Electrochemistry of 2-Bromo-2-methylpropanamides. Reduction Mechanism and Cyclocoupling Reaction with Amide Solvents

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The electrochemical reduction of a series of secondary and tertiary α-bromoisobutyramides has been studied in dipolar aprotic solvents. A carbanion is formed at the mercury electrode as a consequence of two-electron C–Br bond cleavage. Voltammetry and macroelectrolysis point to a self-protonation mechanism, the carbanion undergoing protonation by a parent molecule to yield the isobutyramide. Concurrently, tertiary 2-bromoamides undergo 1,2-elimination to yield an αβ-unsaturated amide, while secondary 2-bromoamides are deprotonated at the nitrogen atom, affording a bromo-containing anion. The decay of the latter is strongly dependent on the solvent and the substituent at nitrogen. In acetonitrile, elimination and fragmentation products are identified in the electrolysed solution. On the other hand, in *N,N*-dimethylformamide or *N,N*-dimethylacetamide, the bromo-containing anion is eventually cyclocondensed onto the carbonyl group of the amide solvent, to yield an oxazolidin-4-one derivative. Preliminary data suggest that an analogous cyclocoupling reaction takes place when the reduction is carried out in 1-methyl-2-pyrrolidone.

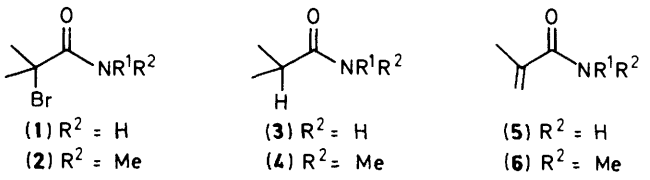
Base-promoted reactions of 2-halogenocarboxamides afford α-lactams,[1] or unrearranged [2,3] and partially rearranged [3,4] self-condensation products. Furthermore, cross-condensation with amide partners leads to competitive formation of oxazolidinone derivatives.[5,6] Even if complex mixtures are often obtained, regioselectivity based both on the character of the halide function and the substituent at the nitrogen atom was observed, granting a peculiar reactivity to 2-bromoamides with a tertiary carbon atom.

To promote deeper knowledge of the parameters affecting the behaviour of 2-halogenoamides and to gain some insight into the reaction mechanism, we have carried out an electrochemical investigation on this type of compound, whose electrochemical behaviour has been little studied.[7] Our electrochemical approach was based on the grounds that electroreduction of organic molecules can produce basic species that, under suitable conditions, may deprotonate the parent compound according to the so-called self-protonation mechanism.[8] This possibility is based on a knowledge of the behaviour of the title compounds in the presence of a strong exogenous base (*i.e.* H^- of sodium hydride) and is supported by preliminary electrochemical data.[9]

In this paper we report the results obtained with a selected series of 2-bromo-2-methylpropanamides in which the amide moiety was modulated by varying both substituents at the nitrogen. Accordingly, we studied the electroreduction of the following substrates: (i) *N*-phenyl- and *N*-benzyl-2-bromo-2-methylpropanamides (**1a,b**); (ii) the corresponding *N*-methyl-*N*-phenyl and *N*-methyl-*N*-benzyl analogues (**2a,b**); (iii) *N*-cyclohexyl- and *N*-t-butyl-2-bromo-2-methylpropanamides (**1c,d**), whose base-promoted behaviour was unknown or, respectively, little known.[1b,5a]

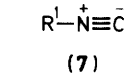
Our previous findings on the incorporation of *NN*-dimethylformamide (DMF) into some reaction products [6,9] prompted us to investigate further the behaviour of DMF and to check whether the alternative dipolar aprotic solvents *NN*-dimethylacetamide (DMA) and 1-methyl-2-pyrrolidone (MP) enter into reaction with 2-bromoamides.

† In partial fulfilment for the requirements for a Doctoral Thesis, University of Ferrara.

