The Reduction of Acetamide by Solvated Electrons Electrochemically Generated in Lithium Chloride–Hexamethylphosphoramide

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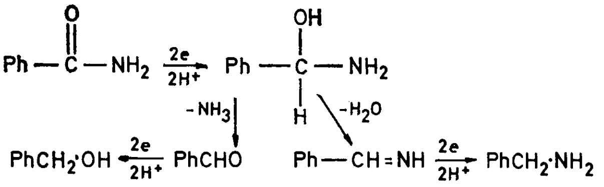
The reduction of acetamide by electrochemically generated electrons in the presence of a proton donor has been studied in the LiCl–hexamethylphosphoramide system. The ratio of the two products, ethanol and ethylamine, was found to depend upon the acid-sensitive decomposition route of the *gem*-amino-alcohol intermediate. Sufficiently acidic conditions could be achieved using hydrochloric acid as proton donor to make ethylamine the major product. This relatively high acidity did not cause excessive hydrogen evolution.

UNSUBSTITUTED aliphatic amides are reducible only under highly forcing conditions, *e.g.*, the corresponding amine is produced by reaction with lithium aluminium hydride or diborane in tetrahydrofuran.[1] It has been suggested that the first step in this process is dehydration of the amide to form the nitrile which is then reduced to the amine.[2] Aliphatic or aromatic substituents on the nitrogen atom facilitate reduction.[3] *N*-Phenyl substituted compounds have been reduced using sodium in liquid ammonia,[4] the product being the aldehyde or alcohol and not the amine. Unsubstituted aromatic amides have also been reduced under similar conditions,[5] although such compounds are quite readily reducible and milder conditions are normally employed to prevent simultaneous reduction of the aromatic system. In fact, compounds such as benzamide are sufficiently activated to be reducible electrochemically in an acid aqueous medium, the product being the corresponding amine[6] or a mixture of the amine and alcohol[7,8] depending upon the decomposition route of the *gem*-amino-alcohol intermediate (Scheme 1).



SCHEME 1

In the case of the amides of certain heterocyclic carboxylic acids, the reaction stops at the aldehydic stage

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[1] (*a*) N. G. Gaylord, 'Reduction with Complex Metal Hydrides,' Interscience, 1956, p. 544; (*b*) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 1964, **86**, 3566.

[2] M. S. Newman and T. Fukunaga, *J. Amer. Chem. Soc.*, 1960, **82**, 693.

[3] N. I. Gavrilov and A. V. Koperina, *Zhur. obshchei Khim.*, 1939, **9**, 1394 (*Chem. Abs.*, 1940, **34**, 1615).

[4] A. J. Birch, J. Cymerman-Craig, and M. Slaytor, *Austral. J. Chem.*, 1955, **8**, 512.

[5] M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, 1959, **81**, 4278.

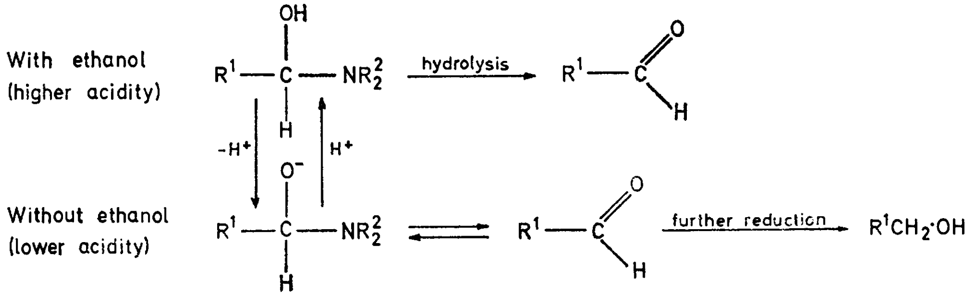
[6] A. V. Koperina and N. I. Gavrilov, *J. Gen. Chem.* (*U.S.S.R.*), 1947, **17**, 1651.

