Preprotonation of the Substrate by Protonated Alkaloid in Asymmetric Electrosynthesis

By MICHEL JUBAULT,* EUGÈNE RAOULT, and DANIEL PELTIER
(*Laboratoire d'Electrochimie, Université de Rennes, Avenue du Général Leclerc, 35042 Rennes Cédex, France*)

Summary Preprotonation of the substrate by the protonated adsorbed inductor is shown to occur in the asymmetric electroreduction of methyl phenylglyoxylate oxime in the presence of strychnine.

THERE has been considerable recent interest in asymmetric electrosynthesis. Among the various methods investigated, the electrochemical reduction of prochiral ketones[1,2] (or oximes[3]) to optically active alcohols (or amines) in the presence of a very small amount of an adsorbed alkaloid has been extensively studied. The mechanism of the asymmetric induction has been discussed and protonation of an intermediate carbanion (or its enolic form) by the protonated alkaloid acting as a chiral acid has been suggested.[1] We report here experiments which show that the strychninium ion may act as a proton donor in the preprotonation preceding the electron transfer during the asymmetric electroreduction of methyl phenylglyoxylate oxime (**1**).

$$\underset{(\mathbf{1})}{PhC(=NOH)CO_2Me} \xrightarrow[\text{strychnine}]{4e,\ 4\ H^+} \underset{(\mathbf{2})}{PhCH(NH_2)CO_2Me}$$

First, (**1**) was reduced potentiostatically at a mercury cathode, in aqueous buffer solutions, at various pH values and in the presence of strychninium sulphate. After completion of the electrolysis, the optical rotation of the solution was measured and the optical yield calculated by reference to optically pure (**2**).[4] The results (Table) show that asymmetric induction occurs in mild acidic or basic solutions.

TABLE. Effect of pH on the asymmetric electroreduction of (**1**) (24·2 mmol) in aqueous buffer–ethanol (1 : 1) solutions (100 ml), in the presence of strychninium sulphate (0·0329 mmol).

pH of aq. buffer	Potential/V (*vs.* S.C.E.)	Optical yield (%)[a]
ca. 0[b]	−0·70	0·0
	−1·00	0·0
1·8[c]	−0·85	1·1
2·8[d]	−0·90	4·6
4·8[e]	−1·00	3·9—4·3
	−1·15	4·0
	−1·30	4·1
9·8[f]	−1·10	4·7
	−1·30	4·9
	−1·45	4·6

[a] The (*R*)-(−)-enantiomer was predominant. [b] 1N H_2SO_4. [c] Britton–Robinson buffer, prepared by addition of 1N NaOH to a solution of AcOH (0·2M), H_3PO_4 (0·2M) and H_3BO_3 (0·2M). [d] $ClCH_2CO_2H$ (0·5M) + $ClCH_2CO_2Na$ (0·5M). [e] AcOH (0·5M) + AcONa (0·5M). [f] $AcONH_4$ (0·5M) + NH_4OH (0·5M).

As a comparison, preparative electroreduction of (**1**) was also performed in the presence of *N*-methylstrychninium iodide which is not a protonating species; very poor optical yields [<0·5% of (*S*) (+)-phenylglycine methyl ester (**2**)] were obtained. Similarly, if strychninium ion is replaced by the *N*-methyl derivative in the asymmetric electroreduction of phenylglyoxylic acid[2] or its oxime derivative,[3] the optical yield decreases from *ca.* 20% to *ca.* 0. A similar result was obtained in the case of acetylpyridines.[1]

The polarographic behaviour of (**1**) was also examined in buffer solutions, both in the absence and the presence of inductor. The polarograms show a single wave, the height and position of which are pH-dependent, thus suggesting that reduction of the protonated oxime $PhC(\overset{+}{N}HOH)CO_2Me$ is occurring. In acidic solutions, the preprotonation of (**1**) is fast; the limiting polarographic current (i_l) is then diffusion-controlled and pH-independent (Figure). In slightly basic solutions, the preprotonation

