CCLXXIV.—*Studies in Complex Salts. Part IV. The Effect of Alkyl Substitution on the Tendency of the Aminoacetate Ion to Co-ordinate with Copper.*

By Harry Lister Riley and Victor Gallafent.

In view of the results obtained in Part III of this series (J., 1930, 1642), it was deemed advisable to extend the investigation of the polar effects of alkyl substitution to another series of compounds. It is highly probable that the effects already recorded are due, not to any inherent property of the alkyl groups concerned, but to an imposed effect due to the presence of two free negative poles in the malonate ion. The enhanced activity of the methylene group in this ion, which is a manifestation of an abnormal electron grouping, is due to the proximity of the two carboxyl groups. A study of the effect of alkyl substitution on the dissociation of copper aminoacetate, therefore, offered a means of determining how far the above effects are imposed upon, or inherent in, the alkyl groups studied. For the methylene group in the aminoacetate ion does not possess the enhanced activity of that in the malonate ion, being attached to only one carboxyl group.

The aminoacetate ion is known to co-ordinate with copper, in the sense that it forms a very feebly dissociated salt. Several alkyl-substituted aminoacetic acids which form soluble copper salts have been reported, indicating that the dissociation constants of the copper salts could be measured by the method already described in Part III (*loc. cit.*). Abderhalden and Schnitzler (*Z. physiol. Chem.*, 1927, **163**, 94) have already made a study of the electrical conductivities of aqueous solutions of the copper salts of several amino-acids. Their results are, however, rather unsatisfactory from the present standpoint, in view of the fact that only specific conductivities and few experimental details are given. The temperature at which the measurements were made is not recorded.

Experimental.

The procedure is very similar to that described in Part III. Glycine (" A.R." quality), alanine, and *dl*-valine (Kahlbaum's pure) were purchased. According to Clark and Fittig (*Annalen*, 1866, **139**, 204), valine forms a copper salt difficultly soluble in hot water, but Barbieri (*J. pr. Chem.*, 1883, **27**, 355) states that it is a blue crystalline compound soluble in water. Since Kahlbaum's acid gave a readily soluble copper salt, its purity was tested by analysis (Found: C, 51·17; H, 9·33. Calc. for $C_5H_{11}O_2N$: C, 51·24; H, 9·40%); its hydrochloride melted at 188° (Slimmer, *Ber.*, 1902,

35, 401, gives m. p. 189°). There can therefore be little doubt that the above statement of Clark and Fittig is erroneous.

Dimethylaminoacetic acid was prepared by the method of Zelinsky and Stadnikoff (*Ber.*, 1906, **39**, 1726) by converting acetone into the aminonitrile by the action of ammonium chloride and potassium cyanide in a pressure bottle at 60°. The aminonitrile was hydrolysed by fuming hydrochloric acid, and the amino-acid was obtained from the resulting hydrochloride by boiling it with silver oxide, decomposing the separated silver salt with hydrogen sulphide, and evaporating the solution. The acid was purified by crystallising it three times from water.

Diethylaminoacetic acid was prepared in a similar manner by Rosenmund's method (*Ber.*, 1909, **42**, 4473). This acid crystallises with one molecule of water and was therefore air-dried on a porous plate before use. The above anhydrous acids were dried for several days in a vacuum over calcium chloride, before use.

It was not found possible to carry out experiments with any other simple α-amino-acids, owing to the sparingly soluble nature of their copper salts. When 0·01*M*-copper sulphate solution was added to an excess of solutions of the sodium salts of the following acids, immediate dense precipitates resulted : leucine, tyrosine, ethylaminoacetic (Heintz, *Annalen*, 1879, **198**, 65), monopropylaminoacetic (prepared by the method of Lipp, *ibid.*, 1882, **211**, 359), and α-aminophenylacetic.

Solutions of the sodium salts of the acids studied were prepared by adding an exactly equivalent quantity of pure, carbonate-free, standard caustic soda solution to the required quantity of the acid. This procedure was necessary owing to the impossibility of isolating pure sodium salts in the manner previously described. All measurements of potential were made at room temperature, and the concentrations employed were the same as with the malonates (the monobasic aminoacetates were, of course, of twice the molarity in order to be comparable with the dibasic malonate solutions). By the introduction of a third half-element, it was possible to carry out two simultaneous titrations, the results of which were, in every experiment, in excellent agreement. Each set of readings was also checked several times by repeating the titrations, freshly prepared solutions being used. The results obtained with the sodium salt of glycine are shown in Table I.

The same assumptions are made in calculating the constants of instability, *viz.*, (1) that [Cu$^{\cdot\cdot}$] may be obtained from the expression $E = 0{\cdot}029 \log 0{\cdot}00629/C$, where E is the potential of the concentration cell; (2) that by reason of the relatively minute concentration of the free copper ions in equilibrium with the aminoacetate ions, the

TABLE I.

Sodium aminoacetate.