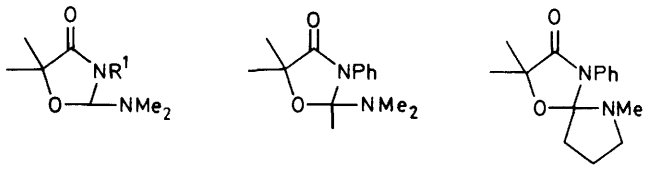


(**1**) R^2 = H
(**2**) R^2 = Me
(**3**) R^2 = H
(**4**) R^2 = Me
(**5**) R^2 = H
(**6**) R^2 = Me

a; R^1 = Ph
b; R^1 = $PhCH_2$
c; R^1 = C_6H_{11}
d; R^1 = Bu^t



(**7**)



(**8**) (**9**) (**10**)

Experimental

Solvents and Electrolytes.—*NN*-Dimethylformamide (Erba) was vacuum distilled. Acetonitrile (Merck), *NN*-dimethylacetamide (Erba), and 1-methyl-2-pyrrolidone (Fluka) were used without distillation. Each solvent was stored over neutral alumina (Merck, activity grade 1) activated by heating at 350 °C for 24 h. Tetrabutylammonium perchlorate was prepared by neutralizing the corresponding hydroxide (Fluka) with perchloric acid. Tetrabutylammonium perchlorate, tetrabutylammonium bromide (Fluka), and tetraethylammonium perchlorate (Erba) were recrystallized from water–ethanol, acetone–diethyl ether, and ethanol, respectively, and carefully dried under vacuum at 60 °C. Tetrabutylammonium hydroxide was dried under vacuum over P_2O_5.

Known Compounds.—The following compounds were prepared as described in the literature; only unreported spectral data are given.

2-Bromo-2-methyl-*N*-phenyl- and -*N*-benzyl-propanamides (**1a**,**b**).[2,5b]

2-Bromo-2-methyl-*N*-t-butylpropanamide (**1d**),[1a] δ($CDCl_3$) 1.35 (9 H, s, Bu^t), 1.9 (6 H, s, Me_2C), and 6.6 (1 H, br s, NH).

2-Bromo-2,*N*-dimethyl-*N*-phenylpropanamide (**2a**),[10] δ($CDCl_3$) 1.75 (6 H, s, Me_2C), 3.35 (3 H, s, MeN), and 7.35 (5 H, m, Ph).

2-Methyl-*N*-phenylpropanamide (**3a**),[11] δ($CDCl_3$) 1.2 (6 H, d, Me_2C), 2.5 (1 H, sept, CH), and 7.1—7.7 (6 H, m, NH, Ph).

2-Methyl-*N*-benzylpropanamide (**3b**),[12] δ($CDCl_3$) 1.14 (6 H, d, Me_2C), 2.3 (1 H, sept, CH), 4.38 (2 H, d, CH_2), 6.2 (1 H, br t, NH), and 7.26 (5 H, s, Ph).

2-Methyl-*N*-cyclohexylpropanamide (**3c**),[13] $\nu_{max.}$ 3 440, 1 690, and 1 510 cm^{-1}; δ($CDCl_3$) 1.15 (6 H, d, Me_2C), 1.0—2.1 (10 H, m, C_6H_{10}), 2.32 (1 H, sept, CH), 3.8 (1 H, m, HCN), and 5.4 (1 H, br m, NH).

2-Methyl-*N*-t-butylpropanamide (**3d**),[14] δ($CDCl_3$) 1.1 (6 H, d, Me_2C), 1.3 (9 H, s, Bu^t), 2.2 (1 H, sept, CH), and 5.5 (1 H, br s, NH).

2,*N*-Dimethyl-*N*-phenylpropanamide (**4a**)[15] was obtained from isobutyric acid and *N*-methylaniline in the presence of dicyclohexylcarbodi-imide.

Methacrylanilide (**5a**).[16]

N-Benzylmethacrylamide (**5b**),[17] δ($CDCl_3$) 1.98 (3 H, s, MeC=), 4.5 (2 H, d, H_2CN), 5.3 and 5.7 (2 H, two unresolved m, H_2C=), 6.2 (1 H, br t, NH), and 7.3 (5 H, s, Ph).

N-Cyclohexylmethacrylamide (**5c**),[16] $\nu_{max.}$($CDCl_3$) 3 300, 1 655, and 1 530 cm^{-1}; δ($CDCl_3$) 1.0—2.0 (10 H, m, C_6H_{10}), 1.93 (3 H, m, MeC=), 3.8 (1 H, m, HCN), and 5.3 and 5.6 (2 H, 2 m, H_2C=).

N-t-Butylmethacrylamide (**5d**).[14]

2,*N*-Dimethyl-*N*-phenylpropenamide (**6a**),[10] $\nu_{max.}$(KBr) 1 650, 1 630, 1 600, and 1 500 cm^{-1}; δ($CDCl_3$) 1.75 (3 H, s, MeC=), 3.3 (3 H, s, MeN), 5.0 (2 H, m, H_2C=), and 7.25 (5 H, m, Ph).

