Hydrogen Exchange Reactions of Esters in Relation to Reactivity in Condensation Reactions

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A study has been made of the base catalyzed hydrogen exchange reactions of representative esters of various types with deuteroalcohol in order to evaluate the effect on acidity[2] of structural variations and their consequent effect on reactivity in condensation reactions. Pertinent to the behavior of esters of monocarboxylic acids in the Claisen condensation, the effect of various alkyl groups has been investigated in some detail, and similarly, but less extensively, the effect of substitution has been traced in the phenylacetic and malonic ester series and correlated with the relative reactivities in alkylation reactions.

Preliminary experiments by W. R. Sprowls[3] indicated that the simple aliphatic esters do not undergo hydrogen exchange with deuteroalcohol in the presence of small amounts of sodium hydroxide either at room temperature or at 100° for long periods of time. Likewise no exchange was observed on addition of only a small quantity of metallic sodium (sufficient to form a 0.05 M sodium ethylate solution), evidently because of water present. We observed hydrogen exchange at a measurable rate even at room temperature, and without appreciable β-keto ester formation, on increasing the amount of sodium used to about 0.02 g. atom per mole of alcohol. A much weaker base, sodium salicylate, was required in the experiments on malonic ester and its derivatives.

Experimental Part

While the extent of hydrogen exchange has formerly been determined at this Laboratory[4,5] through density measurements on the water obtained by combustion of the alcohol recovered from reactions by distillation methods, the use of volatile esters in the present work precluded separations of the alcohol. Accordingly, in such cases, the reaction products were washed with saturated salt solution to remove the alcohol, samples (2 g.) of the separated esters were then burned and the water of combustion was collected in a cooled trap. The water, purified by heating with potassium permanagate and sodium carbonate at 180° for one hour and distilled twice in vacuo, was finally collected in a small tube (attached to the distilling apparatus through a ground joint) in which the density was determined with a quartz float and the deuterium content was then estimated by suitable interpolations.

Deuteroalcohol, with the C_2H_5OD content in the range 15–23 mole per cent. was prepared according to our previously described method.[4] The esters were obtained from commercial sources and purified, or were prepared according to directions in the literature.

TABLE I

HYDROGEN EXCHANGE REACTIONS OF ESTERS WITH DEUTERO-ALCOHOL[a]

Ethyl ester	M.-moles ester	Initial % D_2O[b]	Final % D_2O[c]	H at. exch.[d]	% completion
At 25°, four hours, with 38 = 2 mg. sodium					
Acetic	51.1	3.13	1.70E	1.30	56
Propionic	43.6	3.13	0.28E	0.24	14
Butyric	37.8	3.13	0.18E	.11	6.4
Lauric	37.0	2.60	2.48	.11	6.3
Stearic	37.0	2.60	2.50	.09	5.2
Isobutyric	37.5	3.13	0.03E	.02	1.9
Isovaleric	37.0	2.60	0.06E	.05	2.9
Cyclohexylacetic	37.0	2.60	2.50	.09	5.4
α-Methoxypropionic	37.0	2.60	0.04E	.03	3.5
Crotonic	37.0	2.73	0.81E	.63	
Sorbic	37.0	2.73	2.50	.20	
ββ-Dimethylacrylic	36.0	2.60	0.39E	.35	
Citraconic	37.0	2.73	2.02	.78	
Mesaconic	37.0	2.73	2.64	.07	
At 110°, 12 hours, with 40 mg. of sodium					
o-Toluic (16 hr.)	31.5	2.60	2.56	.04	
p-Toluic	31.2	2.60	2.36	.28	
2,4,6-Trimethylbenzoic	15.2	2.73	2.68	.09	
At 0°, five minutes, with 40 mg. of sodium					
Phenylacetic	10.0	3.03	2.73	.91	48
Diphenylacetic	10.0	3.03	2.94	.25	24
α-Methoxyphenylacetic	10.0	3.03	2.97	.17	17
α-Phenylpropionic	20.8	3.03	2.94	.13	13
At 25°, four hours, with 5 mg. of sodium salicylate					
Malonic	23.0	2.60	1.78	1.71	85
Methylmalonic	23.0	2.60	2.44	0.25	25
Phenylmalonic	23.0	2.60	2.39	0.33	30

[a] The quantity of alcohol used in each experiment was 5 cc. (85.3 millimoles). [b] Data refer to deuterium content of water of combustion from stock deutero-alcohol. [c] Data refer to deuterium content of water of combustion from recovered alcohol or, where designated by "E," from the recovered ester. [d] Calculated on the assumption of statistical distribution of deuterium.

