

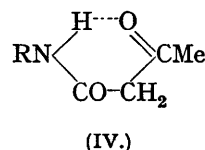
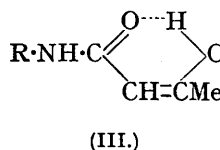
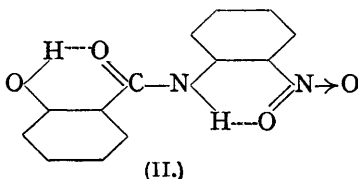
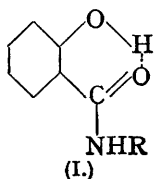
111. The Associating Effect of the Hydrogen Atom. Part IV. Salicyl- and Acetoacet-anilides.

By HUBERT O. CHAPLIN and LOUIS HUNTER.

Measurements of molecular weight in naphthalene solution of some salicyl- and acetoacet-anilides, as well as wet melting-point determinations, indicate that these substances, although less associated than the parent benz- and acet-anilides, still display considerable association. The possibility of hydroxyl association (through the phenolic or enolic groups) is excluded, and it is probable that the association is due to hydrogen-bond formation between the amide hydrogen atom and an already chelate oxygen atom (phenolic or amidic).

Chelate copper derivatives of the acetoacetanilides have been prepared, the properties of which give support to the formula (III) proposed for the latter.

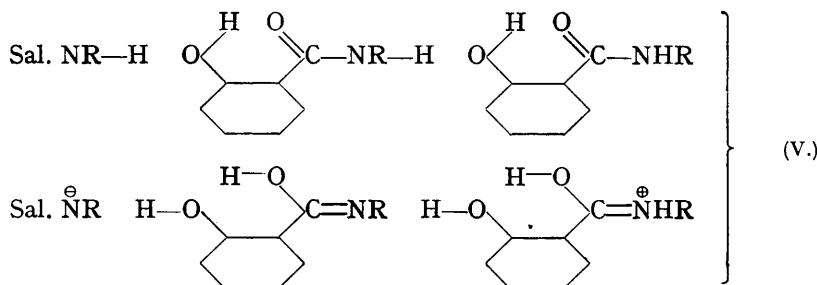
THE mechanism suggested in Part I (J., 1937, 1114) to account for the association of amides depends upon the formation of a hydrogen bridge between the nitrogen atom of one amide group and the oxygen atom of another. This view gains support from the marked suppression of association brought about by the replacement of the amide hydrogen atoms (*loc. cit.*) and, in the case of anilides, by the engagement of the anilide hydrogen atom in chelate ring formation with a suitable *o*-substituent (Part II; J., 1938, 375). It should not be overlooked, however, that the similar engagement of the amide oxygen atom by intramolecular co-ordination might equally well suppress the association of amides. In order to test this view an examination has been made of some salicyl-alkyl- and -aryl-amides (I) and acetoacetyl-amides (III), in which co-ordination of the amide oxygen atoms internally might be expected. As in previous parts of this series, molecular association was deduced from wet melting-point measurements and from molecular-weight determinations in naphthalene solution. Conclusions are based, not on the absolute values of the association factors (which may have no real significance), but rather on the slope of the association-concentration curves, a steep curve indicating high association and a flat curve low association. By comparing the slopes of these curves, anomalies arising from departures from the laws of dilute solutions are very much diminished.



The results of molecular-weight determinations (Fig. 1), however, indicate that, far from being unassociated, the salicyl-amides and -anilides are only slightly less associated than benz-amide and -anilide. That this association is due to phenolic association (*i.e.*, through the salicyl hydroxy-groups) appears to be unlikely, since the salicylalkylanilides are unassociated, as is also salicyl-*o*-nitroanilide. In the former the anilide hydrogen atom has been replaced by alkyl, and in the latter (II) it is presumably co-ordinated with the *o*-nitro-group, thus rendering amidic association impossible. It is evident, therefore, that in these compounds phenolic association is similarly suppressed by chelation of the hydroxyl hydrogen with the neighbouring amide oxygen atom.

