Alkali-metal Complexes in Aqueous Solution

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1 Introduction

Although sodium and potassium co-ordination compounds have been known for fifty years[1] and ion-pairs have been studied extensively in non-aqueous solution,[2] the aqueous chemistry of these compounds has received little systematic attention. The outstanding characteristic of alkali-metal complexes in aqueous solution is their weakness, but they are important because of the common occurrence of alkali-metal ions at high concentrations, *e.g.* in biological systems, in sea water, in constant ionic media, or when added in a reagent.

Because the complexes are weak, they have often been ignored, and, at high, constant concentrations of alkali metal, consistent results may be obtained from a model that ignores the complex, because the fraction of ligand bound to the alkali metal is constant. In the past, the evidence for such complexes has often been indirect or difficult to interpret, but the accumulation of results and the use of ion-selective electrodes for direct study of the equilibria allow a more confident treatment of the subject.

The term 'complex' as used here does not imply any particular kind of bonding in the associated species, which may be an ion pair, a solvent-separated ion pair, or a co-ordination compound.

A. Abbreviations.—The following abbreviations are used to indicate the least protonated forms of the ligands.

edta; ethylenediamine-*NNN'N'*-tetra-acetic acid;
pdta: propylenediamine-*NNN'N'*-tetra-acetic acid;
cdta: cyclohexenediamine-*NNN'N'*-tetra-acetic acid;
egta: 2,2'-ethylenedioxybis[ethyl-iminodi(acetic acid)];
nta: nitrilotriacetic acid;
ida: iminodiacetic acid;
uda: uramil-*NN*-diacetic acid;
ATP, ADP, AMP: adenosine tri-, di-, and mono-phosphate, respectively.

Protonated and complexed forms are indicated thus:
Hedta, H_2edta, Naedta, *etc.*

2 Inorganic Complexes

Representative values of the stability constants of inorganic complexes are given

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[1] N. V. Sidgwick and S. G. P. Plant, *J. Chem. Soc.*, 1925, 209.

[2] 'Ions and Ion Pairs in Organic Reactions', ed. M. Szwarc, Vol. 1, Wiley, New York and London, 1972.

in Table 1. For sulphate, persulphate, thiosulphate, ferricyanide, and ferrocyanide the stability constants decrease in the order Cs > Rb > K > Na > Li, whereas phosphates show the opposite preference, although the difference between stabilities of potassium, rubidium, and caesium complexes is often small.

Complex formation is favoured by a high charge on the ligand and by the ease with which chelation can occur, *e.g.* cyclic condensed phosphates give stronger complexes than linear condensed phosphates.

Table 1 *Stability constants* (log β) *of inorganic complexes at* 25 °C *and* $\mu = 0$

Ligand	Li	Na	K	Rb	Cs	*Ref.*
Sulphate	0.64	0.70	0.82	—	—	*a*
Persulphate	—	0.58	0.91	1.17	1.42	67
Thiosulphate	—	0.58 ± 0.02	1.00 ± 0.04	—	—	33
Ferrocyanide	1.78	2.08	2.3	2.65	2.85	65[b]
	—	—	2.35 ± 0.2	—	—	32
Ferricyanide	—	—	1.46 ± 0.02	—	—	32
	—	-0.32 ± 0.13	0.30 ± 0.04	0.52 ± 0.03	—	93[c]
Carbonate	—	0.55	—	—	—	*d*
Bicarbonate	—	0.16	—	—	—	*d*
Phosphate	0.72 ± 0.04	0.59 ± 0.04	0.48 ± 0.06	—	—	*e*
Trimetaphosphate	—	0.88	no ev.	—	—	*b, f*
Tetrametaphosphate	—	1.42	1.26	—	—	*b, f*
Triphosphate	2.87 ± 0.06	1.64 ± 0.06	1.37 ± 0.06	—	—	*g*
Tetraphosphate	2.64	1.79	1.71	—	—	*g*

[a] $T = 18$ °C, E. C. Righellato and C. W. Davies, *Trans. Faraday Soc.*, 1930, **26**, 592; [b] $\mu = 0.1$; [c] $\mu = 3$; [d] F. S. Nakayama, *J. Inorg. Nuclear Chem.*, 1971, **33**, 1287; [e] $\mu = 0.2$, R. M. Smith and R. A. Alberty, *J. Phys. Chem.*, 1956, **60**, 180; [f] S. Y. Kalliney, *Diss. Abs.*, 1970, **31B**, 1779; [g] $\mu = 1$, J. I. Watters, S. M. Lambert, and E. D. Loughran, *J. Amer. Chem. Soc.*, 1957, **79**, 3651.

3 Organic Complexes

The stability constants of alkali-metal complexes with organic ligands, almost without exception, decrease as the atomic number of the metal increases. Aliphatic and aromatic carboxylic acids do not generally form complexes with the alkali metals, although stability constants have been reported for lithium and sodium acetates.[3] The acids for which there is strong evidence of complexing are either α-hydroxy-acids or dicarboxylic acids. The evidence for association with α-amino-acids is uncertain, although sodium–leucine and –alanine complexes have been reported.[4] Typical stability constants are given in Table 6.

For α-hydroxy-acids, the strength of the complex depends on the number of carboxylate and α-hydroxy-groups, thus the order of strengths is citrate > tartrate > malate > glycollate > lactate. Pyruvate[4] has been found to be stronger than any of those ligands. A protonated complex has been

[3] D. W. Archer and C. B. Monk, *J. Chem. Soc.*, 1964, 3117.

[4] G. A. Rechnitz and S. B. Zamochnick, *J. Amer. Chem. Soc.*, 1964, **86**, 2953.

reported only for tartrate,[5] but similar complexes would be expected with the other polycarboxylic acids.

Among dicarboxylic acids, malonate,[6–8] succinate,[6] phthalate,[6] and maleate[6,7] complexes have been reported. Chelation is probably a necessary condition for complex formation. The ease of ring formation should be important, and succinate, which gives a conformationally strained seven-membered ring, is weaker than malonate, which gives a six-membered ring. Unfortunately, no results have been reported for oxalate, which would form a five-membered ring. If chelation is necessary, protonated complexes of unsubstituted dicarboxylic acids would not be expected, and none have been reported so far. It is interesting to note that methylenediphosphonate[9] is a considerably better ligand for sodium than malonate and that methanehydroxyphosphonate[10] is better than glycollate.

Whereas the above complexes are weak, aminopolycarboxylates can form quite strong complexes, with stabilities: cdta > pdta > uda > edta > nta > ida. Representative stability constants are summarized in Table 2. The order is broadly as expected, the affinity increasing with the number of acetic acid groups and the charge.

Table 2 *Stability constants* (log β) *of aminopolycarboxylate complexes*

Ligand	μ	T/°C	Li	Na	K	Rb	Cs	*Ref.*
edta	0.1	20	2.79	1.66	—	—	—	*a*
	0	—	—	2.61	—	—	—	13
	[b]	25	2.85	1.79	0.96	0.59	0.15	14
pdta	0.5	25	4.01	2.55 ± 0.05	0.90 ± 0.07	—	—	15
cdta	0.1	25	—	4.40 ± 0.07	1.52 ± 0.02	—	—	120
	0.5	25	6.11 ± 0.1	4.66 ± 0.1	1.83 ± 0.05	—	—	15
nta	0	20	3.28	2.18	—	—	—	*c*
	0.1	20	2.51[d]	1.22[d]	0.6[e]	—	—	*d, e*
uda	0	20	5.40	3.32	—	—	—	*f*
	0.1	20	4.90 ± 0.02	2.72 ± 0.01	1.23 ± 0.03	—	—	70
o-hydroxyphenyl -ida	0.1	20	2.20 ± 0.02	1.0 ± 0.1	—	—	—	12

[a] G. Schwarzenbach and H. Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798; [b] μ variable; [c] G. Schwarzenbach, E. Kampitsch, and R. Steiner, *Helv. Chim. Acta*, 1945, **28**, 828; [d] ref. 11; [e] G. Anderegg, *Helv. Chim. Acta*, 1967, **50**, 2333; [f] G. Schwarzenbach, E. Kampitsch, and R. Steiner, *Helv. Chim. Acta*, 1946, **29**, 364.

