

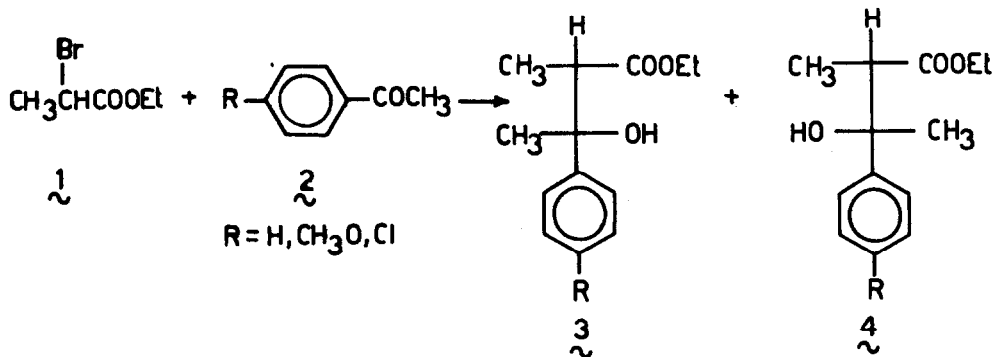
DIRECT EVIDENCE FOR EQUILIBRATION IN A REFORMATSKY REACTION AND FOR DEPENDENCE OF ITS STEREOSELECTIVITY ON ELECTRONIC SUBSTITUENT EFFECT

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Received in UK 21 January 1974; accepted for publication 8 February 1974)

Although the Reformatsky reaction¹ has been extensively investigated, there are still many uncertain points about its mechanism,² and particularly on whether the formation of diastereoisomeric hydroxyesters is under kinetic or thermodynamic control;^{1,2a,b,3} indirect evidence in favor or against equilibration of these products has been reported.³ We have now obtained direct evidence for an initial kinetic control and for a slower equilibration of the diastereoisomers in the reaction medium.

The condensation of ethyl α -bromopropionate (1) with acetophenone (2, R=H) in benzene in the presence of zinc, yields mixtures of the two diastereoisomeric β -hydroxyesters erythro (3, R=H) and threo (4, R=H), in which the former predominates.^{2b,4} However, when samples are withdrawn during the reaction, it is found that the ratio of 3, R=H to 4, R=H increases with reaction time until a constant value is reached (see Figure 1). The analogous reactions of *p*-chloro (2, R=Cl) and *p*-methoxyacetophenone (2, R=CH₃O) show a similar behaviour; although the extrapolated initial ratios between 3 and 4 and the rates are different, the ratios at equilibrium are very similar (ca. 7:3) in all three cases. Esters 3 and 4 were separated through preparative TLC (silica gel) and GLPC (Carbowax on Chromosorb G) and their mixtures were analyzed by GLPC (NPGS on Chromosorb W); after reaction times longer than 10 min, no products other than



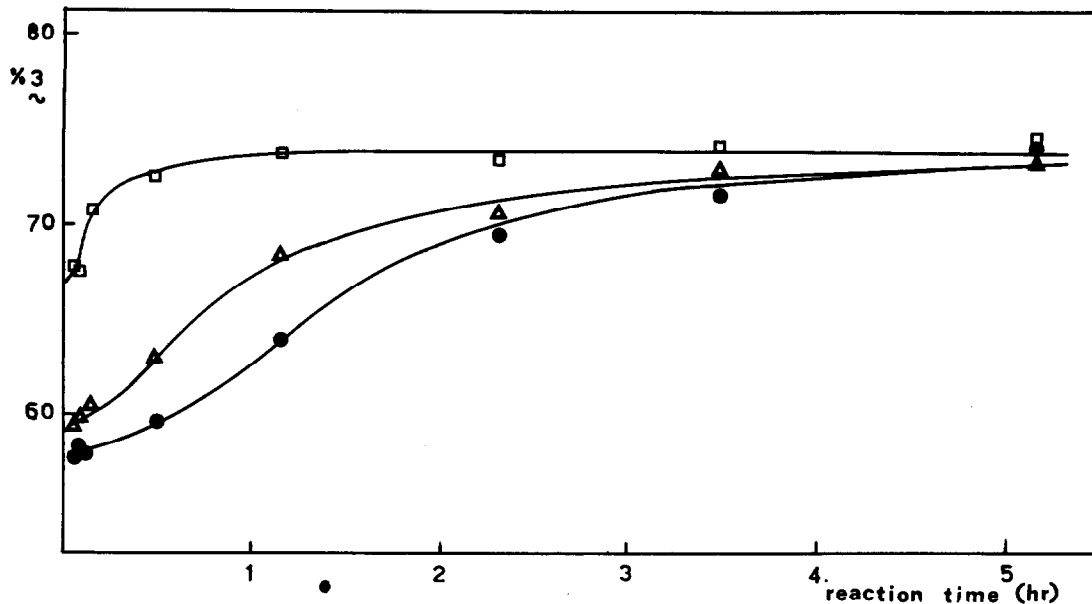
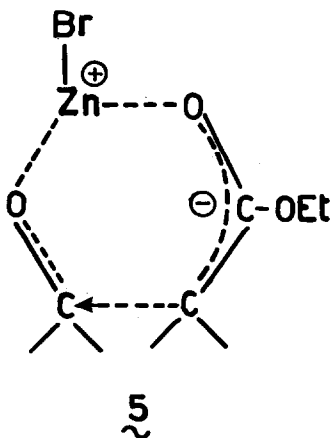


Figure 1. Variations of the percentage of erythro hydroxyesters 3 and 4 with reaction time.