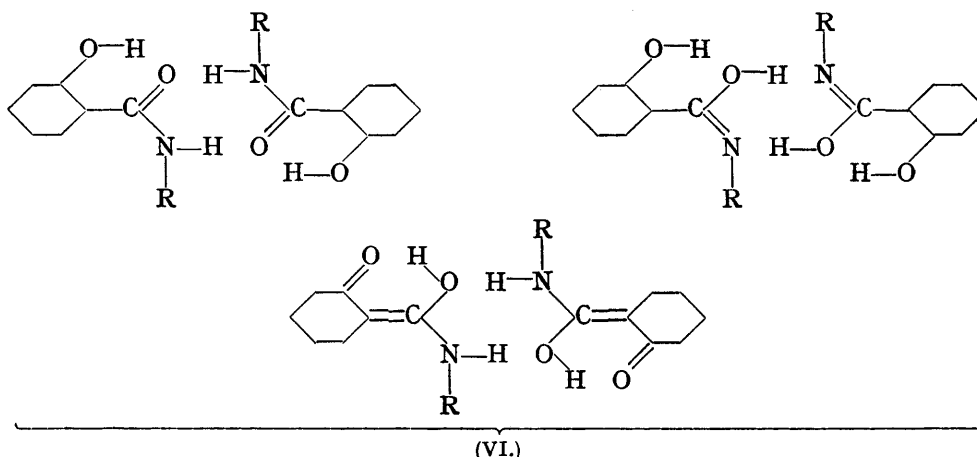
These cryoscopic results are fully borne out by evidence from wet melting points, that for the salicylnitroanilides being particularly significant: salicyl-*o*-nitroanilide (II), shown cryoscopically to be unassociated, gave a wet melting-point depression of 12°, whereas the *m*- and *p*-isomers, in each of which the anilide hydrogen atom is free to undertake inter-molecular bonding, gave depressions of 32° and 39° respectively. Unfortunately, the last two substances were too sparingly soluble to provide molecular-weight evidence of association.

It is clear that the association found in the salicyl-amides and -anilides, but suppressed in salicyl-*o*-nitroanilide and the salicylalkylanilides, must be due to the formation of a hydrogen bond between the amide hydrogen atom of one molecule and an electron-donor atom of another. Such bridge formation may occur in one or more of three ways: (*a*) to the amide nitrogen atom, *viz.*, N-H-N; (*b*) to the phenol oxygen atom, *viz.*, N-H-O(phenolic); (*c*) to the amide oxygen atom, *viz.*, N-H-O(amidic). Method (*a*) is unlikely in view of the relative weakness of this bond (Sidgwick, *Ann. Reports*, 1934, **31**, 43) in competition with (*b*) and (*c*). Since both the phenolic and the amidic oxygen atoms are members of a chelate ring system, methods (*b*) and (*c*) are possible only if such atoms, whilst still preserving their chelate character, are at the same time capable of extending their co-ordinating function to atoms outside the chelate ring. Such an assumption is easily conceivable on the resonance theory, and indeed receives some support from the solubility measurements of Copley, Zellhoefer, and Marvel (*J. Amer. Chem. Soc.*, 1938, **60**, 2666), who deduce from them that chelate oxygen still possesses a residual, though reduced, capacity for co-ordination. Association by method (*b*) will then result in a linear polymer of two or more molecules involving, in one resonance form, the separation of terminal charges, and formula (V; Sal = *o*-OH·C₆H₄·CO) depicts the two resonance states of a trimer of this type. Method (*c*), which is essentially that proposed for amides and sulphonamides in Part I (*loc. cit.*), can be similarly expressed by a cyclic dimer, three resonance states of which are depicted in (VI), or by a linear polymer similar to (V) but involving the amide instead of the phenolic oxygen atoms in bridge formation.



It is not possible, in the present state of our knowledge, to make any choice between the various possibilities set out above. Our original suggestions (Part I, *loc. cit.*) as to the complex nature of amide association have been fully confirmed by subsequent workers from such widely different aspects as infra-red absorption spectra (Buswell, Rodebush, and Roy, *J. Amer. Chem. Soc.*, 1938, **60**, 2444), solubility (Copley, Zellhoefer, and Marvel, *loc. cit.*), and dielectric polarisation (Le Fèvre and Vine, *J.*, 1938, 1790), and it may be concluded that the structure of the salicylanilides may well involve several of the alternatives enumerated above.