Uramil-*NN*-diacetic acid is exceptional: the presence of α-hydroxy- or α-oxo-groups enables quadridentate co-ordination to occur, and the possibility of

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[5] H. S. Dunsmore and D. Midgley, *J. C. S. Dalton*, 1972, 64.

[6] D. W. Archer, D. A. East, and C. B. Monk, *J. Chem. Soc.*, 1965, 720.

[7] J. A. Barclay, M. J. Hickling, and K. White, *Biochem. J.*, 1966, **99**, 11P.

[8] S. L. Dygert, G. Muzii, and H. A. Saroff, *J. Amer. Chem. Soc.*, 1970, **74**, 2016.

[9] R. L. Carroll and R. R. Irani, *Inorg. Chem.*, 1967, **6**, 1994.

[10] H. Wada and Q. Fernando, *Analyt. Chem.*, 1972, **44**, 1640.

resonance hybrids may increase the stability of the complex, although substitution by methyl groups on one or both of the nitrogen atoms in the pyrimidine ring has little effect on the stability.[11] In general, uda forms weaker complexes than edta, *e.g.* with thallium(I) ion and the alkaline-earth ions, and its affinity for the alkali metals is thus anomalous. Substituted iminodiacetate complexes are much weaker than those with uda.[12]

It is most unlikely that all the carboxylate groups in the edta series of ligands participate in co-ordination of alkali-metal ions, since, for example, *trans*-cdta is a stronger ligand than the more flexible edta. From the limited number of results available, it seems that alkyl-substituted edta derivatives form stronger complexes as the degree of substitution increases. Protonated complexes of edta[13,14] and cdta[15] and diprotonated complexes of pdta[16] and cdta[15] have been reported. Polynuclear edta complexes have been proposed.[14]

4 Binding by Macrocyclic Compounds

Many macrocyclic compounds bind alkali-metal ions unusually strongly and with great selectivity. These electrically neutral compounds contain rings of at least twelve members, including four or more oxygen, sulphur, or nitrogen atoms, and adopt conformations such that a central cavity is formed, with the polar heteroatoms directed inwards while the hydrocarbon backbone is directed outwards. The effect of this structure is to make the inside of the molecule hydrophilic and the outside hydrophobic. Mono- bi-, and tri-cyclic structures are known.

Macrocyclic compounds with ion-binding properties occur naturally, *e.g.* the antibiotics valinomycin [(VI) in the Figure], monactin, nonactin, nigericin, and enneatin; many others have been synthesized. The two main classes of synthetic compounds are the 'crown' polyethers prepared by Pedersen[17] and the macrobicyclic diamines ('cryptates') of Lehn, Sauvage, and Dietrich.[18] The Figure shows the structures of some typical macrocyclic ligands and enables the 'crown' nomenclature to be understood: thus (II) is 18-crown-6, having an 18-membered ring containing six oxygen atoms, and (III) is dicyclohexyl-18-crown-6. Reviews have given many structures[19] and syntheses.[20] The chemistry of the macrocyclic polyethers has been reviewed by Pedersen and Frensdorff.[21]

Stability constants for aqueous complexes are given in Table 3. The affinity of a macrocycle for an ion is highly dependent on the size of the cavity and the

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[11] H. Irving and J. J. R. F. da Silva, *J. Chem. Soc.*, 1963, 458.

[12] H. Irving and J. J. R. F. da Silva, *J. Chem. Soc.*, 1963, 3308.

[13] V. Palaty, *Canad. J. Chem.*, 1963, **41**, 18.

[14] J. Botts, A. Chashin, and H. L. Young, *Biochemistry*, 1965, **4**, 1788.

[15] J. D. Carr and D. G. Swartzfager, *Analyt. Chem.*, 1971, **43**, 1520.

[16] J. D. Carr and D. G. Swartzfager, *Analyt. Chem.*, 1971, **43**, 583.

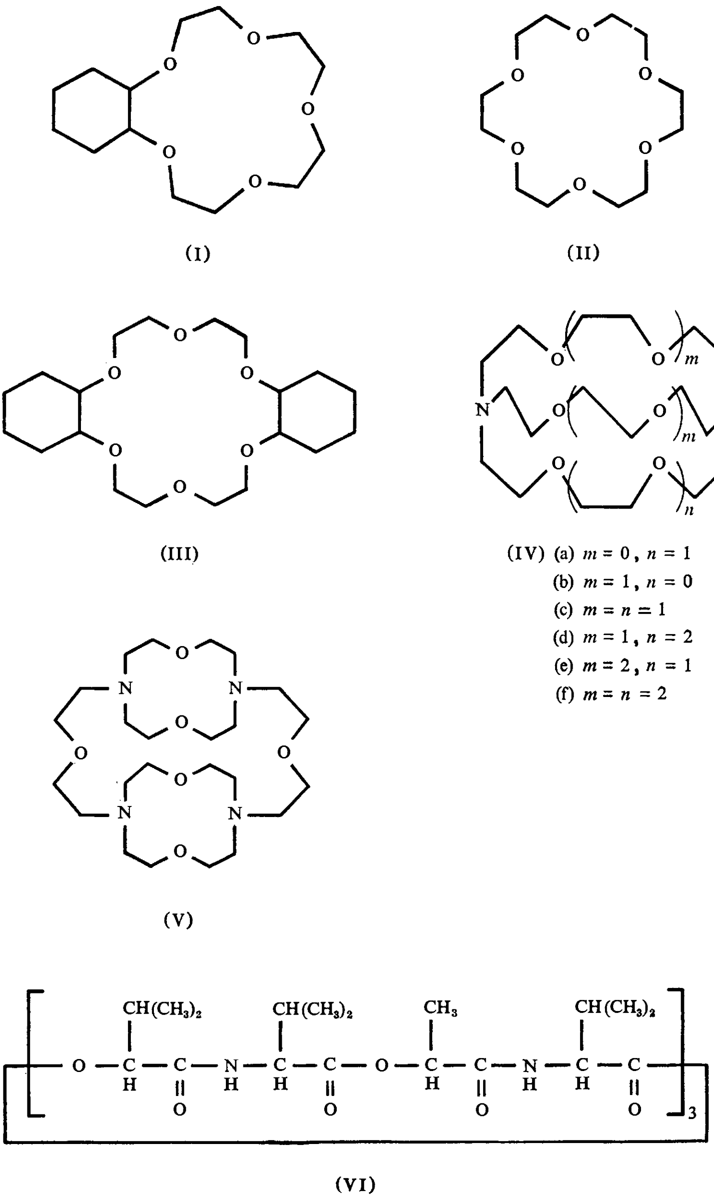
[17] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 2495, 7017.

[18] B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Letters*, 1969, **34**, 2889.

[19] J. J. Christensen, R. O. Hill, and R. M. Izatt, *Science*, 1971, **174**, 459; A. Lévêque and R. Rosset, *Analusis*, 1973, **2**, 218.

[20] C. Kappenstein, *Bull. Soc. chim. France*, 1974, 89.

[21] C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16.