5,5-Dimethyl-2-dimethylamino-3-phenyl-, -3-benzyl-, and -3-t-butyl-oxazolidin-4-one (**8a**,**b**,**d**).[6,9]

New Products.—*2-Bromo-2-methyl-*N*-cyclohexylpropanamide* (**1c**). 2-Bromo-2-methylpropanoyl bromide (33.3 g, 0.145 mol) in chloroform (20 ml) was dropped at 0 °C during 40 min under stirring to cyclohexylamine (14.3 g, 0.145 mol) and triethylamine (14.7 g, 0.145 mol) in chloroform (50 ml). Stirring was continued for 5 h at room temperature, then the mixture was washed with water (3 × 150 ml) and dried (Na_2SO_4) overnight. Concentration to dryness gave crude (**1c**) (31.8 g, 82%). The solid was purified by percolation on a column of SiO_2 (40 × 2.5 ml) using ethyl acetate–toluene (1:1; 150 ml), and treatment with active carbon–Celite; the solution was concentrated to yield a solid which was recrystallized from ethanol–water, prisms, m.p. 108—109 °C; $\nu_{max.}$($CHCl_3$) 3 410br, 1 660, and 1 510 cm^{-1}; δ($CDCl_3$) 1.92 (6 H, s, Me_2C), 1—2.1 (10 H, m, C_6H_{10}), 3.72 (1 H, br m, HCN), and 6.58 (1 H, br m, NH) (Found: C, 48.3; H, 7.4; N, 5.5. $C_{10}H_{18}BrNO$ requires C, 48.4; H, 7.4; N, 5.6%).

*2-Bromo-*2,N*-dimethyl-*N*-benzylpropanamide* (**2b**) was prepared from 2-bromoisobutyryl bromide and *N*-methylbenzylamine, oil, $\nu_{max.}$(neat) 1 635 cm^{-1} (CO); δ($CDCl_3$) 2.0 (6 H, s, Me_2C), 3.1 (3 H, s, MeN), 4.75 (2 H, s, CH_2), and 7.25 (5 H, s, Ph) (Found: C, 52.75; H, 6.0; Br, 29.7; N, 5.1. $C_{12}H_{16}BrNO$ requires C, 53.3; H, 6.0; Br, 29.6; N, 5.2%).

2,N-*Dimethyl*-N-*benzylpropanamide* (**4b**) was prepared from isobutyryl chloride and *N*-methylbenzylamine, oil, δ($CDCl_3$) 1.16 (6 H, d, Me_2C), 2.4 (1 H, unresolved m, CH), 3.0 (3 H, s, MeN), 4.6 (2 H, s, H_2C), and 7.3 (5 H, s, Ph) (Found: C, 73.1; H, 8.9; N, 7.1. $C_{12}H_{17}NO$ requires C, 75.35; H, 9.0; N, 7.3%).

2,N-*Dimethyl*-N-*benzylpropenamide* (**6b**) was prepared from methacryloyl chloride, *N*-methylbenzylamine (1 mol), and 20% NaOH (1 mol) in dichloromethane at −10 °C, or using 2 mol of the amine, oil, $\nu_{max.}$(neat) 1 620 cm^{-1} (conjugated CO); δ($CDCl_3$) 2.0 (3 H, s, MeC=), 3.0 (3 H, s, MeN), 4.6 (2 H, s, H_2C), 5.1 and 5.2 (2 H, 2 unresolved m, H_2C=), and 7.3 (5 H, s, Ph) (Found: C, 74.1; H, 8.0; N, 7.2. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7.4%).

5,5-Dimethyl-2-dimethylamino-3-cyclohexyloxazolidin-4-one (**8c**). Sodium hydride (192 mg, 4 mmol) was covered with anhydrous DMF (3 ml) and the bromoamide (**1c**) (1 g, 4 mmol) in DMF (7 ml) was dropped under stirring at room temperature over 40 min. After further stirring for 24 h, the mixture was centrifuged and the solution was taken to dryness *in vacuo*. The resulting yellow wax was purified by two chromatographic runs, using a column of SiO_2 and ethyl acetate–toluene (1:1 and 1:4), to yield (**8c**) (0.56 g, 58%), waxy solid or needles, m.p. 65 °C (softening 40 °C); $\nu_{max.}$(Nujol) 1 700 cm^{-1} (br, CO); δ($CDCl_3$) 1.3, 1.4 (6 H, 2 s, Me_2C), 1.0—2.0 (10 H, m, C_6H_{10}), 2.3 (6 H, s, Me_2N), 3.6 (1 H, m, HCN), and 5.6 (1 H, s, 2-H) (Found: C, 65.0; H, 10.3; N, 11.0. $C_{13}H_{24}N_2O_2$ requires C, 65.0; H, 10.1; N, 11.65%).