[7] A. V. Koperina and M. M. Klyuchareva, *J. Gen. Chem.* (*U.S.S.R.*, 1941, **11**, 51.

[8] L. Horner and H. Neumann, *Chem. Ber.*, 1965, **98**, 3462.

due to the high stability of the hydrated form of the aldehyde at low pH.[9-12]

While the present work was in progress, details were published of the selective reduction of aliphatic amides to aldehydes or alcohols using electrochemically generated solvated electrons in the methylamine–lithium chloride system.[13] If additional proton donor was not present during electrolysis, the alcohol was formed, whereas in the presence of ethanol, it was suggested that the reduction stopped at the amino-alcohol stage and subsequent work-up led to the aldehyde. It was proposed that acid–base equilibrium (Scheme 2) was the determining factor.



Scheme 2

However, no cell divider was employed between anolyte and catholyte and therefore the acidic products of the anode reaction would be available to influence the course of the reduction in an uncontrolled manner. This would be particularly important in view of the fact that a large quantity of electricity was passed in each experiment. Therefore, the ratio of methylammonium ion and methylamide ion and the proton availability would change considerably during the course of the electrolysis. The amine product was not observed and, in the case of the unsubstituted amides, the coulomb yields were very low.

It is clear that it would be desirable to develop good methods for the reduction of non-substituted aliphatic amides selectively to the amine or alcohol without involving the use of hazardous materials.

It has been shown that solvated electrons in the LiCl–hexamethylphosphoramide (HMPA) system are highly active reducing agents and they are readily formed by electrochemical means.[14,15] This system has the additional advantage that large quantities of proton donor (67 mole % of ethanol) can be tolerated without the production of large quantities of hydrogen, a unique property for a system containing solvated electrons. This property could be of particular utility in the reduction of amides since the decomposition routes of the intermediates depend markedly upon the acidity of the medium.

EXPERIMENTAL

The solvent, HMPA, was purified by vacuum distillation (twice), collecting the middle fraction only. Lithium chloride, used as supporting electrolyte, was dried by melting. The solutions were prepared in a nitrogen-filled dry box. The other reagents were dried in a vacuum oven and used without further purification since they were found to be free of impurities when analysed by v.p.c. The concentration of the support electrolyte was fixed at 0·3M to maximise the conductivity. For most experiments, vitreous carbon cathodes were employed to minimise hydrogen evolution under the more strongly acidic conditions used, and to eliminate penetration of lithium into the cathode material.

The electrolysis cell was of the conventional three-electrode type with a sintered glass diaphragm separating the anolyte from the catholyte. The reference electrode used to check the electrode potential, consisted of a piece of freshly cut lithium metal immersed in a saturated solution of lithium chloride in HMPA. A vitreous carbon rod of 3 mm diameter sealed in glass with only the flat disc-shaped surface exposed, served as the cathode, and a platinum foil as the anode. During electrolysis the catholyte was stirred by a glass-enclosed magnetic stirring bar.

All electrolyses were carried out using Chemical Electronics 150V of type TR 70/2A potentiostats, either connected in the usual way for potential controlled operation or as a constant current supply. The identification of the products was carried out using a combination of v.p.c. and mass spectroscopy. Quantitative analysis was by v.p.c., comparing the experimental results against synthetic samples of approximately the same composition.

RESULTS AND DISCUSSION

Acetamide dissolved in HMPA together with a source of protons was reduced by solvated electrons produced by electrolysis at constant current. Preliminary experiments were carried out to determine the most suitable proton donor. Ethanol was rejected since it is a possible reduction product, and other aliphatic alcohols gave rise to copious gel formation. Water also led to gel production in addition to considerable gas evolution. Glacial acetic acid, oxalic acid, and hydrochloric acid

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[9] H. Lund, *Acta Chem. Scand.*, 1963, **17**, 972, 1077, 2325.

[10] P. E. Iversen and H. Lund, *Acta Chem. Scand.*, 1967, **21**, 279.

[11] P. E. Iversen and H. Lund, *Acta Chem. Scand.*, 1967, **21**, 389.