(I)

(II)

(III)

(IV) (a) $m = 0, n = 1$
(b) $m = 1, n = 0$
(c) $m = n = 1$
(d) $m = 1, n = 2$
(e) $m = 2, n = 1$
(f) $m = n = 2$

(V)

$$\left[-\mathrm{O}-\underset{\mathrm{H}}{\overset{\mathrm{CH(CH_3)_2}}{\mathrm{C}}}-\underset{\mathrm{O}}{\overset{}{\underset{\|}{\mathrm{C}}}}-\underset{\mathrm{H}}{\mathrm{N}}-\underset{\mathrm{H}}{\overset{\mathrm{CH(CH_3)_2}}{\mathrm{C}}}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{O}-\underset{\mathrm{H}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\underset{\mathrm{H}}{\mathrm{N}}-\underset{\mathrm{H}}{\overset{\mathrm{CH(CH_3)_2}}{\mathrm{C}}}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\right]_3$$

(VI)

Figure *Macrocyclic ligands:* (I), *cyclohexyl-15-crown-5;* (II), *18-crown-6;* (III), *dicyclohexyl-18-crown-6;* (IV), *diazapolyoxa-macrobicycles* ('cryptates'); (V), *tetra-azahexaoxa-macrotricycle;* (VI), *valinomycin* radius of the ion. Far-i.r. spectra, however, indicate that the forces binding sodium and potassium ions in crown complexes are nearly equal,[22] and that the solvent plays a big role in selectivity. The same order of selectivity is maintained in different solvents, but the selectivity is reduced as the polarity of the solvent decreases. In dry hexadeuteriated acetone nonactin binds sodium, potassium, and caesium ions to approximately the same degree, but in wet hexadeuteriated acetone it develops a selectivity for potassium.[23] The apparent stability constants of 1:1 crown complexes in water[24] depend on the metal but not on the ligand concentration. Although, in methanol, 2:1 complexes were found with potassium and caesium, such side-reactions could not account for the behaviour in water. The nature of the anion (chloride or hydroxide) did not affect the stability constants.

Table 3 *Stability constants* (log β) *for macrocyclic complexes in water at* 25 °C

Ligand	*Cavity diameter* /Å	Li (1.36)^{a}	Na (1.94)	K (2.66)	Rb (2.94)	Cs (3.34)	*Ref.*
cyclohexyl-15-crown-5 (I)	1.7—2.2^{b}	<1.0	<0.3	0.6	—	—	24
18-crown-6 (II)	2.6—3.2^{b}	—	<0.3	2.06	—	0.8	24
cyclohexyl-18-crown-6	2.6—3.2^{b}	<0.7	0.8	1.90	—	0.8	24
dicyclohexyl-18-crown-6 (III)	2.6—3.2^{b}						
isomer A		0.6	1.5—1.85	2.18	—	1.25	24
		—	—	2.02	1.52	0.96	73
isomer B		—	1.2—1.6	1.78	—	0.9	24
		—	—	1.63	0.87	—	73
dicyclohexyl-21-crown-7	3.4—4.3^{b}	—	—	—	—	1.9	24
dicyclohexyl-24-crown-8		—	—	—	—	1.9	24
cryptate 112 (IVa)	1.6^{c}	4.30	2.80	<2.0	<2.0	<2.0	*d, e*
cryptate 221 (IVb)	2.3^{c}	2.50	5.40	3.95	2.55	<2.0	*d, e*
cryptate 222 (IVc)	2.8^{c}	<2.0	3.90	5.40	4.35	<2.0	*d, e*
cryptate 223 (IVd)	3.6^{c}	<2.0	<2.0	2.2	—	2.20	*d, e*
cryptate 332 (IVe)	4.2^{c}	<2.0	<2.0	<2.0	—	<2.0	*d, e*
cryptate 333 (IVf)	4.8^{c}	<2.0	<2.0	<2.0	—	<2.0	*d, e*
tricyclic cryptate (V)		←——— 1.0—1.7 ———→					*d, f*

[a] ionic crystal diameter/Å; [b] cavity diameter estimated from models (C. J. Pedersen, *J. Amer. Chem. Soc.*, 1970, 92, 386); [c] cavity diameter estimated from models (ref. *e*); [d] temperature not given; [e] J. M. Lehn and J. P. Sauvage, *Chem. Comm.*, 1971, 440; [f] J. Cheney, J. M. Lehn, J. P. Sauvage, and M. E. Stubbs, *J.C.S. Chem. Comm.*, 1972, 1100.

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[22] A. T. Tsatsas, R. W. Stearns, and W. M. Risen, *J. Amer. Chem. Soc.*, 1972, **94**, 5247.

[23] J. H. Prestegard and S. I. Chan, *Biochemistry*, 1969, **8**, 3921; *J. Amer. Chem. Soc.*, 1970, **92**, 4440.

[24] H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600.

The solubility of these ligands in water is fairly low, and most studies have been made in methanol or in non-polar solvents. This is especially true of the naturally occurring antibiotics, and results for these compounds in alcohols[25] may be compared with those for synthetic ligands.[19] The ability of the ligands to dissolve large amounts of alkali-metal salts in non-polar solvents is one of their most remarkable properties. Frensdorff[26] and Pedersen[27] have studied distribution equilibria for crown complexes.

A surprisingly large isotope effect in the distribution of ^{22}Na and ^{24}Na between ion-exchange resins and solutions of monactin has been reported.[28] The heavier isotope is concentrated in the monactin complex by about 3.5%.

Magnetic resonance studies[29] of macrocyclic complexes in organic solvents show that the exchange reaction

$$M + L \rightleftarrows ML$$

predominates over the alternatives ($^*M + ML \rightleftarrows {}^*ML + M$ and $L^* + ML \rightleftarrows ML^* + L$). With crown polyethers there is first a fast conformational transition of the ligand, then a slow complexation reaction.[30]

5 Spectroscopic Evidence for Alkali-metal Complexes

It is usually difficult to isolate the spectra of alkali-metal complexes from the background, partly because of the limited extent of complex formation and partly because complex formation may make only a small difference to the spectrum.

A. Ultraviolet Spectroscopy.—Ultraviolet spectroscopy may not reveal complexing that other methods show to occur, *e.g.* potassium ion has no effect on the u.v. spectrum of ferricyanide ion,[31,32] although conductivity, solubility, and potassium selective electrode measurements show that complexes are formed. This discrepancy is explained in terms of the formation of outer-sphere complexes.

Since the complexes are weak, it is difficult to determine their extinction coefficients, since these may differ little from those of the ligands. An extrapolation method has been used to obtain the extinction coefficients, and hence the stability constants, of thiosulphate complexes.[33] Symons [34] has pointed out the dangers of explaining changes in absorbance at a single wavelength by postulating equilibria between species having definite extinction coefficients, with particular reference to sodium iodide solutions.

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[25] W. E. Morf and W. Simon, *Helv. Chim. Acta*, 1971, **54**, 2683.

[26] H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 4684.

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[28] H. S. Räde and K. Wagener, *Radiochim. Acta*, 1972, **18**, 141.

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[31] V. E. Mironov and Yu. I. Rutkovskii, *Zhur. neorg. Khim.*, 1966, **11**, 1792.

[32] W. A. Eaton, P. George, and G. I. H. Hanania, *J. Phys. Chem.*, 1967, **71**, 2016.

[33] F. G. R. Gimblett and C. B. Monk, *Trans. Faraday Soc.*, 1955, **51**, 793.

[34] M. C. R. Symons, *Discuss. Faraday Soc.*, 1957, **24**, 117.

B. Infrared and Raman Spectroscopy.—Infrared spectroscopy has been little used because high concentrations are necessary, and because it is difficult to compensate for the intense absorption of water with sufficient exactness for accurate quantitative information to be obtained. Potassium ferricyanide and ferrocyanide solutions showed no evidence of direct interactions,[35] although other methods show that complexes exist. It may be inferred that outer-sphere complexes are formed, but u.v. spectroscopy indicates an interaction for ferrocyanide but not ferricyanide, so conclusions about the nature of a complex from the absence of a change in spectrum must be drawn with caution. There is clear evidence for the formation of a potassium–monactin complex in methanol.[36]

Raman spectroscopy has not given direct evidence of ion-pairing in sodium sulphate, but a complex has been detected from the change in absorption of the spectrum of HSO_4^- ion.[37] Splitting in the spectra of alkali-metal sulphates at high concentrations[38] was attributed to ion-pairing, and occurs at 2, 4, and 5 mol l^{-1} for the lithium, sodium, and potassium salts, respectively, indicating the opposite order of strength to that found by other methods (Table 1). The stability constant of the sodium–ATP complex was calculated by an empirical method from the pH dependence of the Raman spectra of ATP solutions containing calcium or magnesium ions with and without sodium present.[39]

C. Nuclear Magnetic Resonance.—The need for relatively high concentrations of reactants (*ca.* 0.1 mol l^{-1}) restricts the scope of n.m.r. studies. Alkali-metal complexes are too labile for the spectrum characteristic of the complex to appear, and nuclei in the free and associated species give an average spectrum, from the shape and chemical shift of which much useful information can often be derived.

