preliminary studies indicated that [Cu(Me$_4$edta)$_4$]$^{2+}$ underwent base hydrolysis in the pH range 4—5·4. This pH is probably much lower than the pK_a of possible aqua-ligands, suggesting that if internal nucleophilic attack by co-ordinated hydroxide ion occurs the reaction is much faster than attack by ' external ' hydroxide ion. For this reason we have studied the kinetics of the reaction in detail.



(I)



(II)

EXPERIMENTAL

The tetramethyl ester of ethylenediaminetetra-acetic acid, Me$_4$edta, was prepared by a modification of a previously reported method.[6] A suspension of H$_4$edta (30 g) in methanol (100 cm^3) was cooled in an ice-bath and thionyl chloride (10 cm^3) added dropwise with stirring. The temperature was maintained below 10 °C during the addition. Continuous stirring of the reaction mixture reduced the reaction time from 20 d [6] to less than 24 h, after which time the initial suspension had completely dissolved. The methanol solution was made basic with sodium hydrogencarbonate solution and the ester extracted into diethyl ether. The ether phase was dried with anhydrous sodium sulphate and the solvent removed by evaporation under reduced pressure. The residual light yellow oil was distilled (b.p. 189—191 °C at 3 mmHg) (Found: C, 48·2; H, 6·85; N, 7·8. Calc. for $C_{14}H_{24}N_2O_8$: C, 48·3; H, 6·9; N, 8·0%). The i.r. spectrum (liquid film) had ν(CO) at 1 740 cm^{-1}. The ^{1}H n.m.r. spectrum (perdeuterioacetone as solvent) displayed signals at δ 3·60 (12 H) and 3·57 (8 H) downfield from SiMe$_4$. These absorptions may be assigned to the OCH$_3$ protons (12) and to the methylene protons adjacent to the ester group (8), respectively. The methylene protons N–CH$_2$–CH$_2$–N gave rise to a singlet at δ 2·83 p.p.m. (4 H).

Kinetics and Measurements.—All kinetic measurements were carried out with a Radiometer TTT2 automatic titrator used as a pH-stat. A high-alkalinity glass electrode, type G202B, was used as indicator electrode and a saturated calomel electrode with a diffusion filter, type K401, as reference. The electrode system was standardised at 25 ± 0·1 °C with 0·05M-potassium hydrogenphthalate (pH 4·008) and 0·01M-$Na_2B_4O_7$·10OH$_2$ (pH 9·185).‡ The general technique employed in the kinetic measurements has been outlined.[7] All kinetic studies were carried out at I = 0·1M (NaClO$_4$) and 25 ± 0·1 °C. Values of the hydroxide-ion

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† H$_4$edta, MeH$_3$edta, Me$_2$H$_2$edta, Me$_3$Hedta, and Me$_4$edta are ethylenediaminetetra-acetic acid and its mono-, di-, tri-, and tetra-methyl esters, respectively.

‡ 1M = 1 mol dm^{-3}.

[1] R. J. Angelici and B. E. Leach, *J. Amer. Chem. Soc.*, 1967, **89**, 4605.

[2] R. J. Angelici and B. E. Leach, *J. Amer. Chem. Soc.*, 1968, **90**, 2499.

[3] B. E. Leach and R. J. Angelici, *J. Amer. Chem. Soc.*, 1968, **90**, 2504.

[4] F. J. C. Rossotti and H. Sunshine, *Chem. Comm.*, 1968, **447**.

[5] M. C. Bennett and N. O. Schmidt, *Trans. Faraday Soc.*, 1955, **51**, 1418.

[6] D. J. Alner, P. A. Claret, and A. G. Osborne, *J. Appl. Chem. Biotechnol.*, 1972, **22**, 1267.

[7] R. W. Hay, L. J. Porter, and P. J. Morris, *Austral. J. Chem.*, 1966, **19**, 1197.

concentration were obtained from the pH using a molar activity coefficient of 0·775 [8] and a value of $pK_w = 14{\cdot}00$ at 25 °C.[9] The solutions used in the kinetic measurements were $2{\cdot}5 \times 10^{-3}$M in both the ligand and the metal ion. Reactions were monitored for 2—3 half-lives in all cases. Rate constants were calculated from data obtained from plots of log $(V_\infty - V_t)$ against time, where V_∞ is the final volume of base consumed and V_t that consumed at time t.