(1) Taken in part from the thesis of Kenneth Eberly submitted in partial fulfilment of the requirements for the Ph.D. degree at the University of Chicago, December, 1938.

(2) The term acidity is used throughout in the generalized sense. Since, in the condensation reactions to be considered, the anion concentration is maintained at the equilibrium value, the acid strength, not merely the rate of formation of anions as given by the rate of hydrogen exchange, is of importance. Brönsted and co-workers [see Brönsted, *Chem. Rev.*, **5**, 231 (1928)] have shown empirically, and Horiuti and Polanyi theoretically [*Acta Physicochimica, U. R. S. S.*, **2**, 505 (1935)], that the rate of proton transfer and the acid strength, in comparisons of acids of the same structural type, are directly and simply, though not linearly, related and undoubtedly the relative reactivities of similar esters in hydrogen exchange reactions will indicate correctly the order of acidity.

(3) W. R. Sprowls, Ph.D. Thesis, University of Chicago, 1938.

(4) Kharasch, Brown and McNab, *J. Org. Chem.*, **2**, 36 (1937).

(5) Brown, Kharasch and Sprowls, *ibid.*, **4**, 442 (1939).

Experiments in which the exchange reactions were substantially complete yielded values for the number of exchanging hydrogen atoms, assuming simple statistical distribution, of which the following are typical: ethyl acetate 2.25, propionate 1.74, butyrate 1.73, isobutyrate 0.91, β-dimethylacrylate 5.45, N-dimethylaminoacetate 1.98, phenylacetate 1.92, diphenylacetate 1.07, phenylmalonate 1.08. These limiting values, or estimated values in the absence of specific data, were then used in estimating the degree of completion of the exchange reaction in a series of experiments in which the reactions were interrupted before equilibrium was attained so as to obtain a quantitative comparison of the reactivities of the various esters. Typical results are given in Table I.

Discussion

The order of acidity in esters of the type RCH_2COOEt according to our results is as follows: $C_6H_5 > H > CH_3 > C_2H_5 > n\text{-}C_3H_7 > C_{10}H_{21}$, $C_{16}H_{33} > \text{cyclo-}C_6H_{11} > i\text{-}C_3H_7$. Alkyl groups, relative to hydrogen, thus exert a de-activating effect which depends more upon whether the group is primary or secondary than upon the length of the chain. A second alkyl group (one example: ethyl isobutyrate) causes a further decrease in acidity, even after allowing for statistical effects. The phenyl group in phenylacetic ester appears strongly activating but a second phenyl group, as in diphenylacetic ester, fails to enhance the effect, and again, as a substituent in malonic ester, it has nearly the same (de-activating) effect as a methyl group.[6]

Vinylogic effects[7] in unsaturated esters diminish with increasing length of the conjugated bond system (cf. series, ethyl acetate, crotonate, sorbate) and are highly dependent upon geometrical configuration (cf. ethyl citraconate, mesaconate), the *trans* relationship between carbethoxy and β-methyl groups being more favorable.

The results for the esters of monocarboxylic acids are to be correlated with reactivity in the Claisen condensation, which, according to current theory,[8,9,10] involves anion formation by proton transfer as the first step, followed by reaction of

the anion with another molecule of ester, etc., each step being reversible. The acid strength appears as a factor both in the rate and in the over-all equilibrium, and the failure of certain esters (notably ethyl isobutyrate and ethyl isovalerate) to undergo self-condensation under the usual conditions is ascribed to low acid strength, a conclusion supported by the observations[9,11] that condensation will occur if sufficiently powerful bases are used. Our results confirm this deduction regarding the acid strengths of ethyl isobutyrate and ethyl isovalerate, and the available data, chiefly of Roberts and McElvain[12] and Briese and McElvain,[13] on the rates and yields in condensations indicate close agreement throughout with the reactivity in hydrogen exchange. Quantitatively the correlation is less convincing, as we find, for example, the acid strength of ethyl laurate to be twice that of ethyl isovalerate, while in the acetoacetic ester condensation the former yielded 79%[13] and from the latter, under comparable conditions, "no trace of keto ester could be found."[12] The over-all equilibrium in the latter case is clearly much more unfavorable than by a factor of two, and we conclude that the variations in acidity, while similar in trend, are not wholly responsible for the variations in reactivity.[14]