Conc. of Na salt, m.-mols./l.	*P.D.*, millivolts.	$[Cu^{\cdot\cdot}]\times10^{16}$.	$[X']^3\times10^4$.	$K_1\times10^{15}$.	$K_2\times10^{17}$.	$K_3\times10^{19}$.
6·0	3	5·0 $\times10^{13}$				
11·8	24	0·94 $\times10^{13}$				
17·4	54	0·086$\times10^{13}$				
23·0	273	24,000		2·2		
28·6	303	2,200		1·7		
34·0	316	800	0·00064	1·6	0·051	
39·2	321	540	0·00779	2·0	0·42	
44·4	332	220	0·0299	1·3	0·67	0·0084
54·6	344	86	0·149	1·0	1·3	0·39
64·2	352	46	0·400	0·89	1·8	1·6
82·8	366	15	1·47	0·58	2·2	5·1
100·0	375	7·4	3·43	0·47	2·5	9·6
116·2	382	4·2	6·39	0·39	2·7	14
145·4	392	1·9	15·4	0·30	2·9	24
171·4	399	1·1	28·3	0·25	3·1	33
200·0	401	0·94	49·1	0·30	4·6	61

concentration of the undissociated complex will be equal to that of the total copper present, *i.e.*, 0·01*M*; (3) that the concentration of the free aminoacetate ions will, to a first approximation, be equal to the total molarity of the aminoacetate added to the half-element, less that which is removed in the formation of the complex. Now this last assumption is not strictly accurate, owing to the incomplete dissociation of the sodium aminoacetate, so it can be anticipated that the mass-action " constant " calculated on this assumption will gradually increase owing to the error introduced becoming greater as the concentration of the aminoacetate increases. It will be noticed, however, that the value of

$$K_1 = \frac{[Cu^{\cdot\cdot}][NH_2\cdot CH_2\cdot COO']^2}{[(NH_2\cdot CH_2\cdot COO)_2Cu]} \quad \text{(Table I)}$$

shows a progressive decrease as the concentration of the aminoacetate increases. The possibility that other complex ions were formed was therefore considered. Under K_2 are shown the constants calculated on the assumption that the complex ion

$$[Cu(NH_2\cdot CH_2\cdot COO)_3]'$$

is formed, and under K_3 the values for the ion $[Cu(NH_2\cdot CH_2\cdot COO)_4]''$. The recorded values afford strong evidence that the triaminoacetatocupriate anion is the one formed when excess of aminoacetate ions is added to a solution containing copper ions. Support was obtained for this view by experiments on the solubility of copper aminoacetate. This salt is considerably more soluble in a solution of sodium aminoacetate than in water. In fact, it was possible to evaporate a solution containing sufficient of the sodium salt to prevent the separation of the normal copper salt, to a thick syrup

without any crystallisation occurring. This proves that a complex salt is formed, but gives no evidence as to its constitution.

The results obtained by using other amino-acetates are shown in Table II.

TABLE II.

Conc. of Na salt, m.-mols./l.	*P.D.*, millivolts.	$[Cu^{\cdot\cdot}] \times 10^{16}$.	$[X']^3 \times 10^4$.	$K \times 10^{17}$.
		Sodium methylaminoacetate.		
6·0	5	$4{\cdot}2 \times 10^{13}$		
11·8	11	$2{\cdot}6 \times 10^{13}$		
17·4	3	$5{\cdot}0 \times 10^{13}$		
23·0	205	5,400,000		
28·6	237	420,000		
34·0	254	110,000	0·000640	7·0
39·2	269	33,000	0·00779	26
44·4	286	8,600	0·0299	26
54·6	313	1,000	0·149	15
64·2	326	360	0·400	14
82·8	345	80	1·47	12
100·0	354	39	3·43	13
116·2	362	21	6·39	13
145·4	373	8·6	15·4	13
171·4	379	5·4	28·3	15
200·0	386	3·1	49·1	15
		Sodium dimethylaminoacetate.		
6·0	4	$4{\cdot}6 \times 10^{13}$		
11·8	21	$1{\cdot}2 \times 10^{13}$		
17·4	57	$0{\cdot}068 \times 10^{13}$		
23·0	277	18,000		
28·6	288	7,400		
34·0	325	390	0·000640	0·025
39·2	331	240	0·00779	0·19
44·4	340	120	0·0229	0·35
54·6	348	63	0·149	0·94
64·2	358	28	0·400	1·1
82·8	366	15	1·47	2·2
100·0	371	10	3·43	3·5
116·2	379	5·4	6·39	3·4
145·4	386	3·1	15·4	4·7
171·4	389	2·4	28·3	6·9
200·0	396	1·4	49·1	6·8
		Sodium diethylaminoacetate.		
6·0	2	$5{\cdot}4 \times 10^{13}$		
11·8	17	$1{\cdot}6 \times 10^{13}$		
17·4	80	$0{\cdot}011 \times 10^{13}$		
23·0	211	3,300,000		
28·6	267	39,000		
34·0	287	8,000	0·000640	0·51
39·2	301	2,600	0·00779	2·0
44·4	312	1,100	0·0229	3·3
54·6	330	260	0·149	3·9
64·2	343	94	0·400	3·7
82·8	360	24	1·47	3·6
100·0	369	12	3·43	4·2
116·2	375	7·4	6·39	4·7
145·4	385	3·3	15·4	5·1
171·4	391	2·1	28·3	5·8
200·0	395	1·5	49·1	7·4

TABLE II (*contd.*).

