

Short Communications

 The Importance of Alkali Chelates
 in the Alkylation of β -Ketoesters

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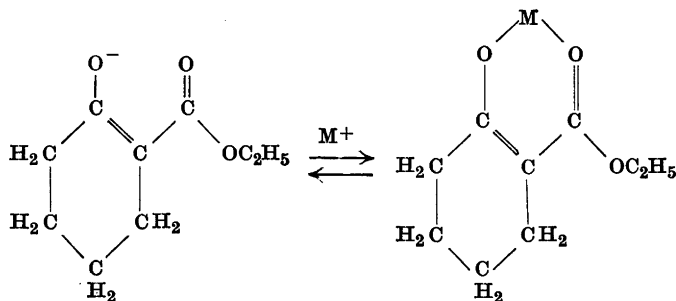
In a recent review of the chemistry of metal chelate compounds¹ Martell and Calvin gave an interesting example showing the difference in velocity of the alkylation of the sodium derivative of a β -ketoester from that of the corresponding potassium derivative. Thus the potassium compound of α -carbethoxycyclohexanone is alkylated about one hundred times as fast as the sodium compound in a toluene solution. In a tertiary butyl alcohol solution the reaction velocity of the potassium compound is nearly the same as that in the toluene solution. The potassium compound is alkylated twelve times as fast as the sodium compound when tertiary butyl alcohol is the solvent.

This remarkable difference in reactivity of the sodium and potassium derivatives

was explained on the basis that the reaction was considered to take place with the enolate ion and that this ion was also engaged in a chelate formation reaction. See formulae below.

The tendency for K^+ to form chelates was considered much weaker than that of Na^+ with the effect that more enolate ions are available for alkylation when the potassium compound was used than when the sodium compound was employed. *The results are, however, better explained in the opposite manner.*

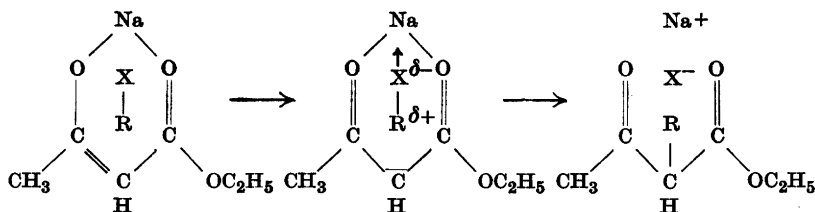
The statement, that the tendency for K^+ to form chelates is much weaker than that of Na^+ , was based on the assumption that for chelate compounds of the primarily ionic type the strength of chelation should increase with increasing ionic charge of both metal ion and donor and increase with decreasing ionic radius of the metal ion. This assumption is, however, valid only when all other factors such as tendency for homopolar bonding, double-bond formation, and valence bond resonance are not important for the chelate formation. This is the case when, for example,



ethylenediamine tetraacetic acid is the chelation agent and the stability of the chelates formed with different alkali ions ² is in this case in good agreement with those calculated on this purely ionic basis.

When the resonance effects are great, the above assumption is, however, not valid. This can be seen from the fact that no 2-covalent Li⁺ compounds could be isolated from a great variety of β -ketoesters and related compounds by Sidgwick and Brewer ³. Although many 2-covalent Na⁺ compounds could be obtained, the K⁺ had a still higher tendency to form such

compound gives a C-alkylation product is good evidence that this reaction will not go *via* the enolate anion, as the sodium and the ammonium derivative should then give the same product which is not the case. The C-alkylation reaction will then very probably go *via* a chelate mechanism which is quite possible as chelate sodium compounds of ethyl acetoacetate have been isolated ³. A chelate mechanism satisfactorily explains the fact that the sodium compound of ethyl acetoacetate gives C-alkylation compounds. This is best illustrated by the following formulae



compounds. In the case under consideration (α -carbethoxycyclohexanone) the potassium compound is very soluble in toluene ⁴ but the sodium compound has only a limited solubility in the same solvent ⁵ indicating that K⁺ in this case has a stronger tendency than Na⁺ to form a chelate compound.

There are many indications which support the assumption, that the chelate compound and not the enolate ion is the one entering the C-alkylation reaction, but as this will be fully treated in a subsequent paper only one example will be given here.

The ammonium derivative of ethyl acetoacetate gives the O-alkylation compound with chloroacetone, whereas the sodium compound gives the C-alkylation compound ⁶. This indicates that the enolate anion gives the O-alkylation product. (No chelate ammonium derivative is possible.) The fact that the sodium

The difference in the reaction rates of the Na⁺ and K⁺ compounds of α -carbethoxycyclohexanone can thus be explained in the following way:

The K⁺ has a stronger tendency than Na⁺ to give a chelate ring with the anion of α -carbethoxycyclohexanone, and thus, the C-alkylation reaction, which goes via the chelate compound, has a higher velocity with K⁺ than with Na⁺.

In tertiary butyl alcohol the alkali ions are more highly solvated and the difference in chelate formation of the K⁺ and Na⁺ ions is probably less in this medium than in toluene which can be seen from the fact that four covalent compounds are formed with Li⁺, Na⁺, and K⁺ whereas two covalent ones are formed with Na⁺ and K⁺ only. The difference in reaction rates will hence be less in tertiary butyl alcohol than in toluene, which was also observed. In ethyl alcohol this difference is probably even less than in tertiary butyl

alcohol which can be seen from the fact that the relative reaction rates of the potassium and the sodium derivative of ethyl acetoacetate are almost equal⁷.

In this connection it can be pointed out that a similar difference in reaction rates with different alkali derivatives of acetylacetone has been reported by the present author^{8,9}. This was at first considered as a pure solubility effect⁸, but further measurements showed that this is not the complete truth. Similar effects were observed in the methylation of ethyl α -cyanopropionate, ethyl α -carbethoxypropionate and ethyl acetoacetate with different alkali carbonates¹⁰, but these kinetic results were not accurate enough to give any precise information about the mechanism.

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On the Structure of Nebularine

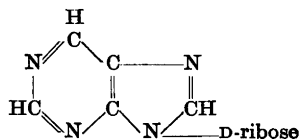
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Nebularine, a principle active against *Mycobacteria* and present in the mushroom *Agaricus (Clitocybe) nebularis*

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Batsch., has been studied since 1945 by Löfgren *et al.*¹⁻³. — We have now succeeded in isolating the compound in a pure state, m.p. 181–182° (corr.). The elementary analysis shows that the compound has the empirical formula $C_{10}H_{12}N_4O_4$. The hydrolysis gave the components purine and D-ribose. This is the first time purine has been demonstrated to be a component of a natural product. From spectroscopical data it can be concluded with high probability that the D-ribose is connected at position 9 of the purine nucleus. It is therefore possible to state that nebularine is 9-(D-ribose)purine:



Nebularine has a high activity against different types of tubercle bacilli *in vitro* (no experiments performed *in vivo*). Thus for instance, the bacteriostatic activity of nebularine on *Mycobacterium avium* in Dorset substrate is 1 : 3 000 000 after 12 days and 1 : 2 000 000 after 30 days*. — We found it to retard strongly the growth of barley seedlings and furthermore experiments on *Allium* roots show C-mitosis and chromosome breaks in a dilution of 1 : 100 000**.

A full report will be published later.

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* Experiments performed by H. Hedström.

** Experiments performed by B. Kihlman.