^{1}H *N.m.r.* The chemical shifts and spin–spin coupling constants of the methylene and methine protons of alkali-metal malates dissolved in D_2O show that all the salts form complexes, whereas the tetramethylammonium salt does not.[40]

The position of the break in the step curve obtained when the chemical shifts of ethylenic and methylenic protons in edta complexes were plotted against pH indicated the relative strengths of the complexes.[41] Lithium formed a sufficiently strong complex for a stability constant to be calculated.

Sudmeier and Senzel[42] have shown that the rotational conformation of the pdta tetra-anion is sensitive to co-ordination of both ends of the ligand, and they have calculated stability constants for potassium and rubidium complexes.

^{31}P *N.m.r.* Crutchfield and Irani[43] have studied the ^{31}P n.m.r. spectra of tetra-

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[35] N. Tanaka, Y. Kobayashi, and M. Kamada, *Bull. Chem. Soc. Japan*, 1966, **39**, 2187.

[36] L. A. R. Pioda, H. A. Wachter, R. E. Dohner, and W. Simon, *Helv. Chim. Acta*, 1967, **50**, 1373.

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[39] M. E. Heyde and L. Rimai, *Biochemistry*, 1971, **10**, 1121.

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[42] J. L. Sudmeier and A. J. Senzel, *Analyt. Chem.*, 1968, **40**, 1693.

[43] M. M. Crutchfield and R. R. Irani, *J. Amer. Chem. Soc.*, 1965, **87**, 2815.

methylammonium polyphosphate solutions in the presence of varying concentrations of lithium ion. In tripolyphosphate the central phosphorus atom differed from the two outer ones, but a plot of the chemical shifts against the $[Li^+]/[P_3O_{10}^{5-}]$ ratio showed breaks at 1:1 for both atoms. The phosphorus atoms in pyrophosphate were equivalent, and no break was observed in the plot, although the lithium ions still lowered the field in their vicinity. There was little effect on the chemical shift of trimetaphosphate and tetrametaphosphate.

In lithium isohypophosphate complexes[44] both P^{III} and P^{V} nuclei responded in the same manner, indicating that the ligand was bidentate. The magnitude of the chemical shift was about two-thirds that observed with lithium pyrophosphate solutions.

^{23}Na *and* ^{39}K *N.m.r.* Wertz and Jardetzky[45] have measured the amplitude and linewidth of the ^{23}Na nuclear spin resonance absorption of inorganic sodium salts in water. Two classes of salts were found; (i) those with constant linewidth and linearly increasing amplitude up to saturation, *e.g.* chloride, fluoride, sulphate and ferricyanide; (ii) those whose linewidth increases with concentration and whose amplitude either levels off or goes through a maximum, usually at concentrations > 6 mol l^{-1}. Notable in this second group were phosphate and pyrophosphate, which had maxima at 1—2 mol l^{-1}. Organic salts showed similar divisions:[46] formate, acetate, and benzoate gave no increase in line width, but α-hydroxy- and α-oxo-acids had pronounced effects. Rechnitz and Zamochnick[4] found a linear correlation between the stability constants of sodium complexes with organic ligands and the linewidths reported by Jardetzky and Wertz.

Eisenstadt and Friedman's[47] measurements of the relaxation rate of ^{23}Na in a number of salts gave evidence of association which sometimes conflicted with the results of Jardetzky and Wertz; thus, pyruvate gave no stronger interaction than perchlorate, and sulphate showed ion-pairing. Measurements by other means support Jardetzky and Wertz in the former case and Eisenstadt and Friedman in the latter.

James and Noggle[48] have studied the relaxation time of the ^{23}Na nucleus as a function of pH and metal and ligand concentration in solutions of edta, *N'*-(2-hydroxyethyl)ethylenediamine-*NNN'*-triacetic acid, nta, and histidine. The interaction was weak with histidine but marked with other ligands, enabling stability constants to be calculated. A series of phosphate compounds was similarly investigated.[49] ^{23}Na n.m.r. has been used in biological studies to indicate binding of sodium by soluble RNA[50] and in tissues such as brain,[51] liver,[52] and muscle.[52,53]

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[44] R. L. Carroll and R. E. Mesmer, *Inorg. Chem.*, 1967, **6**, 1137.

[45] J. E. Wertz and O. Jardetzky, *J. Chem. Phys.*, 1956, **25**, 357.

[46] O. Jardetzky and J. E. Wertz, *Arch. Biochem. Biophys.*, 1956, **65**, 569; *J. Amer. Chem. Soc.*, 1960, **82**, 318.

[47] M. Eisenstadt and H. L. Friedman, *J. Chem. Phys.*, 1967, **46**, 2182.

[48] T. L. James and J. H. Noggle, *J. Amer. Chem. Soc.*, 1969, **91**, 3424.

[49] T. L. James and J. H. Noggle, *Analyt. Biochem.*, 1972, **49**, 208.

[50] T. L. James and J. H. Noggle, *Proc. Nat. Acad. Sci. U.S.A.*, 1969, **62**, 644.

[51] F. W. Cope, *J. Gen. Physiol.*, 1967, **50**, 1353.

[52] D. Martinez, A. A. Silvidi, and R. M. Stokes, *Biophys. J.*, 1969, **9**, 1256.

[53] F. W. Cope, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **54**, 225.

Extension of the technique to other cations is governed by their relative sensitivity, in the order $^{7}Li \sim {}^{23}Na > {}^{87}Rb \sim {}^{133}Cs \gg {}^{39}K$. Evidence of potassium complexes has been found using a ^{39}K spin-echo technique.[54]

D. Polarimetry.—Alkali-metal-ion-specific effects have been noted in the polarimetry of tartrates in various conditions,[55] but without having been quantified. Carr and Swartzfager[15,16] have used polarimetry to study alkali-metal pdta and *trans*-cdta complexes. The molar rotations of the complexed species were obtained iteratively, except for the relatively strong sodium and lithium complexes. The values of the stability constants, β, were high compared with others in the literature, which may be due to the use of values of the fourth dissociation constants, K_4, of the ligands that had been determined simultaneously with β. The substitution of an independently obtained K_4 in Carr and Swartzfager's equations gave smaller values for β. The difference between the polarimetrically obtained stability constants and literature values was smaller for pdta, where the acid dissociation constants also agreed more closely. Evidence was presented for the existence of protonated species, but the apparent distribution was so strange that it must be treated with reserve, *e.g.* $Kpdta^{3-}$ and KH_2pdta^- complexes were found, but not $KHpdta^{2-}$. A particular complex will be difficult to detect it it is not a major component of an equilibrium mixture and its molar rotation does not differ much from that of another species. So far there has been no report of optical activity caused by the formation of a complex between an alkali metal and an optically inactive ligand.

6 Electrochemical Evidence for Alkali-metal Complexes

A. Potentiometry.—The use of glass electrodes that are responsive to alkali-metal ions is well established, and calibration procedures for complexing studies have been described.[56] The method has been used for all the alkali metals,[24,57] but commonly only for sodium and potassium. Because of the sensitivity of these electrodes to hydrogen ions, measurements can usually only be made in neutral or alkaline solutions. Liquid ion-exchange electrodes of the neutral carrier type are less affected by pH and have been used to study potassium–ATP complexes.[58] Sodium amalgam electrodes have been used to study sulphate and carbonate equilibria,[59] but they are far less convenient than selective ion electrodes.

B. Conductivity.—Conductivity measurements are best suited to dilute solutions

[54] F. W. Cope and R. Damadian, *Nature*, 1970, **228**, 76.

[55] H. T. S. Britton and P. Jackson, *J. Chem. Soc.*, 1934, 998; M. T. Beck, B. Csiszár, and P. Szarvas, *Nature*, 1960, **188**, 846; L. I. Katzin and E. Gulyas, *J. Phys. Chem.*, 1960, **64**, 1739; V. Frei, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2450.