The case of the acetoacetanilides is complicated by the possibility of keto-enol change within the acetoacetyl group, thus giving rise to two possible alternative chelate structures (III and IV). Measurements show, however, that the acetoacetanilides, though less associated than acetanilide, still exhibit considerable association (Fig. 2); it would seem that the case is similar to that of the salicylanilides, and that the true formulation is as represented in (III). On this view (III), having a free imino-hydrogen atom, can associate, whereas (IV), in which the imino-hydrogen atom is a member of a chelate ring, cannot. The possibility of association of the enol form of (IV) is remote, since such a structure would almost certainly revert to (III) on account of the much greater stability of an internal O-H-O bridge.



Support is given to this choice by the preparation of a number of copper derivatives of the acetoacetanilides, all of which exhibit properties typical of chelate compounds. They

FIG. 1.

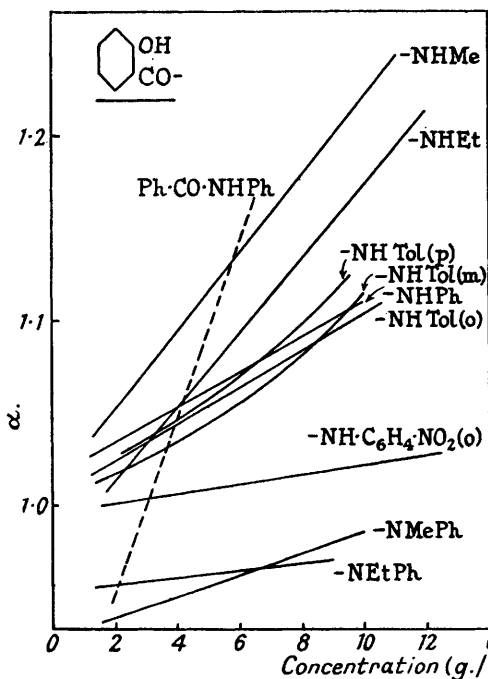
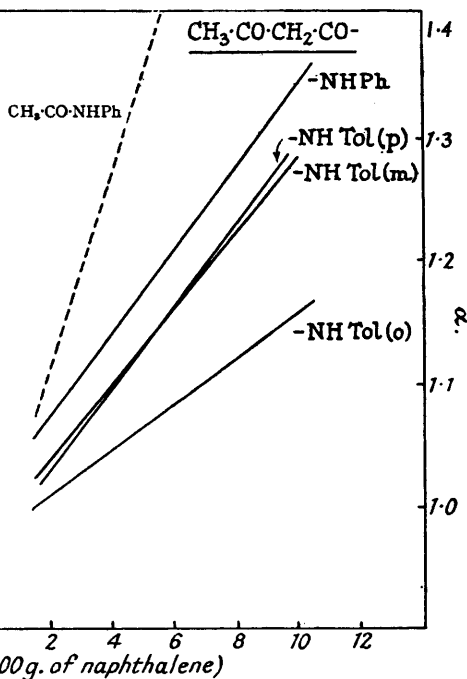


FIG. 2.



are green crystalline substances, insoluble in water, but soluble in most organic solvents, and fusible at about 200°. The formation of chelate copper derivatives in all respects similar to these is shared by acetoacet-methyl- and -ethyl-anilides, and since the latter possess no anilide hydrogen atom, their copper derivatives must have formula (VII). It is reasonable to suppose, therefore, that the acetoacetanilides are (III) rather than (IV), and that their molecular association is probably achieved in a manner similar to that suggested for the salicylanilides, *viz.*, by the intermolecular sharing of the anilide hydrogen atom of one molecule with the phenolic or amidic oxygen atom of another.

