Studies on Succinic Acids

II.* Equilibrium Constants for the Interconversion of Meso- and Racem-\(\alpha,\alpha'\)-dialkylsuccinic Acids

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This paper deals with the determination of the equilibrium constants of the reaction meso acid \(\rightleftharpoons\) racemic acid for \(\alpha,\alpha'\)-dimethyl-, \(\alpha,\alpha'\)-diethyl-, and \(\alpha,\alpha'\)-diisopropylsuccinic acid at 170° in the solvents dioxane, water, and 5 N aqueous hydrochloric acid. In certain cases the interpretation of the results is complicated by the occurrence of simultaneous anhydridization, but it is clearly established that the racemic forms are relatively more stable, contrary to the findings of several other investigators. The stability order found can be explained by assuming the existence of an intramolecular hydrogen bond which selectively stabilizes one of the racemic acid conformations. A similar stabilizing effect is not probable for any of the meso acid conformations.

It has been known for a long time that diastereoisomers of \(\alpha,\alpha'\)-disubstituted succinic acids can be converted into each other under certain conditions, e. g. by heating with hydrochloric acid at elevated temperatures. Wagner-Jauregg has cited a number of cases of such interconversions, which all point to the meso forms being the most stable ones. Linstead and Whalley have stated without experimental proof that the meso form of \(\alpha,\alpha'\)-dimethylsuccinic acid should be the more stable isomer. Later on, Golden and Linstead have semiquantitatively investigated the equilibration of mesoid and racemoid \(\alpha\)-methyl-\(\alpha'\)-ethylsuccinic acid under varying conditions. In two cases the equilibrium mixture contained more than 50 % of the racemoid form, i. e., the stability order was in line with that of the corresponding anhydrides and contrary to the cases cited above. Barton and Cookson used the data of Wagner-Jauregg as evidence for the stability order of erythro and threo isomers predicted from the conformational point of view. According to this reasoning the erythro (meso) form should be the more stable one.

However, a critical examination of the original literature on equilibria of \(a,a'-\)dialkylsuccinic acids revealed that the table set up by Wagner-Jauregg was based on an unreliable experimental material of great inhomogeneity. Thus, in most cases it has not been established whether the inversions are reversible or not, the analysis of the equilibrated samples has been made by

<table>
<thead>
<tr>
<th>Succinic acid</th>
<th>Melting point of equilibrium mixture, mean value and maximum deviation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In dioxane</td>
<td>In water</td>
<td>In 5 N aq. HCl</td>
</tr>
<tr>
<td>Racem-(a,a'-)dimethyl-</td>
<td>156.0</td>
<td>171.0</td>
<td>169.6</td>
</tr>
<tr>
<td>Meso-(a,a'-)dimethyl-</td>
<td>157.0</td>
<td>172.8</td>
<td>170.6</td>
</tr>
<tr>
<td>Racem-(a,a'-)diethyl-</td>
<td>157.8</td>
<td>173.2</td>
<td>168.6</td>
</tr>
<tr>
<td>Meso-(a,a'-)diethyl-</td>
<td>158.8</td>
<td>174.6</td>
<td>170.6</td>
</tr>
<tr>
<td>Racem-(a,a'-)disopropyl-</td>
<td>143.4</td>
<td>166.6</td>
<td>169.0</td>
</tr>
<tr>
<td>Meso-(a,a'-)disopropyl-</td>
<td>144.0</td>
<td>167.0</td>
<td>161.2</td>
</tr>
<tr>
<td>Racem-(a,a'-)disopropyl-</td>
<td>142.4</td>
<td>166.7</td>
<td>168.0</td>
</tr>
<tr>
<td>Meso-(a,a'-)disopropyl-</td>
<td>142.0</td>
<td>167.6</td>
<td>183.0</td>
</tr>
</tbody>
</table>

* Measured by potentiometric titration.
preparative methods, which only qualitatively give the direction of the changes, the temperatures and times used for equilibration have been extraordinarily varying, and the inversions have been carried out with strong hydrochloric acid as solvent, which might influence the equilibrium state. Besides, in several cases the equilibria actually were at about 50 % inversion \(^7,6\) and in one case (\(\alpha,\alpha'-diisopropylsuccinic acid\)) in favour of the \(\text{racemic acid}\) \(^11\).