2,5,5-Trimethyl-2-dimethylamino-3-phenyloxazolidin-4-one (**9**). A sample of 2-bromo-2-methylpropananilide (**1a**) (48 mg, 0.2 mmol) dissolved in anhydrous DMA–0.1M-$Bu^n_4NClO_4$ (20 ml) was electrolysed at −1.4 V. When the substrate (**1a**) became < 5%, a second sample (49.8 mg) was introduced into the cell and the electrolysis was repeated as above. Concentration to dryness and extraction with dry diethyl ether (20 ml) left undissolved $Bu^n_4ClO_4$ (477 mg); the ethereal extract gave on evaporation a crude oil (263 mg) having the following composition: compound (**9**): $\nu_{max.}$ 1 700 cm^{-1} (CO); δ($CDCl_3$) 1.65 (6 H, s, 5-, 5-, or 2-Me), 1.75 (3 H, s, 2- or 5-Me), 2.57 (6 H, s, Me_2N), and 7.5 (5 H, m, Ph); 2-methylpropananilide (**3a**); methylacrylanilide (**5a**); phenyl isocyanide (**7a**); ^1H n.m.r. yields: 32, 50, 13, and < 5%, respectively.

1′,5,5-Trimethyl-3-phenylpyrrolidine-5′-spiro-2-oxazolidin-4-one (**10**). An electrolysis of (**1a**) in MP–0.1M-$Bu^n_4NClO_4$ at −1.4 V gave an almost identical electrochemical pattern as in DMA. Work-up as above gave a crude oil in which (**3a**) (50%) and (**5a**) (15%) were detected by ^1H n.m.r. Mass spectroscopy revealed the presence of (**10**) by the following main peaks, *m*/*z* (M^+, 260 ± 2), $M^+ - 42$, $M^+ - 86$, and $M^+ - 114$.

Electrochemical Apparatus.—A conventional three-electrode cell was used and measurements were carried out under an atmosphere of argon or nitrogen at room temperature. The mercury microelectrode employed in voltammetric measurements was obtained by slow galvanostatic electrodeposition from a 10^{-3}M-$HgSO_4$–0.5M-H_2SO_4 solution on a Pt bead. The electrode was then dipped in mercury and there stored after each measurement. In this way the surface proved uncontaminated and the geometrical area was constant during some months. Controlled-potential electrolyses were carried out with a stirred mercury-pool cathode. The reference electrode (Ag–AgCl) and the counter-electrode have been described.[18] Potential values are given with respect to the saturated aqueous calomel electrode, calibration being made after each measurement.

Electrochemical experiments were carried out in acetonitrile, DMF, DMA, or MP containing 0.1M-Bu^n_4NBr, -$Bu^n_4NClO_4$, or -Et_4NClO_4. The anhydricity of the medium was assured by repetitive cycling of the solvent–electrolyte solution through an activated Al_2O_3 column,[19] prior to the introduction of the substrate.

All measurements were carried out with conventional

instrumentation: PAR 173/179 potentiostat–digital coulometer, PAR 175 universal programmer, Nicolet 3091 digital oscilloscope, and Amel 863 *X*/*Y* recorder. The feedback correction was applied in order to minimize the ohmic drop between the working and reference electrodes during voltammetric runs.

Electrolyses and Analysis of the Products.—In controlled-potential electrolyses, the concentration of the starting material was *ca.* 1×10^{-2}M and more than one addition was sometimes made after the first electrolysis, in order to accumulate the products. It was verified that the repetitive electrolysis procedure did not affect the nature and relative yields of the products. In all electrolyses the limiting reduction current was allowed to decay to 5% of its initial value or lower. To check the disappearance of the starting material and the presence of electroactive products, voltammograms were recorded before and after each electrolysis. The charge flow was monitored and the apparent number of electrons per molecule was calculated by evaluating the extent of the reduction both electrochemically (through the first voltammetric peak) and chemically.