In the malonic ester series we have but one example, methylmalonic ester, showing the effect of an alkyl group in decreasing the acidity but the effects of other alkyl groups are doubtless as characteristic as in the previous series, and the relative reactivity in alkylation reactions parallels that observed in the Claisen condensations of monocarboxylic esters. An outstanding example is the failure of isopropylmalonic ester to undergo further alkylation under the usual conditions, previously attributed to steric hindrance,[15]

(6) This apparently anomalous behavior of phenyl groups finds a ready explanation in the theory of damped resonance [Birtles and Hampson, *J. Chem. Soc.*, 10 (1937); Ingham and Hampson, *J. Chem. Soc.*, 981 (1939)]. The hydrogen lability of esters is due primarily to resonance stabilization of the anion and an α-phenyl group would normally reinforce this resonance by providing additional resonance forms, in which it appears doubly bonded to the α carbon, and which are therefore most effective if the benzene ring and the carbethoxy group can become coplanar. With two phenyl groups and one carbethoxy group (or one phenyl group and two carbethoxy groups) attached to the α carbon, the condition of coplanarity could not be fulfilled for steric reasons.

(7) Fuson, "The Principle of Vinylology," *Chem. Rev.*, **16**, 1 (1935).

(8) Arndt and Eistert, *Ber.*, **69**, 2381 (1936).

(9) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937).

(10) Renfrow and Hauser, *ibid.*, **60**, 463 (1938).

(11) Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

(12) Roberts and McElvain, *ibid.*, **59**, 2007 (1937).

(13) Briese and McElvain, *ibid.*, **55**, 1697 (1933).

(14) Spielman and Schmidt (*loc. cit.*) attributed the failure of ethyl isovalerate and isobutyrate to undergo self-condensation (with sodium ethylate) to the low acidity, indicated by negative ferric chloride tests, of the β-keto esters derived from them, and, in our opinion, this should be admitted as a contributing factor. We considered the second step of the Claisen condensation (reaction of anion with another molecule of ester) as similar in form to the alkoxy group interchange reactions of esters, and we observed in such a reaction (RCOOAm + OEt⁻ ⟶ RCOOEt + OAm⁻, Am = optically active amyl) that ethyl isobutyrate reacted only one-fifth as rapidly than ethyl *n*-butyrate. We believe, therefore, that the influence of structure on reactivity in the Claisen condensation is threefold, exerting itself, not only on the extent of the initial anion formation, but also on the rate at which the anion reacts with the ester, and the extent to which the equilibrium is shifted by salt formation of the β-keto ester.

(15) Fischer and Dilthey, *Ann.*, **335**, 337 (1904).

but which could now be interpreted, in view of the analogous behavior of isovaleric ester in the Claisen condensation, as due in part, at least, to low acidity.[16]

(16) The tacit assumption is made that decreased acid strength hinders the alkylation reaction through its effect in lowering the equilibrium anion concentration, and while this assumption appears to be valid in the malonic ester series, this will not be the dominant effect where the acidity is of such a high order that dissociation, under the conditions of alkylation, is practically complete. The introduction of alkyl groups in barbituric acid is known from ordinary acidometric measurements, to depress the acid strength, the isopropyl group being particularly effective [Preiswerk, *Helv. Chim. Acta*, **6**, 192 (1923)], but at the same time the ease of alkylation increases and the isopropyl derivative reacts with great ease. Less extreme illustrations are to be seen in the acetoacetic and cyanoacetic ester series, in which the isopropyl derivatives undergo alkylation readily [Fischer, Rohde and Brauns, *Ann.*, **402**, 364 (1913)] and which differ also from malonic ester in that a second alkyl group is

We take pleasure in acknowledging the active interest of M. S. Kharasch throughout this work.