[56] G. A. Rechnitz and J. Brauner, *Talanta*, 1964, **11**, 617; H. S. Dunsmore and D. Midgley, *J. Chem. Soc.*, 1971, 3238; G. L. Gardner and G. H. Nancollas, *Analyt. Chem.*, 1969, **41**, 202.

[57] G. A. Rechnitz and S. B. Zamochnick, *Talanta*, 1964, **11**, 1061.

[58] M. S. Mohan and G. A. Rechnitz, *J. Amer. Chem. Soc.*, 1970, **92**, 5839.

[59] R. F. Platford and T. Dafoe, *J. Marine Res.*, 1965, **23**, 63; J. N. Butler and R. Huston, *J. Phys. Chem.*, 1970, **74**, 2976.

of a single electrolyte in which only one complex is formed, and their application is therefore rather limited. Stability constants have been determined for sulphate,[60] ferrocyanide,[61] ferricyanide,[62] and various condensed phosphate[63] complexes. In all these cases the complex is charged, and no independent value of its equivalent conductivity is known. A value may be assigned by analogy or be determined simultaneously with the stability constant.[64]

C. Electromigration.—Shvedov and Nichugovsky[65] have calculated stability constants for alkali-metal ferrocyanides relative to potassium ferrocyanide from the amount of cation transferred from one compartment of the electromigration cell to the other. The constants are not of high accuracy.

D. Polarography.—Alkali-metal ions give well-defined polarographic waves in a supporting electrolyte of tetramethylammonium hydroxide or halide. Complexes with cdta, edta, and uda have been reported[66] for lithium and sodium ions, but strong complexing can shift the half-wave potential of lithium beyond the decomposition potential of the medium, thus limiting the quantitative application of the technique.

7 Thermodynamics

The standard free energy, enthalpy, and entropy changes of complex formation can be calculated from the stability constant, β, by means of equations (1)—(3). The enthalpy change may also be measured directly by calorimetry. Values for a number of complexes are given in Table 4.

$$\Delta G^\circ = -RT\ln\beta \tag{1}$$

$$\mathrm{d}\ln\beta/\mathrm{d}t = \Delta H^\circ/RT^2 \tag{2}$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ\ . \tag{3}$$

In principle, the calorimetric determination of ΔH° is to be preferred, but very precise measurements of pH are necessary if protonic equilibria occur simultaneously with the complexing of the alkali metal. Good agreement has been reported for ΔH° values for potassium persulphate from osmometry[67] and ion-selective-electrode[68] measurements at two temperatures. The same authors' results for potassium ferricyanide and ferrocyanide[68] are, however, five times larger than those of Eaton *et al.*,[32] who also used an ion-selective electrode, but at five temperatures, and who obtained very similar results calorimetrically.

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[60] I. L. Jenkins and C. B. Monk, *J. Amer. Chem. Soc.*, 1950, **72**, 2695.
[61] J. C. James, *Trans. Faraday Soc.*, 1949, **45**, 855.
[62] J. C. James and C. B. Monk, *Trans. Faraday Soc.*, 1950, **46**, 1041.
[63] C. W. Davies and C. B. Monk, *J. Chem. Soc.*, 1949, 413; C. B. Monk, *ibid.*, p. 423; G. Kura and S. Ohashi, *J. Inorg. Nuclear Chem.*, 1972, **34**, 3899.
[64] C. W. Davies, 'Ion Association', Butterworths, London, 1962.
[65] V. P. Shvedov and G. F. Nichugovskii, *Radiokhimiya*, 1966, **8**, 66.
[66] A. Bobrovsky and Yu. Zarembsky, *Zhur. analit. Khim.*, 1972, **27**, 1472.
[67] R. W. Chlebek and M. W. Lister, *Canad. J. Chem.*, 1971, **49**, 2943.
[68] R. W. Chlebek and M. W. Lister, *Canad. J. Chem.*, 1966, **44**, 437.

Table 4 *Standard enthalpy and entropy of complex formation at 25 °C*

Ligand	*Method*[a]	*$\Delta H°$/kcal deg^{-1} mol^{-1}*					*$\Delta S°$/cal deg^{-1} mol^{-1}*					*Ref.*
		Li	Na	K	Rb	Cs	Li	Na	K	Rb	Cs	
sulphate	C	0[b]	0.49	1.01	—	—	—	1.3	0.0	—	—	*c*
persulphate	2T	—	4.3	1.6	1.3	−1.0	—	17.0	9.6	9.8	3.2	67
carbonate	11T	—	4.46	—	—	—	—	12.5	—	—	—	*d*
ferrocyanide	C, 5T	—	—	0.8	—	—	—	—	13	—	—	32
ferricyanide	C, 5T	—	—	0.5	—	—	—	—	8	—	—	32
pyrophosphate	C	1.0	1.4	1.7	—	—	20.4	15.2	15.5	—	—	*e*
edta	C	0.1	−1.4	—	—	—	13	3	—	—	—	72[f]
uda	4T	−7.0	−8.7	−11.8	—	—	-1 ± 5	−18	−35	—	—	70[g]
cryptate 221 (IVb)	C	—	−3.2	—	—	—	—	14	—	—	—	*h*
cryptate 222 (IVc)	C?	—	−5.8	−11.1	−10.5	—	—	—	—	—	—	74
dicyclohexyl-18-crown-6:												
isomer A	C	—	~0	−3.9	−3.3	−2.4	—	—	−3.8	−4.2	−3.7	73
isomer B	C	—	~0	−5.1	4.0	—	—	—	−9.6	−9.3	—	73

[a] C = calorimetry, *n*T = measurement of β at *n* temperatures; [b] ref. 69; [c] R. M. Izatt, D. Eatough, J. J. Christensen, and C. H. Bartholomew, *J. Chem. Soc. (A)*, 1969, 45; [d] ref. (*d*) of Table 1; [e] V. P. Vasil'ev and S. A. Aleksandrova, *Zhur. neorg. Khim.*, 1973, **18**, 2055; [f] in 10% Me_4NOH; [g] in 0.1 mol l^{-1} Me_4NNO_3 at 20 °C; [h] ref. (*e*) of Table 3.

Because the enthalpy changes are so small, it may be difficult on the basis of calorimetric evidence alone to decide whether a complex is not formed at all or if $\Delta H \approx 0$, *e.g.* lithium sulphate.[69]

For most of the ligands in Table 4, for which more than one metal ion has been studied, the order for both ΔH° and ΔS° is, algebraically, Li > Na > K > Rb > Cs. This is the order of the degree of hydration of the ions and the inverse order of their crystallographic radii, suggesting that the dominant affects are the endothermic removal of water from the hydration sheath with an accompanying gain in entropy, both of which are more pronounced for the more strongly hydrated ions. The stronger ligands have an overall exothermic heat of reaction, but no more favourable entropy terms.

Results for uda[70] show enthalpy changes that are more exothermic than those for alkaline-earth and rare-earth complexes of ida and edta.[71] Even transition-metal-ion complexes are rarely so exothermically formed. In contrast, the entropy changes are unfavourable, the expected gain on release of water molecules from the hydration sheaths on chelation being apparently counterbalanced by some large loss of configurational entropy, or else the complexes are of the outer-sphere kind. If uda, which is relatively rigid, suffers a large loss of configurational entropy on forming a complex, the flexible edta ion would be expected to show a more pronounced effect, but this is not the case.[72]

Since the interactions between a crown ligand and the metal ions small enough to fit into the cavity produced by the optimum conformation are equal,[22] the difference between the ions arises from the energy required for removal of the hydration sheath before entry into the complex, the smaller more strongly solvated ions giving a more endothermic heat change. This has been observed for both crown[73] and cryptate[74] ligands with a selectivity for potassium over sodium. Similarly, the loss of configurational entropy of the ligand should be approximately the same, but desolvation gives a larger entropy increase for the smaller ions. When the ion is too large to fit the optimum cavity, the interaction between metal and ligand will be weaker, giving less exothermic enthalpy changes and more favourable entropy changes.[73] If the solvation sheath is not completely removed, the changes may be further complicated.