After macroscale reduction at the appropriate potential, the electrolysed solutions (typically 20—30 ml) were worked up along the lines summarized as follows. From the major part of the solution, the solvent was removed either *in vacuo* at *ca.* 40 °C, with condenser at −40 °C and collector at −10 to 0 °C (DMF solutions), or in Rotavapor at 20 °C (acetonitrile solutions). The residue was extracted with anhydrous diethyl ether (20 ml), leaving the supporting electrolyte undissolved. The ethereal extract was then evaporated to yield the product mixture, usually as an oil. The evaluation of the extent of the electroreduction and the identification of the products were carried out through inspection of t.l.c. plates (u.v. light, iodine vapours, ninhydrin spray), i.r. and ^{1}H n.m.r. spectra in comparison with authentic specimens. Mass spectrometry (Varian CH7 high-resolution spectrometer) was performed when specifically indicated.

Analytical instrumentation has been described.[2] ^{1}H N.m.r. chemical shifts of starting materials and products are downfield from the signal for $SiMe_4$, which was used as internal standard.

Parallel to the work-up procedure, the minor part of each electrolysed solution was analysed by h.p.l.c. using a Perkin-Elmer Series 3 liquid chromatograph, equipped with an LC-75 autocontrol u.v. detector and a computer for chromatogram analysis. A 4 mm diameter, 25 cm length stainless steel column packed with LiChrosorb RP8, 10 μm mean particle size, was employed. The eluting solution (50% acetonitrile–50% water) was sometimes enriched with 0.05% propionic acid which proved useful in sharpening the peaks. Quantitative analysis was based on calibration curves constructed with solutions of authentic samples.

Results

The electrochemical reduction of 2-bromo-2-methylpropanamides (**1**) and (**2**) was investigated at the mercury electrode in carefully dried acetonitrile (AN) or DMF containing 0.1M-Bu^n_4NBr, -$Bu^n_4ClO_4$, or -Et_4NClO_4.

In cyclic voltammetry experiments, two main reduction peaks could be detected for all substrates. As far as secondary (N–H protic) amides (**1**) are concerned, both peaks display nearly the same characteristics, *i.e.* irreversibility and similar electron-transfer coefficients. Typical peak potential values obtained in DMF–0.1M-Et_4NClO_4 at 0.2 V s^{-1} are as follows: (**1a**) (−1.03, −1.99 V), (**1b**) (−1.20, −2.22 V), (**1c**) (−1.35, −2.30 V), (**1d**) (−1.44, −2.32 V). The cation of the electrolyte has a relevant effect on both peaks: in particular the second one is shifted towards negative potentials of *ca.* 0.4 V with respect to the first peak when Et_4N^+ is replaced by $Bu^n_4N^+$. Under the same experimental conditions, the voltammetric pattern of the two tertiary (aprotic) amides (**2**), selected for comparison, indicates that a different behaviour arises only within the second reduction step, which can be nearly reversible both electrochemically and chemically, depending on the potential-scan rate and the dryness of the solvent.

To provide more information on the nature of the reducible species, the effect of proton donors or acceptors on the electroreduction pattern was investigated. The presence of a proton donor such as PhOH has a strong effect on the voltammetric pattern of all the 2-bromocarboxamides investigated. Stepwise addition of the proton donor causes an increase of the first reduction peak, coupled with a decrease of the second one, independently of the structure of the substrate. The former peak eventually doubles while the latter one disappears. The effect of a strong base like Bu^n_4NOH was tested on secondary 2-bromoamides (**1**) in DMF. Addition of a slight excess of base into the solution causes a sudden drop of the first voltammetric peak, while the disappearance of the more negative peak is slower. The overall effect of the base is to eliminate any electroactive species within the usual range of potentials.

Macroreduction of compounds (**1**) and (**2**) was carried out

Electrochemical data and product distribution in the reduction of 2-bromo-2-methylpropanamides (**1**), (**2**) at a mercury-pool electrode