The following tables give the measurements on which are based the curves in Figs. 1 and 2. Concentrations are given as g./100 g. of naphthalene, *M* is the apparent molecular weight calculated according to the ideal-solution laws, α is the association factor, and Δ is the depression of m. p. in the presence of water, determined as described in Part II. The figures given under *M* are the means of several determinations. Figures in parentheses indicate the normal molecular weight. Certain figures (in italics) are included for the purpose of comparison, from v. Auwers and Pelzer's measurements in naphthalene (*Z. physikal. Chem.*, 1897, **23**, 449), and are represented in Figs. 1 and 2 by broken lines.

	Concn.	<i>M</i> .	α .	M. p.	Wet m. p.	Δ .
<i>Salicyl-amides and -anilides</i> (Fig. 1).						
Benzanilide (197)	1.79	185	0.94	161°	144°	17°
	3.69	204	1.035			
	5.83	223	1.13			
Salicylomethylamide (151)	1.32	157	1.04	88	64	24
	3.92	164	1.09			
	7.63	176	1.17			
Salicylethylamide (165)	10.80	187	1.24			
	1.84	167	1.01	58	44	14
	4.23	175	1.06			
Salicylanilide (213)	8.64	190	1.15			
	11.73	199	1.21			
	1.17	219	1.03	136	121	15
Salicylo-<i>o</i>-toluidide (227)	2.62	222	1.04			
	5.19	226	1.06			
	7.57	231	1.09			
Salicylo-<i>m</i>-toluidide	9.75	237	1.11			
	1.33	231	1.02	145	130	15
	3.165	235	1.04			
Salicylo-<i>p</i>-toluidide	5.17	237	1.05			
	7.29	242	1.07			
	10.43	251	1.11			
Salicylo-<i>o</i>-nitroanilide (258)	1.09	231	1.02	135—136	125	10—11
	3.22	232	1.02			
	5.30	237	1.045			
Salicylomethylanilide (227)	7.50	243	1.07			
	9.78	252	1.11			
	2.44	233	1.03	155—156	141	14—15
Salicylo-<i>m</i>-nitroanilide	4.36	238	1.05			
	6.64	245	1.08			
	9.27	254	1.12			
Salicylo-<i>p</i>-nitroanilide	1.48	210	0.92	113	104	9
	3.43	216	0.95			
	5.94	218	0.96			
Salicylo-<i>o</i>-nitroanilide (258)	8.23	221	0.975			
	9.77	223	0.985			
	1.37	229	0.95	78	71	7
Salicylo-<i>m</i>-nitroanilide	3.19	233	0.97			
	4.97	231	0.96			
	6.69	232	0.96			
Salicylo-<i>p</i>-nitroanilide	8.49	235	0.97			
	1.56	257	1.00	155	143	12
	3.78	260	1.01			
Salicylo-<i>o</i>-nitroanilide	7.03	261	1.01			
	9.58	264	1.02			
	12.13	265	1.03			
(Too insoluble for measurement)				219	187	32
				230—231	191	39—40

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	Concn.	M.	α .	M. p.	Wet m. p.	Δ .
<i>Acetoacetanilides</i> (Fig. 2).						
Acetanilide (135)	1.57	146	1.08	114°	86°	28°
	6.83	209	1.55			
	10.85	249	1.85			
	13.74	274	2.03			
Acetoacetanilide (179)	1.50	189	1.06	85	63	22
	3.66	202	1.13			
	6.27	217	1.21			
	10.06	243	1.355			
Acetoaceto- <i>o</i> -toluidide (193)	1.30	193	1.00	104	86	18
	3.70	200	1.04			
	7.02	215	1.11			
	10.02	225	1.16			
Acetoaceto- <i>m</i> -toluidide	1.58	198	1.02	57—58	40—41	17
	3.76	213	1.10			
	6.58	228	1.18			
	9.77	247	1.28			
Acetoaceto- <i>p</i> -toluidide	1.72	198	1.03	94	71	23
	4.12	214	1.11			
	6.79	230	1.19			
	9.63	248	1.285			

EXPERIMENTAL.

The following new compounds were prepared in the course of the investigation.