Although there are clear trends in the thermodynamic results, it is desirable that many more data are collected, especially for the weakest complexes, before much confidence can be placed in the absolute values of these quantities.

8 Kinetics

There is a serious lack of direct kinetic measurements on reactions involving alkali-metal complexes in aqueous solution. The generally low stability constants

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[69] J. M. Austin and A. D. Mair, *J. Phys. Chem.*, 1962, **66**, 519.

[70] H. Irving and J. J. R. F. da Silva, *J. Chem. Soc.*, 1963, 448.

[71] G. H. Nancollas, 'Interactions in Electrolyte Solutions', Elsevier, Amsterdam, 1966.

[72] R. G. Charles, *J. Amer. Chem. Soc.*, 1954, **76**, 5854.

[73] R. M. Izatt, D. P. Nelson, J. H. Rytting, B. L. Haymore, and J. J. Christensen, *J. Amer. Chem. Soc.*, 1971, **93**, 1619.

[74] J. P. Sauvage, Thesis, Strasbourg, 1972, (mentioned in ref. 20).

and the consequent high concentration needed to study them lead to formation rates in the micro- to nano-second range. Winkler[75] has given a useful account of the problems involved.

Ultrasonic absorption has been used to study alkali-metal complexes of uda, nta, edta, and egta.[76] The rates of formation vary relatively little ($1—2 \times 10^8$ $\mathrm{l\,mol^{-1}\,s^{-1}}$), but the rates of dissociation show a strong dependence on the metal ($0.1—3\ \mathrm{s^{-1}}$).

The rates of both formation and dissociation increase with the crystal radius of the ions, *i.e.* in the opposite sense to the increase in the stability constants. In contrast to the behaviour of transition-metal complexes, the complex formation does not consist in a simple substitution of a water molecule in the inner hydration sheath but involves a chelation mechanism in which several solvent molecules are successively replaced, all with comparable rates.

The dissociation rate constants for complexes of the macrocyclic diamine 222 (IVc) in D_2O were found to be *ca.* 40 $\mathrm{s^{-1}}$ by means of ^{1}H n.m.r. measurements.[77]

Indirect or secondary effects of alkali-metal complexes on kinetics have been noted. Activated complexes, *e.g.* $[\mathrm{MnO_4{-}K{-}MnO_4}]^{2-}$, have been postulated to explain the dependence of the rate of isotopic exchange between manganate and permanganate ions on the alkali-metal cation present.[78] The rate of the reaction

$$2\mathrm{K_4Fe(CN)_6} + \mathrm{K_2S_2O_8} \rightarrow 2\mathrm{K_3Fe(CN)_6} + 2\mathrm{K_2SO_4}$$

depends on the concentration of potassium ions present[79] rather than on the ionic strength, as predicted by the Brønsted theory. Chlebek and Lister[68] measured the stability constants of the ion-pairs formed between potassium and each anion and tried to fit the kinetic data to the following reaction schemes; (*a*) $[\mathrm{Fe(CN)_6}]^{4-} + \mathrm{S_2O_8}^{2-}$; (*b*) $[\mathrm{KFe(CN)_6}]^{3-} + \mathrm{S_2O_8}^{2-}$; (*c*) $[\mathrm{Fe(CN)_6}]^{4-} + \mathrm{KS_2O_8}^{-}$; (*d*) $[\mathrm{KFe(CN)_6}]^{3-} + \mathrm{KS_2O_8}^{-}$. Only scheme (*d*) fitted all the data. Further work[80] supported this mechanism for the reaction in the presence of the other alkali-metal cations. Apart from the effect of the different degrees of association with the several metal ions, the rate constant itself was found to be specific to the cation, increasing in the order of the atomic number. Extrapolation of the rate data to zero alkali metal concentration suggested that the rate of reaction of the uncomplexed anions [scheme (*a*)] was very slow.

The ligand-exchange reaction

$$\mathrm{Caedta}^{2-} + {}^*\mathrm{edta}^{4-} \rightleftarrows \mathrm{Ca({}^*edta)}^{2-} + \mathrm{edta}^{4-}$$

is retarded by the presence of sodium ion.[81] The decrease in rate is not caused solely by the reduction in free edta^{4-} concentration, but is also affected by a direct

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[75] R. Winkler, *Structure and Bonding*, 1972, **10**, 1.

[76] M. Eigen and G. Maass, *Z. phys. Chem. (Frankfurt)*, 1966, **49**, 163; H. Diebler, M. Eigen, G. Ilgenfritz, G. Maass, and R. Winkler, *Pure Appl. Chem.*, 1969, **20**, 93.

[77] J. M. Lehn, J. P. Sauvage, and B. Dietrich. *J. Amer. Chem. Soc.*, 1970, **92**, 2916.

[78] J. C. Sheppard and A. C. Wahl, *J. Amer. Chem. Soc.*, 1957, **79**, 1020.

[79] J. Holluta and W. Herman, *Z. phys. Chem.*, 1933, **A166**, 453.

[80] R. W. Chlebek and M. W. Lister, *Canad. J. Chem.*, 1967, **45**, 2411.

[81] R. J. Kula and G. H. Reed, *Analyt. Chem.*, 1966, **38**, 697.

exchange between calcium and sodium complexes. The rate constant for this reaction (34 l mol^{-1} s^{-1}) is smaller than that for exchange with free edta^{4-} (120 l mol^{-1} s^{-1}), but larger than that for exchange between the calcium complex and the monoprotonated ligand (5 l mol^{-1} s^{-1}). Identical effects have been reported for the exchange between edta and a lead–pdta complex.[82]

9 Miscellaneous Methods

Davies[64] has shown how stoicheiometric activity coefficients may be interpreted in terms of ion association, with examples of sodium salts. Osmotic coefficients have been similarly treated.[83] The association of sulphates has been measured through the depression of the freezing points of eutectic mixtures, *e.g.* water–potassium perchlorate, produced by addition of the sulphate salts.[84]

Ion exchange has given qualitative information[85,86] and solvent extraction has been useful for studying macrocyclic complexes.[21,26] Permeability and conductivity measurements on biological and synthetic membranes have been applied to macrocyclic complexes.[87–90]

10 The Study of Alkali-metal Complexes by Means of Competitive Reactions

The commonest method of investigating alkali-metal complexes has been through the change in pH as the metal is added to a solution of a ligand with a suitable acidic function. With weak complexes, the method is very sensitive to errors in the acid or base concentrations, the pH, and the dissociation constants of the ligand which should be determined in the absence of the metal but using the same apparatus and materials.

Sodium tetrametaphosphate complexing was studied from the effect of sodium ions on the copper–tetrametaphosphate equilibrium, measured using a copper-amalgam electrode.[91] Similar studies have not been made with the modern ion-selective electrodes available for several metals.

An indirect polarographic study of lithium and sodium cdta complexing used thallium(I) ion as a tracer.[92]

Alkali-metal compounds are usually too soluble for solubility measurements to be easily interpreted, but ferricyanide complexing was inferred from the effect of alkali metals on the solubility of luteo-hexacyanoferrate(III).[31,93]

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[82] J. D. Carr, K. Torrance, C. J. Cruz and C. N. Reilley, *Analyt. Chem.*, 1967, **39**, 1358.

[83] W. L. Masterton and L. H. Berka, *J. Phys. Chem.*, 1966, **70**, 1924.

[84] J. Kenttämaa, *Suomen Kem.*, 1959, **B32**, 55; C. Sinistri, P. Franzosini, and G. Ajroldi, *Ricerca Sci.*, 1960, **30**, 1584.

[85] W. Buser, *Helv. Chim. Acta*, 1951, **34**, 1635.

[86] F. Nelson, *J. Amer. Chem. Soc.*, 1955, **77**, 813.

[87] J. M. Diamond and E. M. Wright, *Ann. Rev. Physiol.*, 1969, **31**, 581.

[88] D. C. Tosteson, *Fed. Proc.*, 1968, **27**, 1269.

[89] D. C. Tosteson, T. E. Andreoli, M. Tieffenberg, and P. Cook, *J. Gen. Physiol.*, 1968, **51**, 373s.