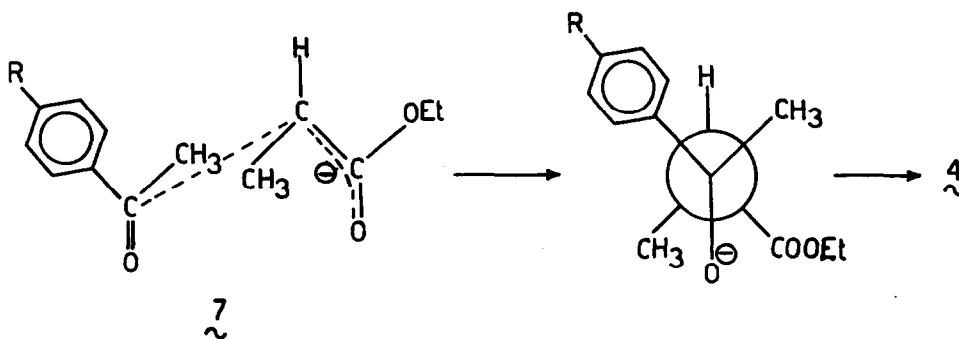
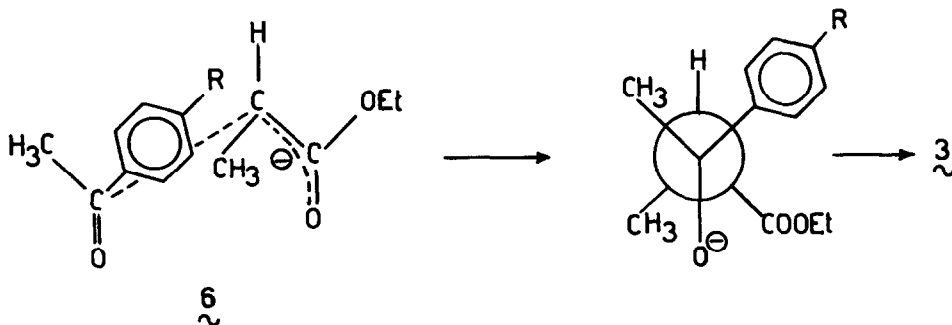
□, R=CH₃O; ▲, R=H; ●, R=Cl.

3 and 4 could be revealed. Structures and configurations were fully characterized by NMR spectroscopy.

Several kinds of transition states have been proposed for the addition step of the Reformatsky reaction, in which the nucleophile is supposed to attack the CO group of the reagent either as a pyramidal carbanion or as an enolate anion.² We assume as the most likely mechanism for this step the one^{2b,f} implying a six-membered transition state, as shown in 5, in which the counter-ion ZnBr⁺ coordinates with the two carbonyl oxygen atoms; the anion of the Reformatsky



reagent, in which the negative charge is delocalized between the carbonyl oxygen atom and the α -carbon atom, attacks the electron deficient p-orbital of the ketone with a gradual change in hybridization from p to sp^3 . It is reasonable to assume that the relative energies of transition state like 5 should closely resemble those of the final products. Analysis of the non-bonding repulsive interactions⁵ indicates that among all the possible conformational arrangements



of the transition states 5 that lead to staggered conformations of the reaction products in the C-C bond forming step, the preferred ones should be 6 leading to 3 and 7 leading to 4, and between these 6 in accordance with the observed prevalence of the erythro hydroxyester 3.

The curves in Figure 1 clearly show the existence of an equilibration between 3 and 4; it is also clear that the equilibrium does not depend on the substituent on the aromatic ring, whereas this substituent influences the initial ratios between 3 and 4 and the equilibration rate. The increase in this rate with the electron-donating properties of the aryl moiety is consistent with the fact that electron donation facilitates the heterolytic rupture of the newly formed C-C bond and therefore the retro-Reformatsky reaction. Both kinetic and thermodynamic control favor the formation of the erythro product. It is also likely that in some of the cases reported in the literature, the diastereoisomeric compositions reported as due to a kinetic control are rather equilibrium ratios.

Although the concurrence of the primary kinetically controlled formation of the products and of the equilibration between them makes an exact extrapolation of the curves in the

Figure 1 to the initial values of the $\frac{3}{4}$ ratio somewhat uncertain, it is quite evident that this ratio decreases in the order *p*-methoxy > unsubstituted > *p*-chloroderivative. An electron-donating substituent such as the *p*-methoxy group would be expected to increase the rate of the initial nucleophilic coordination of the ketonic oxygen on zinc, but to decrease that of the subsequent electrophilic attack on the carbanion. The transition state geometry should therefore be closer to that of the final product in the case of the *p*-methoxy derivative, than in those of the unsubstituted and chloro derivatives, and the kinetic ratios of products more similar to the thermodynamic ones.

This work was supported in part by a grant from the Consiglio Nazionale delle Ricerche. We thank Professor G.Berti for the useful discussion.

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