This paper, which is part of an investigation on the stereochemistry of alkylsubstituted succinic acids, describes an attempt to measure the equi-

\[
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\% \text{ meso acid in the equilibrium mixture} & \text{Equilibrium constant } K_e \\
\hline
\text{In dioxane} & \text{In water} & \text{In 5 N aq. HCl} & \text{In dioxane} & \text{In water} & \text{In 5 N aq. HCl} \\
\hline
34.3 \pm 1.2 & 48.2 \pm 2.0 & 45.2 \pm 1.2 & 1.9 \pm 0.1 & 1.1 \pm 0.1 & 1.2 \pm 0.1 \\
\hline
15.0 \pm 1.0 & 41.5 \pm 2.0 & 34.5 \pm 3.0 & (5.7 \pm 0.5) & 1.4 \pm 0.1 & 1.9 \pm 0.3 \\
\hline
42.2 \pm 2.0 & & & & 1.4 \pm 0.1 & \ \\
\hline
25 \pm 5 & 43 \pm 2 & 22 \pm 2 & (3.0 \pm 1.0) & 1.3 \pm 0.1 & (3.5 \pm 0.5) \\
\hline
\end{array}
\]

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librium constants for the interconversion of the meso and racemic forms of \( a,a'\)-dimethyl-, \( a,a'\)-diethyl-, and \( a,a'\)-diisopropylsuccinic acids at 170° in the solvents dioxane, water, and 5 N hydrochloric acid. The composition of the equilibrium mixtures was determined by thermal analysis and/or by potentiometric titration in the case of \( a,a'\)-diisopropylsuccinic acid. The shape of the melting point curves and the states of the equilibria are such as to permit the evaluation of the constants in an unambiguous manner. The melting point diagrams are shown in Figs 1, 2, and 3, and the results of the inversion experiments in Table 1.

These data clearly indicate that the inversions really are reversible and that the equilibrium mixtures in all cases contain 50 % or more of the racemic acid. Furthermore, there is a trend to an increase of the constant when the steric requirements of the substituents are enhanced. Unfortunately, the two forms of \( a,a'\)-di-(tert.-butyl)-succinic acid do not equilibrate at 170°, but experiments carried out at 220—230° showed that both isomers are converted into the racemic anhydride with no observable contamination of meso acid. The values for \( a,a'\)-diisopropylsuccinic acid are probably somewhat too small as the analytical method necessitated treatment of the equilibrated samples with aqueous base and subsequent acidification with dilute hydrochloric acid, filtration, and washing with water. This procedure should be expected to influence the final result in direction towards lower constants, as the meso acid is less soluble in water than the racemic acid.

**DISCUSSION**

The reason for putting some values in Table 1 in parentheses is the complication introduced in these cases by the formation of anhydride during equilibration, which makes the significance of the corresponding equilibrium constants somewhat questionable. The procedure has been to convert the mixture of acid and anhydride into acids by treatment with water or aqueous base and then analyzing the product of hydrolysis as outlined above. The measured constant will then refer to the system meso material ⇌ racemic material. This behaviour immediately actualizes the question: Could not the stability order found be explained in all cases, even when anhydride formation is not observed, by assuming the existence of the equilibrium in aqueous or dioxane

\[
\begin{align*}
\text{meso acid} & \iff K_s \iff \text{racemic acid} \\
\text{meso anhydride} & \iff \text{racemic anhydride} \\
+ \text{H}_2\text{O} & \iff + \text{H}_2\text{O}
\end{align*}
\]

solution at 170°? In that case the driving force would be the formation of the racemic anhydride, which is the stable form of the anhydrides. When the equilibrium has been frozen in and the system returned to room temperature, the anhydrides would have the possibility of passing into the acids again during the analytical work, except when their rate of hydrolysis is low. There is

evidence for the existence of an equilibrium between acid and anhydride in aqueous solution at elevated temperatures in a number of cases. For example, steam-distillation of an aqueous solution of tetramethyloxalic acid gives tetramethyloxalic anhydride, which is then slowly hydrolyzed by cold water again.