[90] S. G. A. McLaughlin, G. Szabo, G. Eisenman, and S. Ciani, *Biophys. Soc. Abs.* 14th Annual Meeting, 1970, p. 96a.

[91] R. J. Gross and J. W. Gryder. *J. Amer. Chem. Soc.*, 1955, **77**, 3695.

[92] R. Sundaresan, S. C. Saraiya, and A. K. Sundaram, *Current Sci.*, 1967, **36**, 255.

[93] Yu. I. Rutkovskii and V. E. Mironov, *Zhur. neorg. Khim.*, 1967, **12**, 3287.

From the effects of lithium and sodium ions on the rate of ligand substitution between zinc(II)–4-(2-pyridylazo)resorcinol and egta, the stability constants of their egta complexes were calculated.[94]

11 Chemical Interference by Alkali-metal Complexing

When alkali metals can compete for ligands, allowance must be made for them, especially when they are present at high concentrations, *e.g.* in the determination of stability constants by spectrophotometry,[95] pH,[6] and solubility measurements,[6] in calculating the pH dependence of the potential of the ferricyanide–ferrocyanide couple,[96] and in the electrode kinetics of the reduction of iodate ion on mercury.[97] Interference in the kinetics of hydrolysis,[44] ligand substitution,[82,94] and ligand exchange[81] has been found.

The error produced in the dissociation constant of a weak acid by neglecting the complexing of alkali metals has been discussed by Dunsmore and Midgley[5] for the case of an acid in a constant ionic medium, where concentrations as high as 3 mol l^{-1} are often used. The apparent, K', and true, K, dissociation constants are related by equation (4), where β is the stability constant of the alkali-metal

$$K' = K(1 + \beta[\mathrm{M}]) \tag{4}$$

complex and [M] the concentration of free alkali metal. Since the total alkali-metal concentration is usually much greater than the total acid concentration, [M] is virtually constant, and K' will appear to be a 'good' constant, *i.e.* its standard deviation will not be significantly larger than that which would be expected from normal experimental error. Comparison of the dissociation constant with that of an acid that does not form complexes may be misleading. If the constant K' is used in the calculation of the stability constant of the acid with a second metal, little error will entail, since K' itself compensates for the effect of the alkali metal.

12 Sea Water and Brines

The composition of sea water is basic to the chemical aspects of oceanography. The concentration of salts is so high that some form of ion association must be expected, and Garrels and Thompson[98] have proposed a model based on the formation of ion-pairs between sulphate, bicarbonate, and carbonate ions and the principal cations.

Although sodium and potassium are present predominantly (99%) as the free ions, the complexing of alkali metals has a considerable effect on the distribution of anions. Sodium forms much weaker complexes than calcium or magnesium, but its high concentration ensures that significant proportions of the anions are present as sodium complexes (sulphate 21%, bicarbonate 8%, carbonate 17%).

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[94] M. Tanaka, S. Funahashi, and K. Shirai, *Inorg. Chem.*, 1968, **7**, 573.
[95] M. Walser, *J. Phys. Chem.*, 1961, **65**, 159.
[96] J. D. Winefordner and G. A. Davison, *Analyt. Chim. Acta*, 1963, **28**, 480.
[97] P. Delahay and A. Aramata, *J. Phys. Chem.*, 1962, **66**, 1194.
[98] R. M. Garrels and M. E. Thompson, *Amer. J. Sci.*, 1962, **260**, 57.

Experimental studies of association in sulphate and carbonate systems[99] have been carried out, and measurement of the free sodium[100] in sea water showed that it agreed with that predicted by the model. All the preceding work was performed at 25 °C and 1 atmosphere pressure, which are conditions that are unrepresentative of conditions in deep water. Kester and Pytkowicz[101] showed that sodium sulphate has a stability constant $\beta = 3.42$ at 2.4 °C, compared with 2.00 at 25 °C, and that β varies with pressure at 1.5 °C according to equation (5),

$$\ln \beta = 1.26 - 0.70 \times 10^{-3} P \tag{5}$$

where P is the pressure in atmospheres. Similar but unquantified trends have been observed in the association of sodium carbonate.[102] It will be noted that the lower temperatures and greater pressures found in deep water have opposite effects on the association constant.

The influence of ion-pairing on the pH[103] and buffer capacity[104] of sea water has been discussed and the ion-association model has been applied to calculations on calcium carbonate precipitation,[105] barite saturation,[106] and to a derivation of the history of sea-water from the solution equilibria of clay minerals.[107] An alternative model[108] uses the hypothesis of specific ionic interaction,[109] which does not assume the formation of recognizable complex species. While this approach can calculate the osmotic coefficient of sea water more simply, its application is limited for the present by the availability of the appropriate interaction coefficients. Whichever model is used, the associative interactions in sea water must be allowed for in calculations of solubility and exchange processes, and at present the Garrels–Thompson model is more versatile and conceptually simpler.

13 Alkali-metal Complexes in Biology

Biological interest in the alkali metals is concentrated on sodium and potassium, whose roles in biochemistry have been reviewed by Williams[110] and Hughes.[111] The concentration of potassium inside cells is much higher than it is outside, whereas the internal sodium level is generally much lower. To maintain an activity

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[99] R. M. Pytkowicz and D. R. Kester, *Amer. J. Sci.*, 1969, **267**, 217; R. M. Garrels, M. E. Thompson, and R. Siever, *ibid.*, 1961, **259**, 24.

[100] D. R. Kester and R. M. Pytkowicz, *Limn. Oceanog.*, 1969, **14**, 686.

[101] D. R. Kester and R. M. Pytkowicz, *Geochim. Cosmochim. Acta*, 1970, **34**, 1039.

[102] A. Distèche and S. Distèche, *J. Electrochem. Soc.*, 1967, **114**, 330.

[103] P. J. Wangersky, *Limn. Oceanog.*, 1972, **17**, 1.

[104] M. Whitfield, *Limn. Oceanog.*, 1974, **19**, 235.

[105] W. S. Broeker and T. Takahashi, *J. Geophys. Res.*, 1966, **71**, 1575.

[106] J. S. Hanor, *Geochim. Cosmochim. Acta*, 1969, **33**, 894.

[107] J. R. Kramer, *Geochim. Cosmochim. Acta*, 1965, **29**, 921.

[108] M. Whitfield, *Marine Chem.*, 1973, **1**, 251; *J. Marine Biol. Assoc. U.K.*, 1973, **53**, 685; *Limn. Oceanog.*, 1974, **19**, 235.

[109] E. A. Guggenheim and J. C. Turgeon, *Trans. Faraday Soc.*, 1955, **51**, 747.

[110] R. J. P. Williams, *Quart. Rev.*, 1970, **24**, 331.

[111] M. N. Hughes, 'The Inorganic Chemistry of Biological Processes', Wiley–Interscience, London and New York, 1972, p. 256.

gradient requires energy and a selective 'pump' which discriminates between the two cations.[87,112]

The importance of macrocyclic complexes in transport across membranes has been demonstrated, although it is probable that the presence of complexes in the membrane rather than in its aqueous surroundings is the critical feature, since the distribution of these hydrophobic species would favour the former. Tosteson[88] has demonstrated that the ionic permeability and selectivity for potassium over sodium of both artificial and natural membranes is increased by macrocyclic compounds, but that naturally occurring antibiotics are more effective than synthetic cyclic polyethers. The influence of the ring size of the antibiotic on cation transport in red blood cells has been discussed.[84] An extensive theoretical treatment of ion-binding and transport in membranes has been given by Eisenman *et al.*[113]

The importance of oxidative phosphorylation as a source of energy for biochemical reactions has led to the study of complex formation between alkali-metal ions and ATP and other phosphates (Table 5). The binding of alkali-metal ions was studied in relation to the effect of edta and pyrophosphate on the ATPase activity of myosin.[14] Graven *et al.*[114] have demonstrated the influence of antibiotics on oxidative phosphorylation and found that the presence of alkali-metal ions is essential for ATP hydrolysis. Jardetzky and Wertz have studied sodium complexing with many common metabolites.[46] The stability constants of complexes with some biologically important ligands are summarized in Table 6.

