Exchange Reactions of Carboxylic Acid Salts. Kinetics and Mechanism[1,2]

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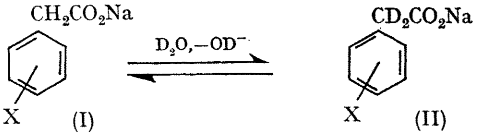
Summary Kinetic results are reported for the exchange of the α-protons of substituted sodium phenylacetates in alkaline D_2O which indicate that a C–H bond is broken in the rate-determining step.

WE have recently reported on the unexpectedly ready exchange of the α-protons of a series of carboxylic acid salts in alkaline D_2O, and its use to prepare α-deuteriocarboxylic acids.[3] We now report on the kinetics of exchange of a series of substituted sodium phenylacetates† in order to obtain a more detailed picture of the mechanism of the reaction (Eq. 1).

Rates were obtained by standard n.m.r. techniques[4] on a series of substituted sodium phenylacetates and the Table contains the kinetic results of these exchanges. A plot of log k against σ values of the substituents yielded a ρ value of $+\ 2{\cdot}06 \pm 0{\cdot}06$ at 50° by the least-square method. This ρ value indicates a rather important development of a negative charge in the transition state. It compares favourably with ρ values of $2{\cdot}5 \pm 0{\cdot}5$ obtained by several groups[5] for the E_2 eliminations of β-phenylethyl derivatives.

Comparison of runs 1 and 2 reveals an isotope effect in the reverse reaction of equation 1, with $k_H/k_D = 4{\cdot}4$. This is a clear indication that a C–H bond is broken in the rate-determining step.

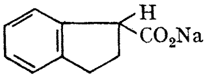
Positive salt effects were also observed when the exchange was carried out in solution of both sodium chloride and sodium perchlorate,′ indicating strongly that the rate-determining step involves reaction between two species of similar charge,[6] in this case between arylacetate anion and deuteroxide anion. In addition, the reaction shows a clean first-order dependence on deuterioxide concentration and without added base, the reaction is extremely slow as no



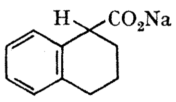
(I) (II) (1)

X = (a) H; (b) *p*-OMe; (c) *p*-Me; (d) 3,4-$(MeO)_2$; (e) *m*-MeO; (f) *p*-Cl; (g) *m*-Cl; (h) *p*-CN

$PhCHR{\cdot}CO_2Na$ (III) a; R=Me, b; R=Et, c; R=Pr^i



(IV)



(V)

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† The lithium and potassium salts with their respective deuterioxides gave the same results, within experimental error.

exchange was observed after 10 days at 85° for compound (Ia). Under the standard conditions, the exchange at this temperature has a half-life of 14 min.

Rates of exchange of 1M *substituted sodium phenylacetate in* 0·63M-NaOD–D_2O

Run No.	Sodium phenylacetate	$k \times 10^4$ min.$^{-1}$ [a]
	50°	
1	(Ia)	9·2
2[a]	(II)	2·1
3	(Ib)	2·8
4	(Ic)	3·5
5	(Id)	4·1
6	(Ie)	15·8
7	(If)	25·1
8	(Ig)	42·6
9	(Ih)	1050
	95°	
10	(Ia)	1152
11	(IIIa)	4·32
12	(IIIb)	0·50
13	(IIIc)	0·028
14	(IV)	377
15	(V)	9·98

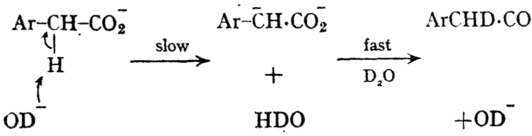
[a] Rate constants are the average of at least three independent determinations. The standard deviation is not greater than 5%.

[b] Exchange of sodium $[\alpha\alpha\text{-}^2H_2]$phenylacetate by NaOH–$H_2O$ under standard conditions.