Substrate	Solvent–electrolyte[a]	Potential (V)[b]	Charge[c] (F mol^{-1})	Products, yield (%)[c] (3) or (4)	(5) or (6)	(8)	(7)[d]
(**1a**)	AN–Bu^n_4NBr	−1.0	0.98	50	45		
	DMF–Bu^n_4NBr	−1.4	0.98	50		50	
(**1b**)	AN–Et_4NClO_4	−1.5	1.04	50	35		
	DMF–Bu^n_4NBr	−1.7	1.07	50	<5	45	
(**1c**)	AN–Et_4NClO_4	−1.6	1.02	50	<5		~ 20
	DMF–Et_4NClO_4	−1.5	1.09	55	<5	30	tr
(**1d**)	AN–Et_4NClO_4	−1.4	0.98	50	5		~ 20
	DMF–$Bu^n_4NClO_4$	−1.9	1.02	50	tr	40	
(**2a**)	AN–Et_4NClO_4	−1.5	1.03	50	45		
	DMF–Et_4NClO_4	−1.7	1.08	55	45		
(**2b**)	AN–Bu^n_4NBr	−1.4	1.07	55	45		
	DMF–Bu^n_4NBr	−1.4	0.99	50	50		

[a] The electrolyte concentration was 0.1M. [b] All potentials were measured *versus* the saturated calomel electrode. [c] In most cases, coulometric data and yields were averaged from two or more electrolyses. [d] Isocyanides had the expected medium-strength i.r. maxima.[20]

through controlled-potential electrolysis at the stirred mercury pool in AN or DMF at room temperature. Electrochemical data, products, and yields are reported in the Table. Provided that the solvent–electrolyte system was carefully dried, the quantitative reduction of each compound at potentials of the first wave took one electron per molecule. Under these conditions, the corresponding reduced products, amides (**3**) or (**4**), were formed in all cases in yields close to 50%. Conversely, when the electrolyses were carried out in the presence of a proton donor (PhOH), the reduced products (**3**) or (**4**) were obtained quantitatively and the apparent number of electrons per molecule increased from one to two.

In aprotic conditions, the voltammetric profile recorded after electrolysis exhibits a reduction peak in the range from *ca.* −2.3 to −2.6 V only when the pertinent αβ-unsaturated amide was identified among the products. All products reported in the Table were independently prepared and electrochemically tested. Among them, only the αβ-unsaturated amides were reducible before the electrolyte discharge at potentials within the above mentioned range.

The role played by the solvent, and the substitution pattern at the nitrogen atom of the parent amide, on the distribution of coproducts is worth noting. In AN, an αβ-unsaturated amide (**5a, b**) or (**6a, b**) arose as the main coproduct upon reduction of 2-bromo-2-methyl-*N*-phenyl- or -*N*-benzylpropanamide (**1a,b**), *as well* as of the *N*-methyl tertiary analogues (**2a, b**).* On the other hand, from 2-bromo-2-methyl-*N*-cyclohexyl-or-*N*-t-butyl-propanamides (**1c,d**), the corresponding unsaturated amides (**5c,d**) were formed in small amounts, along with variable amounts of cyclohexyl or t-butyl isocyanide (**7c,d**) and acetone. Noteworthy, no or little self-condensation products predominating in parallel reactions promoted by an exogenous base[2–4] became evident in the reduction mixtures.

In DMF, the distribution of coproducts was the same as in AN for aprotic 2-bromoamides (**2**), and the pertinent unsaturated amides (**6**) were recovered in *ca.* 50% yield. Starting from the protic substrates (**1**), in turn, the balance was drastically changed, the coproduct being represented by a cyclocondensation adduct with DMF itself, *i.e.* 2-dimethylamino-3-(phenyl, benzyl, cyclohexyl, or t-butyl)-5,5-dimethyloxazolidin-4-one (**8a—d**). Yields ranged from 30 to 50% depending on the substituent at the nitrogen atom. Derivative (**8**) was unequivocally identified also in some experiments carried out in AN where DMF was introduced in amounts nearly equivalent to the substrate. Again, no self-condensation products were evident.

Compound (**1a**) was also reduced in DMF at −2.0 V, *i.e.* at the second wave. The apparent number of electrons increased to *ca.* 1.3 and work-up showed the following product distribution: (**3a**) (65%), (**8a**) (17%), and (**5a**) (15%).

The identification of five-membered heterocyclic derivatives (**8**) incorporating the DMF molecule prompted us to carry out few representative electroreductions in DMA or MP. The electrolysis of (**1a**) in DMA–0.1-M-$Bu^n_4NClO_4$ at −1.4 V required again 1 F mol^{-1} and afforded 2-dimethylamino-2-methyl-3-phenyl-5,5-dimethyloxazolidin-4-one (**9**), in 30—35% yield, along with the reduced product (**3a**), the unsaturated amide (**5a**), and some phenyl isocyanide (**7a**). The electrolysis of (**1a**) in MP, under otherwise identical conditions, gave similar results. Mass spectrometery gave evidence of the presence of 1′,5,5-trimethyl-3-phenylpyrrolidine-5′-spiro-2-oxazolidin-4-one (**10**). Compounds (**9**) and (**10**) could not be obtained in a pure state.