Visible and i.r. spectra were recorded using Perkin-Elmer 402 and 457 spectrophotometers. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R24 spectrometer. Sodium 3-(trimethylsilyl)propanesulphonate, NA(tps), was used as internal reference for D_2O solutions.

Preparation of Partial Esters of H_4edta.—*Sodium trimethyl ethylenediaminetetra-acetate,* Na(Me$_3$edta). Equimolar quantities of Me$_4$edta and copper(II) perchlorate were dissolved in the minimum volume of water. One equivalent of NaOH was added at such a rate as to maintain the pH at *ca.* 5 (pH-stat). The solution was then treated with H_2S and the precipitated copper(II) sulphide removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residual solid twice recrystallised from the minimum volume of methanol to remove any diester and tetraester present. The *product* was dried *in vacuo*. The sodium salt of the trimethyl ester is extremely hygroscopic and for this reason it was difficult to obtain satisfactory analytical data. However, satisfactory C : N ratios were obtained {Found: C : N = 5·60 : 1. $[Na(OH_2)_n][C_{13}H_{21}N_2O_8]$ requires C : N = 5·57 : 1}. The i.r. spectrum of the sodium salt had strong carbonyl absorptions at 1 745 and 1 620 cm^{-1} assignable to ν(CO) of the ester and the carboxylate groups respectively. The ^{1}H n.m.r. spectrum of a solution of the sodium salt in D_2O displayed signals at δ 3·65 (9 H), 3·60 (6 H), and 3·27 p.p.m. (2 H) corresponding to the ester protons, methylene protons adjacent to the ester groups, and methylene protons adjacent to the carboxylate group, respectively. A complex pattern at δ 2·7—2·98 p.p.m. is due to the four methylene protons between the two nitrogen atoms.

Disodium dimethyl ethylenediaminetetra-acetate, Na$_2$(Me$_2$-edta). The diester was prepared as for the triester, except that two equivalents of NaOH were added at pH 6·5. The resulting solution was passed through a column of mixed-bed ion-exchange resin to remove any traces of $[Cu(Me_3edta)]^+$ and $[Cu(Meedta)]^-$. The eluate was treated with H_2S, filtered, and the filtrate evaporated to dryness. The residual solid (very hygroscopic) was purified by recrystallisation from boiling methanol to which a few drops of water had been added. The i.r. spectrum of the *product* (Nujol mull) had ν(CO) at 1 740 (ester) and 1 630 cm^{-1} (carboxylate). The ^{1}H n.m.r. spectrum (D_2O solution) had signals at δ 3·72 (6 H, ester), 3·65 (4 H, CH_2 adjacent to ester), and 3·27 p.p.m. (4 H, CH_2 adjacent to carboxylate). The singlet at δ 2·80 p.p.m. (4 H) is due to the central methylene protons and is consistent with a symmetrical diester structure {Found: C : N = 5·18 : 1. $[Na(OH_2)_n]_2[C_{12}H_{18}N_2O_8]$ requires C : N = 5·14 : 1}.

Trisodium methyl ethylenediaminetetra-acetate, Na$_3$(Meedta). The monomethyl ester was prepared by addition of three equivalents of NaOH solution to the $[Cu(Me_4edta)]^{2+}$ complex at pH 8·0—8·5. The solution was worked-up as previously and the *product* recrystallised from methanol–water. The sodium salt is very hygroscopic. The ^{1}H n.m.r. spectrum (D_2O solution) had δ 3·87 (3 H, ester), 3·77 (2 H, CH_2 adjacent to ester), 3·33 (6 H, CH_2 adjacent to carboxylate), and 2·7—2·98 p.p.m. (N–CH_2–CH_2–N) {Found: C : N = 4·75 : 1. $[Na(OH_2)_n]_3[C_{11}H_{15}N_2O_8]$ requires C : N = 4·71 : 1}.