[12] P. E. Iversen, *Acta Chem. Scand.*, 1970, **24**, 2459.

[13] R. A. Benkeser, H. Watanabe, S. J. Mels, and M. A. Sabol, *J. Org. Chem.*, 1970, **35**, 1210.

[14] H. W. Sternberg, R. E. Markby, I. Wender, and D. M. Mohilner, *J. Amer. Chem. Soc.*, 1969, **91**, 4191.

[15] H. W. Sternberg, R. E. Markby, I. Wender, and D. M. Mohilner, *J. Amer. Chem. Soc.*, 1967, **89**, 186.

were found to be satisfactory. In the latter case, the white solid obtained by passing dry gaseous HCl through pure HMPA was employed by dissolving an appropriate amount in the electrolyte. This solid was presumably the 1 : 1 addition complex.[16]

The reduction products as identified by v.p.c. and mass spectroscopy were ethanol and ethylamine. In addition, a strong smell of ammonia was noticed from electrolysed catholyte. Table 1 gives details of the results for the different experimental conditions employed. Under standard conditions (experiments 2 and 5) ethanol was the major product, ethylamine being found in only 10% yield. The total coulomb yield of *ca.* 50% indicates that large concentrations of acetic acid can be used without excessive hydrogen evolution. No attempt was made to account for the remaining current.

TABLE 1

Electrolytic reduction of acetamide

Expt. no.	Experimental conditions	% Coulomb yield (after 200 coulombs)	Relative amounts Ethylamine (%)	Ethanol (%)
1	Low temperature (11 °C)	53	43	57
2	Normal	46	10	90
3	Conc. acetic acid = 1·2M	45	8	92
4	25 mA cm^{-2}	66	51	49
5	Normal	50	10	90
6	Oxalic acid (0·1M) as proton donor	31	32	68
7	Low temperature (11 °C); 25 mA cm^{-2}	69	39	61
8	HCl as proton donor; 11 °C	49	61	39

Normal experimental conditions; 0·3M-lithium chloride in HMPA, 1·5M (0·37 gm) acetamide, 0·4M-acetic acid as proton donor, current density of 125 mA cm^2 and a temperature of *ca.* 25 °C electrode area 0·08 cm^2.

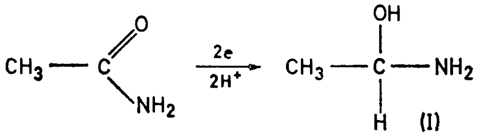
TABLE 2

Alternative decomposition routes for the amino-alcohol intermediate

		Acidity	Products of decomposition	Following reaction	Final product	Examples ref.
	↗	Low	$NHR^2R^3 + R^1C(\colon O)N$ Amine Aldehyde	Further reduction	$R^1CH_2{\cdot}OH$ Alcohol	This work, 4, 7, 8, 10, 13, 18
$R^1CH(OH)NR^2R^3$ Amino-alcohol	→	Intermediate[a]	$R^1CH(OH)NR^2R^3$ Stable amino-alcohol	Hydrolysis (working-up)	R^1CHO Aldehyde	4, 13
	$\searrow$ $R^3 = H$	High	$H_2O + R^1CH{=}NR^2$ Water Schiff base	Further reduction	$R^1CH_2NHR^2$ Amine	This work, 7, 8, 18

[a] Strictly, the formation of a stable amino-alcohol intermediate will not only depend on the acidity of the medium but also on the nature of R¹ since the cleavage of the carbon–oxygen or the carbon–nitrogen bond should be greatly affected by inductive effects.

A lower temperature (experiments 1, 7, and 8), lower current density (experiments 4 and 7) and the use of a more acidic proton donor (experiments 6 and 8), substantially increase the ratio of amine to alcohol such that in experiment 8 the amine was the major product. The lower yield obtained in experiment 6 is probably due to reduction of the proton donor itself.[17]



$$CH_3-C(=O)NH_2 \xrightarrow[2H^+]{2e} CH_3-C(OH)(H)-NH_2 \quad \text{(I)} \qquad (1)$$

The first step in the mechanism of reduction of amides by solvated electrons or by direct cathodic reduction has been assumed to be the formation of the *gem*-amino-alcohol derivative.[4-13] In the present case, this will be reaction (1). The products are then determined by the stability and the decomposition routes of (I).