The Table also shows the striking influence of substituents α to the carboxylate. The presence of a methyl group reduces the rate of exchange by a factor of 270 (run 11). An ethyl group (run 12) reacts 2300 times slower than sodium phenylacetate whereas with an isopropyl group (run 13) the exchange is 42,000 times slower. These decreases in the rates of exchange are thought to be caused by steric effects which affect the ease of formation of a carbanion in the rate-determining step in two ways. The presence of a bulky hydrophobic group prevents the approach of the base to the α-proton and decreases the stabilization of the carbanion by the solvent shell. The other contribution to steric effects is the severe interaction between the α-alkyl group and the *ortho*-hydrogens as the carbanionic character develops. This interaction decreases the stabilization of the carbanion by preventing coplanarity with the ring.

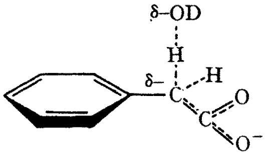
The rates of exchange for compounds (IV) and (V) demonstrate this effect. These compounds have a substituent α to the carboxylate and a *ortho*-substituent. The steric interactions between the *ortho*-position and the alkyl group is decreased to a large extent and, despite the adverse inductive effect of the *ortho*-alkyl group, an acceleration relative to (III) is observed. The sodium salt of 1,2,3,4-tetrahydronaphthoic acid (V) is 20 times more reactive than sodium α-ethylphenylacetate (IIIb). This is even more dramatic with sodium indanecarboxylate (IV) where the geometrical requirements force the carbanion to be coplanar with the ring: (IV) reacts 460 times faster than (IIIb).

The results obtained in this study support a mechanism involving an α-carbanion carboxylate intermediate (eq. 2). The same conclusion has been reached by Bottini and Davidson[7] regarding the exchange of sodium methylenecyclopropane carboxylates, and suggested by Terrill and Reilley[8] in a study of metal chelates of amino-acids.



$$\mathrm{Ar{-}CH{-}CO_2^-}\ (\mathrm{H} \leftarrow \mathrm{OD^-}) \xrightarrow{\text{slow}} \mathrm{Ar{-}\bar{C}H{\cdot}CO_2^-} + \mathrm{HDO} \xrightarrow[\mathrm{D_2O}]{\text{fast}} \mathrm{ArCHD{\cdot}CO_2} + \mathrm{OD^-} \qquad (2)$$

A final detail regards the degree of proton transfer in the transition state of mechanism 2. Since OD^- is a stronger base than OH^- by a factor of 1·88 at 80°,[5] the primary isotope effect has a maximum value of 4·4 and could be as low as 2·3. Thus, the proton must be either somewhat less than half transferred or somewhat more than half transferred in the transition state. Steffa and Thornton[5] have shown that proton transfer is more than 50% complete in the E_2 elimination of β-arylethyl derivatives which have a ρ value of 2·0—2·6; this leads us to favour the transition state (VI) with proton transfer to deuteroxide ion more than half completed and with considerable development of negative charge on the α-carbon atom.



(VI)

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[1] Part of the series, Aspects of Stable Isotope Chemistry. For previous part see J. G. Atkinson, M. O. Luke, and R. S. Stuart, *Chem. Comm.*, 1969, 283.

[2] Presented in part at the 35th Annual Congress of l'Association Canadienne-Française pour l'Avancement des Sciences, Sherbrooke, Québec, November 3—4, 1967.

[3] J. G. Atkinson, J. J. Csakvary, G. T. Herbert, and R. S. Stuart, *J. Amer. Chem. Soc.*, 1968, **90**, 498.

[4] See, for example, J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, 1965, **87**, 5050.

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[7] A. T. Bottini and A. J. Davidson, *J. Org. Chem.*, 1965, **30**, 3302.

[8] J. B. Terrill and C. N. Reilley, *Analyt. Chem.*, 1966, **38**, 1876.