RESULTS AND DISCUSSION

At a 1 : 1 Cu^{II} to ligand ratio and pH < 6, two mol of base were consumed per mol of complex, corresponding to the hydrolysis of two ester groups. On raising the pH to *ca.* 9, two further equivalents of base were consumed. The final product obtained on base hydrolysis had an identical visible spectrum (over a range of pH) to that of a solution of copper(II) and H_4edta at the same concentration and ionic strength.

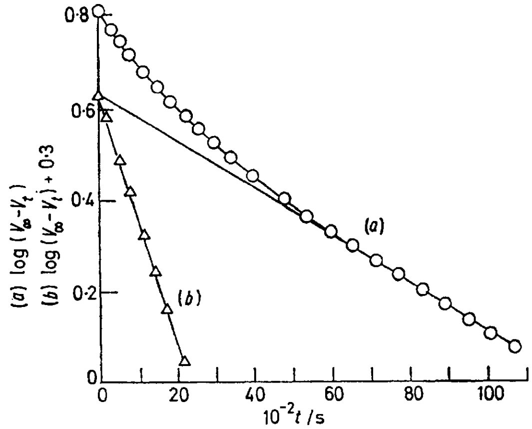

FIGURE 1 Plots of log $(V_\infty - V_t)$ against time for hydrolysis of $[Cu(Me_4edta)]^{2+}$ at pH 5·015 and 25 ± 0·1 °C: (*a*), resolved as outlined in ref. 10; the linear portion of (*a*) refers to the hydrolysis of $[Cu(Me_3edta)]^+$ and (*b*), to that of $[Cu(Me_4edta)]^{2+}$

The hydrolysis kinetics at pH < 6 were monitored under pseudo-first-order conditions using a pH-stat. At constant pH, plots of log $(V_\infty - V_t)$ against time were curved, consistent with two consecutive reactions (1) and (2). It was possible to resolve the curved plots into two

$$[Cu(Me_4edta)]^{2+} \xrightarrow{k_1} [Cu(Me_3edta)]^+ + MeOH + H^+ \quad (1)$$

$$[Cu(Me_3edta)]^+ \xrightarrow{k_2} [Cu(Me_2edta)] + MeOH + H^+ \quad (2)$$

straight lines by techniques described by Frost and Pearson [10] (Figure 1). Values of k_1 and k_2, the observed first-order rate constants at constant pH, were determined at a number of pH values (Table 1). The rate constants obtained at pH 4·10 were independent of the metal concentration when metal to ligand ratios of greater than 1 : 1 were employed. This result indicates that complex formation in the 1 : 1 system is complete at the lowest pH investigated. Plots of k_1 and k_2 against hydroxide-ion concentration were linear with positive

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[8] C. W. Davies, *J. Chem. Soc.*, 1938, 2093.

[9] R. A. Robinson and R. H. Stokes, ' Electrolyte Solutions,' 2nd edn., Butterworths, London, 1965.

[10] A. A. Frost and R. G. Pearson, ' Kinetics and Mechanisms,' 2nd edn., John Wiley, London, 1961.

intercepts (Figure 2), indicating that pH-independent hydrolysis, *i.e.* attack by water, is also occurring. The appropriate rate expressions are (3) and (4), where k_{OH} and k_{OH_2} are second-order rate constants for nucleophilic attack by hydroxide ion and water on the complexes. From the gradients and intercepts of the above plots the following rate constants were obtained: $k_{1(OH)} = 3{\cdot}32 \times 10^5$; $k_{1(OH_2)} = 4{\cdot}50 \times 10^{-6}$; $k_{2(OH)} = 7{\cdot}02 \times 10^4$; and $k_{2(OH_2)} = 5{\cdot}50 \times 10^{-7}$ l mol^{-1} s^{-1}. The second-order rate

$$k_1 = k_{1(OH)}[OH^-] + k_{1(OH_2)}[OH_2] \qquad (3)$$

$$k_2 = k_{2(OH)}[OH^-] + k_{2(OH_2)}[OH_2] \qquad (4)$$

constants for water attack were obtained from the expression $k_{OH_2} = k_{obs.}/55{\cdot}5$. Water attack was *ca.* 10^{11} times slower than attack by hydroxide ion.