The existence of the *gem*-amino-alcohol intermediate has also been postulated in the electroreduction of oxaziridines in aqueous solutions,[18] where it was found that low temperatures and pH favour the dehydration of this intermediate to form the corresponding imine which is further reduced to the amine, while high pH favours the formation of the aldehyde (loss of amine) and further reduction to the alcohol. This mechanism is in accordance with studies on the hydrolysis of Schiff bases [19] where the equilibria (2) and (3) exist.

Considering as exceptions those cases where the amino-alcohol is hydrolysed to the *gem*-diol [9-12] due to particular properties of the system, it is possible to generalise the decomposition pattern of the intermediate in terms of the acidity of the medium, as shown in Table 2. Consequently, the remaining steps in the present reduction process were (4) and (5). The route to ethanol will be base catalysed,[4] whereas the other route will be favoured by acidic conditions and low temperatures. A lower current density will lead to a lower concentration of solvated electrons and will favour more acidic conditions near the electrode, which agrees with the observed trend in the product ratio.

These results show that quite highly acidic conditions

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[16] H. Normant, *Angew. Chem. Internat. Edn.*, 1967, **6**, 1046.

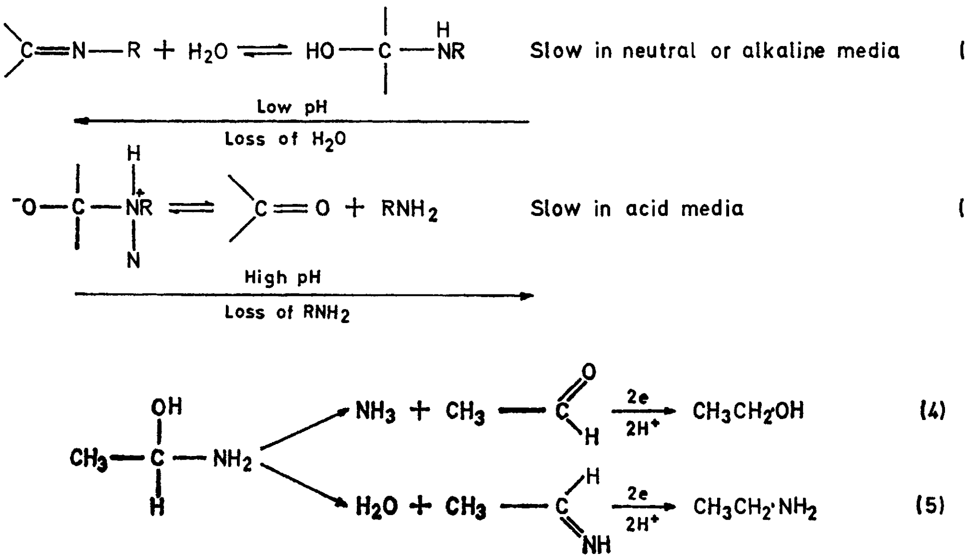
[17] T. Kuwata, Jap.P. 9966/1958 (*Chem. Abs.*, 1960, **54**, 5298).

[18] H. Lund, *Acta Chem. Scand.*, 1969, **23**, 563.

[19] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1963, **85**, 2843.

can be maintained in the LiCl–HMPA system even in the presence of solvated electrons.

Clearly this must be a kinetic effect, the reaction of solvated electrons in HMPA with proton donors being slow compared to the rate of their reaction with the organic substrate. This property is not shared by other systems supporting solvated electrons, *e.g.*, liquid ammonia and amines, in which rapid hydrogen evolution occurs from proton donors. This unique attribute of HMPA might well be usefully employed in other synthetic situations.



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