Discussion

The voltammetric behaviour observed points to a rather complex reduction mechanism of 2-bromo-2-methylpropanamides. The characteristics of the first peak and the effect of proton donors suggest that carbanion (**11**) is formed as a result of a two-electron reduction, whose rate-determining step is the uptake of the first electron [equation (1)]. The basic species (**11**) may be protonated by an added proton donor so that the reduced product (**3**) or (**4**) is formed quantitatively with consumption of 2 F mol^{-1}. In aprotic conditions, on the other hand, the electrogenerated carbanionic base undergoes self-protonation by a parent molecule. In the time scale of slow voltammetry and, consequently, for the longer times required by controlled-potential electrolysis experiments, the self-protonation reaction is quantitative. In fact, by acting as a proton donor, half of the starting material is no longer reducible in the potential range of the first peak and, accordingly, the peak current and the coulometric result are one half of the values measured in the presence of an exogenous proton donor.

Starting from the tertiary amides (**2**) and independently of the solvent, proton abstraction by the electrogenerated base (**11′**) merely represents part of an overall *E*2 dehydrobromination reaction, yielding the unsaturated amides (**4**) [equation (2)]. Reduction of the latter accounts for the second voltammetric peak observed during the reduction of the parent 2-bromoamides.

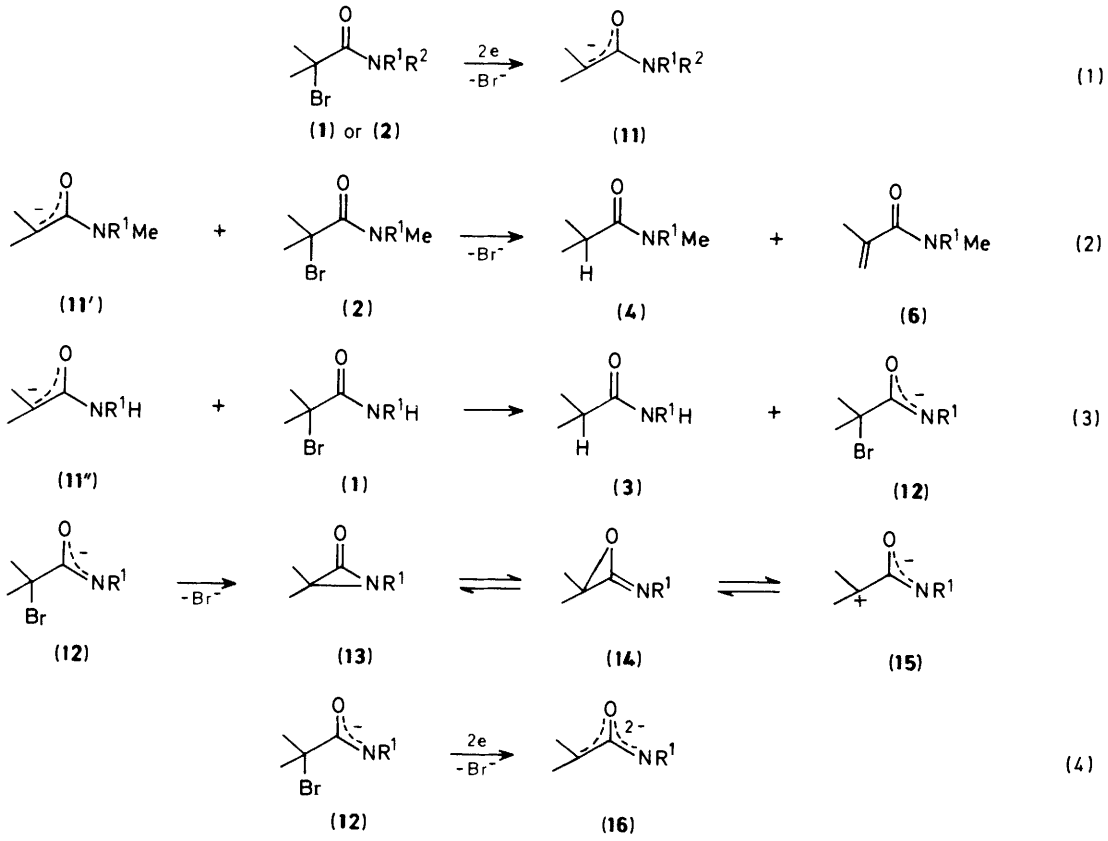
On the other hand, the 'protic' carbanion (**11″**)† arising from secondary 2-bromoamides (**1**) abstracts a proton from the nitrogen of a parent 2-bromoamide; accordingly, the conjugate base of the latter, anion (**12**), is chemically generated along with the reduced product (**3**) [equation (3)]. Half the starting material is then efficiently converted into anion (**12**), whose decay to products will balance the overall yield of the electrolysis. The distribution of coproducts is quite responsive both to the solvent and the amide moiety of the selected 2-bromoamide, thus pointing to a complex decay of anion (**12**). Anion (**12**) itself and, on the basis of previous chemical studies,[1,4,6] the α-lactam (**13**), the imino-oxirane (**14**), and the zwitterion (**15**) may represent intermediate structures[22] towards the cyclocoupling (**8**)—(**10**), elimination (**5**), or fragmentation products (**7**). Whereas α-lactams (**13**) can be isolated upon base-induced cyclization of 2-bromoamides carrying bulky aliphatic groups at the nitrogen and carbon atoms,[1] structure (**14**), favoured by electron-donating groups at the nitrogen, would explain the fragmentation of anion (**12**) into an isocyanide (**7**) and acetone. Finally, zwitterion (**15**) would conceivably lead to an unsaturated amide through proton displacement or to an oxazolidin-4-one (**8**)—(**10**) through a (3 + 2→5) cyclocondensation onto a carbonyl group.