TABLE 1

Observed rate constants for the hydrolysis of $[Cu(Me_4edta)]^{2+}$ (k_1) and $[Cu(Me_3edta)]^+$ (k_2) at 25 °C and $I = 0{\cdot}1$M

pH	$10^{10}[OH^-]$/M	10^4k_1/s^{-1}	10^5k_2/s^{-1}
4·100	1·62	3·03 *	4·22 †
4·395	3·20	3·50	5·30
4·705	6·55	4·60	7·63
5·015	13·40	6·78	12·47
5·370	30·20	12·67	23·83

* Average of the rate constants $3{\cdot}02 \times 10^{-4}$, $2{\cdot}98 \times 10^{-4}$, and $3{\cdot}10 \times 10^{-4}$ s^{-1} using metal to ligand ratios of 1 : 1, 2 : 1, and 4 : 1, respectively. † Average of the rate constants $4{\cdot}31 \times 10^{-5}$, $4{\cdot}31 \times 10^{-5}$, and $40{\cdot}3 \times 10^{-5}$ s^{-1} obtained at metal to ligand ratios of 1 : 1, 2 : 1, and 4 : 1, respectively.

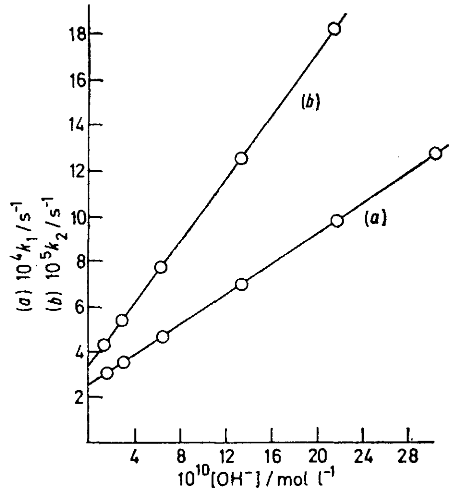
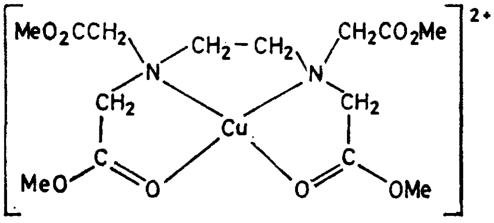


FIGURE 2 Plots of k_1 (*a*) and k_2 (*b*) against hydroxide-ion concentration

A number of metal complexes of the tetraethyl ester of H_4edta have been prepared by Beyer *et al.*[11] On the basis of i.r. and conductivity measurements, quadridentate co-ordination of the ligand was suggested for the complexes $[Cu(Et_4edta)Cl_2]$ and $[Cu(Et_4edta)(OH_2)_2]^{2+}$. The i.r. data suggested the presence of two bonded and two non-bonded ethoxycarbonyl groups. The i.r. spectrum of $[Cu(Me_4edta)]^{2+}$ was studied in aqueous solution. The complex has two carbonyl-stretching frequencies at 1 730 and 1 705 cm^{-1}, consistent with the presence of non-bonded and bonded ester carbonyl groups. On addition of two equivalents of base, no change was observed in the 1 730 cm^{-1} band but the 1 705 cm^{-1} band disappeared and was replaced by a new band at 1 620 cm^{-1} which can be assigned to the bonded carboxylate group.

The kinetic and i.r. evidence thus supports the view that the $[Cu(Me_4edta)]^{2+}$ complex is primarily quadridentate in solution and has the structure (III). The fifth and sixth co-ordination positions may be occupied by water molecules. In view of the dynamic nature of the bonding of Me_4edta to Cu^{II} it is likely that (III) is in equilibrium with small amounts of quinque- and sexidentate complexes in which there is a weak axial interaction between the metal ion and the carbonyl groups which are ' free ' in (III). The rate enhancements noted in Table 3 are consistent with this.