Salicylomethylanilide.—Salol (10 g.) and methylaniline (6 g.) were heated almost to boiling for $\frac{1}{2}$ hour in an open flask. On cooling, the product was shaken with dilute acid; it solidified to a dark mass, which was purified by dissolution in alkali and reprecipitation with dilute acid. After several recrystallisations from cold alcohol by cautious addition of water, the *product* formed small white monoclinic needles or feathered clusters of needles, m. p. 113° (Found: N, 6.2. $C_{14}H_{13}O_2N$ requires N, 6.2%). *Salicylethylanilide*, prepared similarly, formed small white needles, m. p. 78° (Found: N, 5.7. $C_{15}H_{15}O_2N$ requires N, 5.8%).

Cupric Acetoacetanilide.—Copper acetate (1.0 g.), dissolved in the least amount of water, was poured into a warm alcoholic solution of acetoacetanilide (1.8 g.). A dark green granular deposit soon formed, which crystallised from acetone in olive-green platelets, melting sharply at 212° (corr.) (decomp.) (Found: Cu, 15.25. $C_{20}H_{20}O_4N_2Cu$ requires Cu, 15.3%). It was insoluble in water and in dilute alkali, and was decomposed by dilute acids. It was slightly soluble in benzene, chloroform, alcohol, and ether, fairly soluble in acetone, and very soluble in dioxan and in pyridine, forming green solutions. The relationship of this *compound* to the substance prepared by Knorr (*Annalen*, 1886, 236, 76) by heating aqueous acetoacetanilide with an ammoniacal solution of copper sulphate was examined by repeating Knorr's preparation. The substance obtained, when dried at 100°, formed a green powder (Found: Cu, 30.4%) from which acetone extracted a green constituent, leaving a black residue of copper oxide. Repetition of the preparation but without boiling gave cupric acetoacetanilide (Found: Cu, 15.1%) identical with the substance prepared as above.

Cupric acetoaceto-m-toluidide, prepared similarly from acetoaceto-*m*-toluidide, formed a dark green crystalline powder from acetone, m. p. 192° (corr.) (decomp.) (Found: Cu, 14.3. $C_{22}H_{22}O_4N_2Cu$ requires Cu, 14.3%). *Cupric acetoaceto-p-toluidide* formed green crystals, m. p. 220° (corr.) (decomp.) (Found: Cu, 14.15%).

Acetoacetethylanilide.—Equimolecular proportions of ethylaniline and ethyl acetoacetate were heated to boiling (180—200°) in an open flask for 15 minutes. The resulting dark oil was cooled and treated with 2*N*-sodium hydroxide, whereupon a dense white precipitate of *sodium acetoacetethylanilide* separated. This was washed with light petroleum and air-dried for analysis (Found: Na, 9.9. $C_{12}H_{14}O_2NNa$ requires Na, 10.1%); it was soluble in water, giving a slightly alkaline solution, which on acidification with dilute acetic acid deposited *acetoacetethylanilide* as a pale yellow oil which crystallised on standing. Recrystallised from light petroleum, it formed colourless plates, m. p. 49—50° (Found: N, 6.7. $C_{12}H_{15}O_2N$ requires N, 6.8%). The *cupric* derivative, prepared as before, formed dark green needles from acetone, soluble in benzene and chloroform, but less so in alcohol and in ether, m. p. 182° (corr.) (Found: Cu, 13.4. $C_{24}H_{24}O_4N_2Cu$ requires Cu, 13.5%).

Condensation of methylaniline with ethyl acetoacetate in similar circumstances, followed by treatment with sodium hydroxide, gave *sodium acetoacetomethylanilide* (Found: Na, 10.4. $C_{11}H_{12}O_2NNa$ requires Na, 10.8%). Treatment of this sodium derivative with dilute acetic

acid gave a yellow oil which did not solidify after prolonged immersion in a freezing mixture. *Cupric acetoacetomethylanilide* was therefore obtained by the double decomposition of an aqueous solution of the sodium salt with copper acetate. It formed dark green crystals from acetone, m. p. 164—165° (corr.) (Found : Cu, 14.1. $C_{22}H_{24}O_4N_2Cu$ requires Cu, 14.3%).

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