Summary

Sodium ethylate catalyzed hydrogen exchange reactions of various types of esters with deuteroalcohol are reported, and the influence of structure on acidity, as determined by the exchange reaction, is correlated with reactivity in condensation reactions.

introduced somewhat more readily than the first. In these instances the role of acidity is subordinate to the reactivity of the anions (or salts) toward alkyl halides which, as Conrad and Brückner pointed out [*Z. physik. Chem.*, **7**, 283 (1891)], varies inversely with the acid strength.

Mechanism of the Acid-catalyzed Dimerization of Anethole
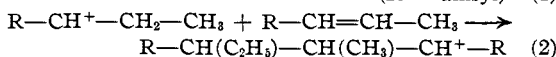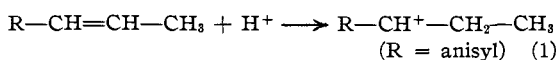
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In connection with the possibility of obtaining evidence regarding the mechanism of the acid-catalyzed polymerization of olefins with the aid of deuterium, a study has been made of the dimerization of anethole catalyzed by deuterium chloride in methyl alcohol solution. This case was considered favorable for a test of the Whitmore[1] theory of acid catalyzed polymerizations because (1) the experimental conditions can be adjusted so as to yield almost exclusively the dimer, (2) the structure of the dimer is known and is in conformity with the Whitmore hypothesis, (3) the structure of the dimer is such that it contains no hydrogen atoms likely to be readily exchangeable under the influence of acids. It was recognized that the monomer contains at least one such hydrogen atom, namely, that attached to the β carbon atom, and that the exchange of this hydrogen with the deuterium of the medium, if fast in comparison with the polymerization process, would obscure the phenomenon we wished to observe.

The formation of isoanethole,[2] according to the mechanism of Whitmore, is shown in the equations

$$R—CH=CH—CH_3 + H^+ \longrightarrow R—CH^+—CH_2—CH_3$$
$$(R = anisyl) \quad (1)$$
$$R—CH^+—CH_2—CH_3 + R—CH=CH—CH_3 \longrightarrow$$
$$R—CH(C_2H_5)—CH(CH_3)—CH^+—R \quad (2)$$

(1) Whitmore, *Ind. Eng. Chem.*, **26**, 94 (1934).
(2) The structure indicated for isoanethole is that established by Goodall and Haworth, *J. Chem. Soc.*, 2484 (1930).

$$R—CH(C_2H_5)—CH(CH_3)—CH^+—R \longrightarrow$$
$$R—CH(C_2H_5)—C(CH_3)=CH—R + H^+ \quad (3)$$
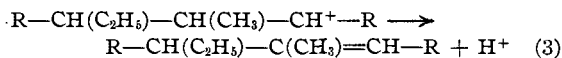
It will be noted that the proton added becomes incorporated in the ethyl side-chain of the dimer and that the proton eliminated is derived from the second molecule of anethole. A polymerization carried out with a deutero acid should therefore yield, if no exchange reactions occur, a product containing one atom of deuterium per molecule of dimer. In the more likely event that a hydrogen exchange reaction of the monomer accompanies the polymerization reaction, but is not too rapid in comparison, it is still possible to predict that the proportion of deuterium in the dimer formed in any small interval of time during the polymerization should be greater than that present in the monomer.

Experimental Part

The polymerization of anethole (Eastman Kodak Co. product, redistilled, b. p. 225° (750 mm.)) was carried out by refluxing with 5 N hydrochloric acid in methyl alcohol, according to the procedure of Goodall and Haworth, except that the methyl alcohol and the hydrochloric acid were partly deuterated. The deuteration was accomplished by treating methyl alcohol with pure heavy water, thus permitting an exchange of the hydroxyl hydrogen of the alcohol with the deuterium of the water, then removing water by repeated treatment with calcium oxide. Dry hydrogen chloride was passed into the anhydrous alcohol to yield a 5 N solution. Analysis for deuterium was carried out by combustion, after having first removed halogen by treatment with dry silver oxide, the water of combustion