(III)

Base hydrolysis of $[Cu(Me_4edta)]^{2+}$ was some 4·6 times faster than for $[Cu(Me_3edta)]^+$, while water hydrolysis was some 8·2 times faster. Base hydrolysis was some 10^{11} times faster than water hydrolysis for both complexes. Base hydrolysis of the diester complex $[Cu(Me_2edta)]$ can be monitored by pH-stat in the pH range 7·23—9·0. Plots of log ($V_\infty - V_t$) against time again indicated two consecutive first-order reactions at constant pH. The constants k_3 and k_4 corresponding to hydrolysis of the third and fourth ester groups were determined as a function of pH. Values of $k_{3(OH)}$ and $k_{4(OH)}$ were obtained by dividing the observed first-order rate constants by the hydroxide-ion concentration. At $I = 0{\cdot}1$M and 25 °C,

TABLE 2

Rate constants for hydrolysis of $[Cu(Me_2edta)]$ (k_3) and $[Cu(Meedta)]^-$ (k_4) at 25 °C and $I = 0{\cdot}1$M

pH	$10^7[OH^-]$/M	10^4k_3/ s^{-1}	10^5k_4/ s^{-1}	$10^{-3}k_3/[OH^-]$ / l mol^{-1} s^{-1}	$10^{-1}k_4/[OH^-]$ / l mol^{-1} s^{-1}
7·235	2·22	3·38	1·66	1·52	7·47
7·430	3·47	5·21	2·61	1·50	7·52
7·625	5·45	8·48	4·10	1·56	7·53
7·850	9·14	1·44	6·79	1·58	7·43
8·040	14·1	*	1·04	*	7·38
8·480	38·9	*	2·80	*	7·20
8·98	122	*	9·48	*	7·77

$k_{3(OH)} = (1{\cdot}54 \pm 0{\cdot}04) \times 10^3$ l mol^{-1} s^{-1}
$k_{4(OH)} = (7{\cdot}47 \pm 0{\cdot}30) \times 10$ l mol^{-1} s^{-1}

* Hydrolysis of $[Cu(Me_2edta)]$ was too rapid for monitoring by pH-stat at pH < 8·0.

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[11] V. L. Beyer, G. Kuhn, and E. Hoyer, *Z. anorg. Chem.*, 1965, **339**, 8.

$k_{3(\mathrm{OH})} = (1{\cdot}54 \pm 0{\cdot}04) \times 10^3$ and $k_{4(\mathrm{OH})} = (7{\cdot}47 \pm 0{\cdot}30) \times 10$ l mol^{-1} s^{-1} (Table 2). Approximate rate constants were obtained by the pH-stat technique for base hydrolysis of $\mathrm{Me_4edta}$ and its partial esters. Thus for reaction (5) the value of k_{OH} is 2·10 l mol^{-1} s^{-1} at 25 °C and $I = 0{\cdot}1$M.

$$\mathrm{Me_4edta} + \mathrm{OH^-} \xrightarrow{k_{\mathrm{OH}}} \mathrm{Me_3edta} + \mathrm{MeOH} \quad (5)$$

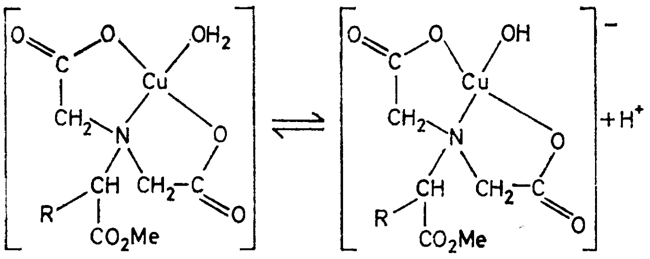
Under these conditions, k_{OH} for the base hydrolysis of methyl glycinate is 1·28 l mol^{-1} s^{-1}.[12] On a statistical basis alone, the $\mathrm{Me_4edta}$ ester would be expected to undergo more rapid hydrolysis.