It would hardly be possible to develop a method for the unambiguous determination of an eventual equilibrium between acid and anhydride at 170° which does not interfere with the reaction. However, the fact that equilibration of the a,a'-dimethyloxalic acids in absolute dioxane yields acid mixtures with no contamination of anhydride makes it probable that the equilibrium

\[
K_0 \quad \text{meso acid} \xrightarrow{\text{meso acid}} \text{racemic acid}
\]

is not influenced to any appreciable extent by anhydrazation in those cases where it has not been observed.

Koskikallio has measured the rate of hydrolysis of acetic anhydride in dioxane containing 0.07% of water and found a second order rate constant of about \(10^{-5} \text{ l. mole}^{-1} \cdot \text{sec}^{-1}\) at 100° and \(10^{-7} \text{ l. mole}^{-1} \cdot \text{sec}^{-1}\) at 40°. Comparison of the rate constants for the hydrolysis of acetic anhydride in various solvent mixtures with those of succinic anhydride under similar conditions indicates that they always are of the same magnitude. The rate constants of the hydrolysis of the two a,a'-dimethyloxalic anhydrides in water at 25° in turn are of roughly the same order as those of acetic and succinic anhydride. If the equilibration of a,a'-dimethyloxalic acids in dioxane would lead to partial anhydride formation, the anhydride portion would not have time to be hydrolyzed during the working-up period (about 4 h), provided the above reasoning holds. In fact, even if an average rate constant of \(10^{-3} \text{ l. mole}^{-1} \cdot \text{sec}^{-1}\) for hydrolysis during this period is allowed, the half-life time would still be about 4 h. Thus it can be concluded with tolerable certainty that these equilibrium constants which have not been put in parentheses actually refer to the reaction \(K_0 \quad \text{meso acid} \xrightarrow{\text{meso acid}} \text{racemic acid}\), and that the others must be interpreted with regard to the complication discussed above.

As already mentioned the results of the earlier investigations in this field have been explained on the basis of conformational analytical considerations. Accordingly, the meso acid would be the more stable isomer, as in its most favoured conformation (I a) all substituents are situated in \textit{trans} staggered positions, thereby allowing a minimum of non-bonded interactions.

The conformations of the racemic acids (II, a—c) are all energetically less favoured than I a, provided these interactions are repulsive, \textit{i. e.}, it must be assumed that the carboxyl groups behave like alkyl groups in this connection. This reasoning cannot be true, as the relative stabilities of the acids reported in this paper are the same as those of their anhydrides. The departure from the expected behaviour must be due to attractive forces between the carboxyl groups, and it is plausible to assume that intramolecular hydrogen bonding is responsible for this effect. The racemic acid conformation II b would then be the most favourable arrangement, as it contains a ring system with two \textit{trans}-situated alkyl substituents. The concept of a seven-membered hydrogen-bonded ring system existing in aqueous solution is perhaps not quite acceptable on these grounds alone, and the topic will be discussed more in detail in

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papers III\textsuperscript{17} and IV\textsuperscript{18} of this series, where dissociation constants and infra-red data will be presented. In fact, the infra-red spectra give further evidence for the existence of an intramolecular hydrogen bond in solutions of peralkyl-substituted succinic acids.

**EXPERIMENTAL**

*Materials.* Commercial dioxane of *purissimum* quality was purified according to Vogel\textsuperscript{19} but the treatment with sodium was repeated once more. The \(a,a'\)-dialkylsuccinic acids were prepared and purified as described in paper I\textsuperscript{20}.

*Determination of the melting point diagrams.* It has been pointed out earlier that the melting points of alkyl-substituted succinic acids are rather sensitive to the method of determination and the heating conditions owing to the decomposition into anhydride and water near the melting point \textsuperscript{24}. However, if the melting point was determined in a sealed capillary, it was found to be satisfactorily reproducible. Naturally the true melting point is not measured by this procedure but instead a mixed melting point for a complex system with the components acid, anhydride, and water. The good reproducibility points to an equilibrium being established, but this problem requires further investigation before it can be fully discussed. For analytical purposes the method is satisfactory provided all determinations are made as identical as possible. Each point of the diagrams was obtained in the following way:

The mixture of the *meso* and *racemic* acid (total 20 mg) was accurately weighed into a small weighing-glass, and one ml of analytical grade acetone was added. If the acids did not dissolve immediately, the mixture was warmed for a few seconds, until complete solution was achieved. The acetone was evaporated in a slow stream of air and the residue finally dried over concentrated sulphuric acid in vacuo for 10–12 h. The crystal mass was finely ground and introduced into melting point capillaries (two determinations.
were made for each mixture) which were sealed in a micro-burner. The whole capillary must be immersed into the heating-block in order to avoid distillation or sublimation during the heating period. The capillary was introduced into the melting point apparatus at a temperature about 10^\circ below the melting point, which was first roughly estimated in the Kofler apparatus. The heating rate was 1^\circ/\text{min}. The melting point was taken as the temperature at which the last crystals disappeared, and this value was generally reproducible within ± 1^\circ.

Equilibration of meso- and racem-\textit{a,a'-dialkyl}
\textit{su}ccinic acids. Samples of meso and racemic acid, 20 mg of each, were introduced into glass ampoules made from 10 mm Pyrex tubing and with a volume of about 3 ml. The solvent (dioxane, water, or 5 N hydrochloric acid), 2.0 ml, was added and the ampoules were sealed in a burner. The thermostat consisted of a large brass block which was heated electrically by means of two heating spirals of Kanthal wire, and was fitted with a contact thermometer (graded in 0.1^\circ in the range 150–200^\circ) and a calibrated thermometer (gradation as above). The block was very carefully isolated with diabas wool and placed in a sheet container. Preliminary experiments had indicated that equilibration occurred with reasonable speed at 170^\circ. With the described apparatus the temperature was maintained within 0.1^\circ, which was quite sufficient for the purpose of this study. The sealed ampoules were placed in a small steel-bomb, which fitted snugly into a hole in the brass block. After some experiments the times for reaching equilibrium were established at 120 h with dioxane as solvent, and 48 h with water or 5 N hydrochloric acid. After the heating period the bomb was removed and rapidly cooled in ice-water (this procedure lasts about 1 min), the ampoules were opened and the contents poured into small beakers. The ampoules were rinsed with a few ml of dioxane. The solvent was then evaporated in \textit{vacuo} over concentrated sulphuric acid and sodium hydroxide pellets for 4 h in the case of dioxane and 12 h in the case of water and 5 N hydrochloric acid. The procedure then differed somewhat for different acids.

For \textit{a,a'-dimethyl}
\textit{su}ccinic acid the residue in all cases consisted of a mixture of the acids with no contamination of anhydride, which is shown by the fact that another treatment with water and subsequent evaporation did not change the melting point.

For \textit{a,a'-diethyl}
\textit{su}ccinic acid the residue from equilibration in dioxane was a mixture of water and anhydride, which first had to be converted into acids by treatment with water and subsequent evaporation. From the equilibrations in water and 5 N hydrochloric acid mixtures of the acids were directly obtained. Consequently, the melting points of these mixtures, determined as described above in connection with the melting point diagrams directly give the composition of equilibrium for \textit{a,a'-dimethyl}
\textit{su}ccinic and \textit{a,a'-diethyl}
\textit{su}ccinic acid.

For \textit{a,a'-diisopropyl}
\textit{su}ccinic acid the residue was in two cases a mixture of acid and anhydride. As the anhydride portion could not be hydrolyzed by water alone a small amount of aqueous potassium hydroxide was added. When the anhydride had dissolved, the acid mixture was precipitated by the addition of a few drops of dilute hydrochloric acid, the crystals were filtered, washed with some water and finally dried in \textit{vacuo}. However, the melting points of these mixtures were too low to be compatible with the melting point diagrams, which was probably due to the presence of minute amounts of anhydride. Fortunately, the dissociation constants of \textit{meso-} and \textit{racem-\textit{a,a'-diisopropyl}
\textit{su}ccinic acid in 50 \% ethanol} (see paper III\textsuperscript{2}) are of an order to permit analysis by means of potentiometric titration. Experiments with mixtures of known composition gave results with an accuracy of about ± 2 \%. As is seen from Table 1, the two methods of analysis give agreeing results in the case where both have been applied.

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