Conc. of Na salt, m.-mols./l.	*P.D.*, millivolts.	$[Cu^{\cdot\cdot}] \times 10^{16}$.	$[X']^3 \times 10^4$.	$K \times 10^{17}$.
		Sodium isopropylaminoacetate.		
6·0	13	2·2 $\times 10^{13}$		
11·8	33	0·46 $\times 10^{13}$		
17·4	71	0·022 $\times 10^{13}$		
23·0	286	8,600		
28·6	322	**500**		
34·0	334	190	0·000640	0·012
39·2	343	94	0·00779	**0·073**
44·4	348	63	0·0229	0·19
54·6	358	28	0·149	0·42
64·2	360	24	0·400	**0·97**
82·8	369	12	1·47	1·7
100·0	371	10	3·43	3·5
116·2	382	4·2	6·39	2·7
145·4	394	1·6	15·4	2·5
171·4	398	1·2	28·3	3·4
200·0	405	0·68	49·1	3·3

For comparison, a titration was also carried out with sodium oxalate. Owing to the sparing solubility of copper oxalate, it was necessary to commence with a sufficient concentration of sodium oxalate in the half-element to prevent the precipitation of the normal copper salt. The results obtained are shown in Table III.

TABLE III.

Sodium oxalate.

Conc. of Na salt, m.-mols./l.	*P.D.*, millivolts.	$[Cu^{\cdot\cdot}] \times 10^9$.	$[X'']^2 \times 10^4$.	$K \times 10^{11}$.
25·0	155	28	0·250	7·1
26·9	166	12	0·476	5·7
30·7	182	3·3	1·15	3·8
34·1	193	1·4	1·99	2·8
38·8	202	0·68	3·53	2·4
44·4	209	0·39	5·96	2·3
49·3	214	0·26	8·59	2·3
58·4	219	0·18	14·8	2·6
66·3	222	0·14	21·4	3·0
75·0	225	0·11	30·3	3·3

Discussion.

The above results indicate that the aminoacetate ion and certain alkyl-substituted aminoacetate ions form extremely stable complex ions of the type $[Cu(NH_2 \cdot CH_2 \cdot COO)_3]'$. The constants of instability obtained show that these ions are considerably less dissociated in aqueous solution than the corresponding malonate and oxalate complexes. This is probably due, in part at least, to the excess positive charge on the copper ion being more nearly balanced by the negative charges on the three aminoacetate ions than is the case in the bivalent dimalonato- and dioxalato-complexes.

The constants of instability show that alkyl substitution has little effect upon the tendency of the aminoacetate ion to co-ordinate with copper. Although the *iso*propyl group effects a pronounced increase, and the dimethyl, diethyl, and dipropyl groups pronounced decreases in this tendency in the case of the malonate ion, yet in the aminoacetate series, only methyl substitution shows any pronounced effect amongst the compounds studied. The increase of the constant in this case is of the same order as, but a little larger than, the corresponding effect of the methyl group on the malonate ion. It is unfortunate that the insolubility of certain amino-acid copper salts does not permit them to be studied by the above method. The results obtained, however, indicate that the effects of alkyl substitution are dependent upon the " activation " of the electron grouping of the adjacent carbon atom by the other powerfully negative groups in the molecule. It is interesting to note, in view of the different effects which the substitution of the *iso*propyl group has in the two cases studied, that Morgan (J., 1924, **125**, 755; 1925, **127**, 2613) has reported instances in which the substitution of an *iso*propyl (or a *sec.*-butyl) group on the median carbon atom of acetylacetone compounds has completely inhibited the formation of the co-ordinated copper compounds of the type formed by other members of the series.

The substitution of an amino-hydrogen to form phenylglycine causes a large decrease in the tendency of the ion to co-ordinate with copper, a preliminary titration having shown a fall of approximately 200 millivolts in the potential of the concentration cell. This change in the stability of the co-ordinated ion is accompanied by a change in colour from deep blue to deep green. It is noteworthy that a similar change from blue to green, which is also accompanied by a large decrease in the stability of the co-ordinated complex, has been recorded in the case of the normal diethyl- and dipropylmalonates of copper already studied (this vol., p. 2010).

The apparatus used in this investigation was purchased out of a grant from the Royal Society, to whom we express our thanks.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W. 7. [*Received, May 22nd,* 1931.]