The complexes $[\mathrm{Cu(Me_4edta)}]^{2+}$ and $[\mathrm{Cu(Me_3edta)}]^+$ underwent base hydrolysis *ca.* 10^5 times faster than the free ligands (Table 3). Such a rate acceleration is consistent with formation of a metal–carbonyl bond as shown in (III). In the present system there was no evidence for an aqua–hydroxo-equilibrium, although such an equilibrium has been noted with terdentate ester ligands such as the iminodiacetic acid in (IV) and its derivatives. p*K* Values for such ionisations are in the range 6—7. Angelici and his co-workers have suggested that such reactions may involve internal nucleophilic attack by the co-ordinated hydroxide ion. If this were the sole reaction path, values of $k_{\mathrm{obs.}}/[\mathrm{OH^-}]$ would be expected to *decrease* with increasing pH since the concentration of the hydroxo-complex would only be a linear function of the hydroxide-ion concentration up to *ca.* 10—15% conversion of the aqua- to the hydroxo-complex. Angelici's results indicate that with (IV; R = $\mathrm{Pr^i}$) values of $k_{\mathrm{obs.}}/[\mathrm{OH^-}]$ are constant in the pH range 7·1—9·0. Since the pK_a of the aqua-ligand is *ca.* 6·1, the results exclude nucleophilic attack by copper-bound hydroxide ion. The present results are consistent with external hydroxide-ion attack on $[\mathrm{Cu(Me_4edta)}]^{2+}$, while the rate accelerations of *ca.* 10^5 suggest direct metal–methoxycarbonyl bonding.

TABLE 3

Second-order rate constants (l mol^{-1} s^{-1}) for base hydrolysis of the esters at 25 ± 0·1 °C and $I = 0{\cdot}1$M

Complex	Ligand	Rate enhancement
$[\mathrm{Cu(Me_4edta)}]^{2+}$ $(3{\cdot}2 \pm 0{\cdot}5) \times 10^5$	$\mathrm{Me_4edta}$ 2·10	$1{\cdot}6 \times 10^5$
$[\mathrm{Cu(Me_3edta)}]^+$ $(7{\cdot}0 \pm 0{\cdot}5) \times 10^4$	$\mathrm{Me_3edta^-}$ 0·86	$8{\cdot}0 \times 10^4$
$[\mathrm{Cu(Me_2edta)}]$ $(1{\cdot}5 \pm 0{\cdot}05) \times 10^3$	$\mathrm{Me_2edta^{2-}}$ 0·35	$4{\cdot}4 \times 10^3$
$[\mathrm{Cu(Meedta)}]^-$ $(7{\cdot}5 \pm 0{\cdot}30) \times 10^1$	$\mathrm{Meedta^{3-}}$ 0·06	$1{\cdot}2 \times 10^3$



(IV) R = H, Pr$^{\mathrm{i}}$, or Bu$^{\mathrm{i}}$

Synthetic Aspects.—The preparation of the mono-, di, and the tri-esters of $\mathrm{H_4edta}$ has not been previously reported. The quite marked differences in the rates of base hydrolysis of the $\mathrm{Cu^{II}}$ ester complexes provides a convenient method for the preparation of these compounds. Thus, for the preparation of $\mathrm{Na(Me_4edta)}$, equimolar quantities of $\mathrm{Me_4edta}$ and $\mathrm{Cu[ClO_4]_2}$ were dissolved in the minimum volume of water. One equivalent of base was added, keeping the pH at *ca.* 5 using a pH-stat. The solution was then treated with $\mathrm{H_2S}$ and the precipitated copper(II) sulphide removed by filtration. Evaporation of the filtrate to dryness gave the sodium salt of trimethyl ethylenediaminetetra-acetate (see Experimental section). The sodium salt is extremely hygroscopic. The i.r. spectrum had bands at 1 745 and 1 620 cm^{-1} which can be assigned to ν(CO) of the ester and the carboxylate group, respectively. The ^{1}H n.m.r. spectrum of a $\mathrm{D_2O}$ solution of the sodium salt has signals at δ 3·65 (9 H), 3·60 (6 H), and 3·27 p.p.m. (2 H) from Na(tps). These signals can be assigned to the methyl protons of the ester, the six protons adjacent to the ester groups, and the two protons adjacent to the carboxylate group. The di- and mono-methyl esters were prepared by similar techniques and showed the expected spectral characteristics.

We thank the S.R.C. for support and for the award of a postdoctoral fellowship (to K. B. N.).

[4/2067 *Received, 7th October,* 1974]

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[12] R. W. Hay and L. J. Porter, *J. Chem. Soc.* (*B*), 1967, 1261.