Table 5 *Stability constants* (log β) *of alkali-metal ions with phosphate compounds at* 25 °C

Ligand	μ	Li	Na	K	Rb	Cs	*Ref.*
ATP	[a]	1.7	1.0	0.9	0.9_5	0.9	14
	0.2	1.53 ± 0.03	1.04 ± 0.03	0.93 ± 0.03	—	—	*b*
	0	—	2.36 ± 0.04	2.35 ± 0.04	—	—	58
ADP	0.2	1.15 ± 0.02	0.73 ± 0.04	0.65 ± 0.05	—	—	*b*
AMP	0.2	0.61 ± 0.04	0.34 ± 0.04	0.26 ± 0.06	—	—	*b*
Pyrophosphate	[a]	3.04	2.20	2.32	2.28	2.18	14
	0	3.1 ± 0.2	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	—	*c*

[a] μ variable; [b] ref. (*e*) of Table 1; [c] J. A. Wolhoff and J. T. G. Overbeck, *Rec. Trav. chim.*, 1959, **78**, 759.

An alternative view of cell chemistry, summarized by Cope,[115] is that the cell can be regarded as 'an organized non-liquid phase', in which the water is highly

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[112] W. Schoner, *Angew. Chem. Internat. Edn.*, 1971, **10**, 882.

[113] G. Eisenman, G. Szabo, S. Ciani, S. McLaughlin, and S. Krasne, *Progr. Surface Membrane Sci.*, 1973, **6**, 139.

[114] S. N. Craven, H. A. Lardy, D. Johnson, and A. Rutter, *Biochemistry*, 1966, **5**, 1729.

[115] F. W. Cope, 'Water Structure at the Water–Polymer Interface', ed. H. H. G. Jellinek, Plenum, New York, 1972, p. 14.

Table 6 *Stability constants* (log β) *of alkali-metal-ion complexes with metabolites*

Ligand	μ	Li	Na	K	*Ref.*
acetate	0	0.26	−0.18	—	3
glycollate	0	−0.11	—	—	*a*
lactate	0	−0.20	—	—	*b*
	[c]	—	1.1 ± 0.1	—	4
pyruvate	[c]	—	2.7 ± 0.1	—	4
malonate	0	—	0.83	—	8
succinate	0	—	0.3	—	6
malate	0.28	0.45 ± 0.04	0.32 ± 0.06	0.23 ± 0.05	40
	0.17	0.38 ± 0.02	0.28 ± 0.02	0.18 ± 0.03	57
tartrate	0.2	—	0.28	0.0	5
citrate	0.17	0.83 ± 0.01	0.70 ± 0.01	0.59 ± 0.01	57
D-glyceric acid 2-phosphate	0.1	—	—	1.18	*d*
phospho-enolpyruvate	0.1	—	—	1.08	*d*

[a] P. B. Davies and C. B. Monk, *Trans. Faraday Soc.*, 1954, **50**, 128; [b] P. B. Davies and C. B. Monk, *Trans. Faraday Soc.*, 1954, **50**, 132; [c] 'Tris' buffer; [d] F. Wold and C. E. Ballou, *J. Biol. Chem.*, 1957, **227**, 301.

structured and the alkali-metal cations are bound by macromolecules. In this model, energy is not necessary to maintain the difference in ion concentration across the membrane. Studies of intracellular complexing by means of ^{23}Na n.m.r. and cation-sensitive microelectrodes have indicated substantial degrees of association (30—70%) in brain,[51] kidney,[51] liver,[52] muscle,[53,116] and other tissues. ^{39}K n.m.r. studies also suggest that potassium in cells is complexed.[54,116] Damadian[117] has shown that potassium is bound by protein in cell-free extracts. Lewis and Saroff[118] have measured binding constants for sodium and potassium ions on muscle protein.

14 Analytical Applications of Alkali-metal Complexes

The complexes are generally too weak to have much direct application to analysis, but 'Thoron', *o*-(2-hydroxy-3,6-disulpho-1-naphthylazo)benzenearsonic acid, forms a stable orange complex with lithium in alkaline solution,[119] permitting the spectrophotometric determination of lithium in the range 1—10 μg ml^{-1}. The colour is more intense in aqueous acetone, extending the range to 0.1 μg ml^{-1}. A fifty-fold excess of sodium is tolerable.

Carr and Swartzfager[120] have developed a method for the complexometric titration of sodium in the presence of the heavier alkali metals. The sample, after adjustment to pH 12.6 with piperidine or caesium hydroxide, is titrated with cdta

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[116] G. N. Ling and F. W. Cope, *Science*, 1969, **163**, 1335.

[117] R. Damadian, *Science*, 1969, **165**, 79.

[118] M. S. Lewis and H. A. Saroff, *J. Amer. Chem. Soc.*, 1957, **79**, 2112; H. A. Saroff, *Arch. Biochem. Biophys.*, 1957, **71**, 194.

[119] P. F. Thomason, *Analyt. Chem.*, 1956, **28**, 1527.

[120] J. D. Carr and D. G. Swartzfager, *Analyt. Chem.*, 1970, **42**, 1238.

solution.The end-point is detected by means of a sodium-sensitive glass electrode. The method is accurate to within 2 per cent for sodium-ion concentrations as low as 10^{-3} mol l^{-1}.

Bobrowski and Zarebski[121] have used cdta to separate the a.c. polarograms of potassium and sodium. In 0.02 mol l^{-1}-cdta, the separation of the half-wave potentials is increased from 25 to 80 mV, giving clearly separated peaks, the amplitudes of which were found to be proportional to the concentrations of the ions.

Buser[85] has separated lithium, sodium, and potassium on a cation-exchanger in the tetramethylammonium or dimethylammonium form by eluting with uda solution. Nelson[86] showed that by adding edta to the solution, lithium, sodium, and caesium could be separated on an anion-exchange resin.

Several reagents for the selective precipitation of alkali metals are available.[122] Sodium is most commonly precipitated with uranyl nitrate to give a compound $NaM(UO_2)_3(OAc)_9,6H_2O$, where M represents zinc, magnesium, or nickel(II), but α-methoxyphenylacetic acid has also been used. Potassium, rubidium, and caesium are precipitated by hexanitritocobalt(III) ion, hexanitrodiphenylamine (dipicrylamine), and 6-chloro-5-nitrotoluene-3-sulphonic acid. The commonest reagent for these ions is tetraphenylborate, which has been used in gravimetric, voltammetric, and potentiometric determinations. Caesium can be determined in the presence of potassium by means of cyanotriphenylborate.[123]

Macrocyclic compounds have been used to make ion-selective electrodes of the neutral carrier type.[124] Although cyclic polyethers have been used, the high selectivity of valinomycin for potassium has made this compound the basis of a number of commercially produced electrodes. A neutral carrier electrode for sodium has been developed[125] which has the advantage over glass electrodes of not being affected by proteins in media such as blood serum.

Macrocyclic compounds have obvious potential for solvent extraction, as masking agents, and even as titrants, but applications[126] have been limited, presumably by cost and availability.

[121] A. Bobrowski and J. Zarebski, *Chem. analit.*, 1970, **15**, 457.

[122] S. Kallman, 'Treatise on Analytical Chemistry', Part II, Vol. 1, ed. I. M. Kolthoff and P. J. Elving, Interscience, New York and London, 1961, p. 301; D. D. Perrin, 'Organic Complexing Reagents', Wiley–Interscience, New York and London, 1964, p. 171.

[123] A. Bauman, *Talanta*, 1968, **15**, 185.

[124] 'Ion-selective Electrodes', ed. R. A. Durst, National Bureau of Standards Special Publication 314, U.S. Dept. of Commerce, Washington, D.C., 1969.

[125] D. Ammann, E. Pretsch, and W. Simon, *Analyt. Letters*, 1974, **7** (1), 23.

[126] J. W. Mitchell, *A.C.S. Abstracts of Papers*, 167th A.C.S. National Meeting, Los Angeles, 1974, Analyt. Chem. No. 173.