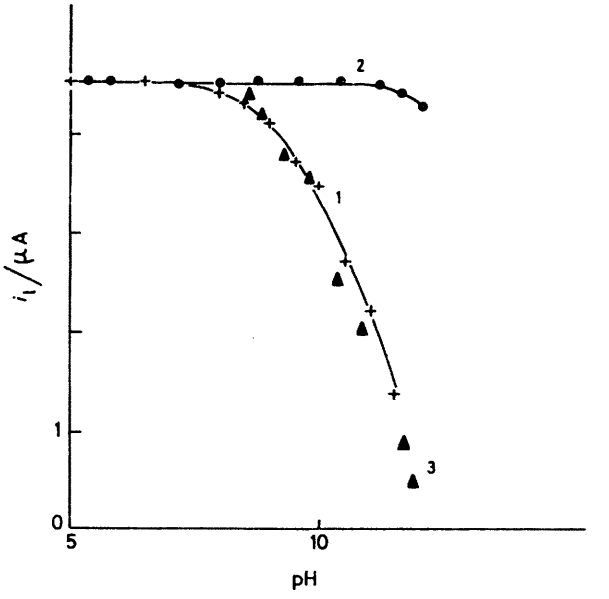

FIGURE. pH-dependence of the limiting polarographic current i_l for $PhC(=NOH)CO_2Me$ (5×10^{-4}M) in Britton–Robinson buffer solutions containing 10% EtOH: (1) (+) without added alkaloid; (2) (●) with strychnine (9×10^{-5}M); (3) (▲) with *N*-methylstrychninium iodide (9×10^{-5}M).

of (**1**) is not sufficiently fast for this to be the case; a kinetic wave is then observed and i_l decreases as the pH increases (Figure, curve 1). However, in the same pH region, if strychninium ion is added, the wave-height is increased and i_l does not decrease (Figure, curve 2), thus indicating that strychninium ion acts as a proton donor in the preprotonation of (**1**). This is in good agreement with the fact that *N*-methylstrychninium ion, which cannot act as a proton donor, does not enhance the limiting current i_l (Figure, curve 3).

The asymmetric induction might result from the stereoselective preprotonation of the two enantiotopic faces of the oxime double bond by the protonated alkaloid acting as a chiral acid. The 'adduct' formed between the substrate and the inductor during this chemical reaction should exist in this form until the final protonation of the intermediate carbanion by any protonating species present at the electrode surface. This picture of the initial step of the asymmetric induction process (preferential presentation of one of the two enantiotopic faces) is like that proposed by Horner.[5] However, we have provided further evidence here for the mechanism of the asymmetric induction: the preferential orientation of the substrate in comparison to the adsorbed inductor might be enhanced by the preprotonation.

(*Received*, 21*st November* 1978; *Com.* 1256.)

[1] J. Kopilov, E. Kariv, and L. L. Miller, *J. Amer. Chem. Soc.*, 1977, **99**, 3450.
[2] M. Jubault, E. Raoult, and D.Peltier, *Electrochim. Acta*, 1974, **19**, 865.
[3] M. Jubault, E. Raoult, J. Armand, and L. Boulares, *J.C.S. Chem. Comm.*, 1977, 250.
[4] Optically pure (*R*)-(−)-phenylglycine methyl ester (**2**) was prepared by the method of H. Reihlen and L. Knöpfle, *Annalen*, 1936, **523**, 205. Its $[\alpha]_D^{25}$ values were measured in the various aqueous buffer–ethanol solutions used in this work (c = 0·4 g per 100 ml); found: −161° (H_2SO_4); −165° (chloroacetate); −164° (acetate); −154° (ammonium buffer).
[5] L. Horner and D. Degner, *Electrochim. Acta*, 1974, **19**, 611; D. Brown and L. Horner, *Annalen*, 1977, 77.