The formation of a cyclocondensation derivative, even when DMF is present in minute amounts in AN solution, suggests that DMF acts as a scavenger of anion (**12**) and/or its daughter species (**13**)—(**15**); the crosscondensation with the solvent-reagent becomes overwhelming *versus* the 1,2-elimination or fragmentation reactions. Although the cyclocoupling of DMA and MP has been studied in minor detail with respect to the one of DMF, this type of solvent should be considered as generally susceptible to enter into reaction with reactive intermediates of the type discussed above.

A further point deserves attention. The above results and accompanying discussion show how anion (**12**), the conjugate base of the starting material, is not a stable species, at variance with the usual behaviour observed in self-protonation

* It is worth noting that a preliminary result on the reaction of compound (**2b**) with metal carbonyls indicated a similar product distribution as revealed by the ^1H n.m.r. spectrum of the reaction mixture.[21]

† Intramolecular proton transfer from nitrogen to the α-carbon could take place within carbanion (**11″**) of secondary amides prior to the self-protonation step. This possibility will be considered in the future.



studies.[7b,8] The existence of a good leaving group such as bromide causes transformation of (**12**) into products (**5**), and (**7**)—(**10**). Nevertheless, in the time scale of a cyclic voltammetry experiment, anion (**12**) can be detected through the reduction of the C–Br bond at the second, more negative peak. The shape and the voltammetric characteristics of this peak would indicate that anion (**12**) undergoes a two-electron C–Br bond cleavage in a similar way as the parent molecule (**1**) [equation (1)]. However, the anionic nature of (**12**) shifts the reductive cleavage of the C–Br bond of *ca.* 1 V towards more negative potentials, and accounts for the strong ion-pairing effect caused by the cations of the electrolyte. Consequently, a dianion, represented by structure (**16**), may be postulated to form at the electrode, according to equation (4).

Comparison between the coulometric data and product distribution resulting upon reduction at the first or second peak of (**1a**) in DMF points to the interference of the electrochemical reaction (4). During controlled-potential electrolysis at potentials of the second wave, the main reduction process is again (1). Self-protonation (3) follows and, consequently, anion (**12**) is formed near the electrode surface. Close inspection of the experimental results indicates that about one third of anion (**12**), not yet transformed into adduct (**8a**), reaches the electrode and undergoes the two-electron reduction (4), increasing the coulometric yield from 1.0 to 1.3 F mol^{-1}. The fate of dianion (**16**) is to be protonated by any available proton source, thus increasing the yield of (**3a**), and to promote the formation of the unsaturated amide (**5a**). Accordingly, the yield in the cyclo-condensation product (**8a**) decreases from 50 to 17% with respect to the first-wave electrolysis.

On the above grounds, the effect of adding a strong base (Bu^n_4NOH) into the solution of a protic 2-bromoamide like (**1a**) in DMF becomes self-explanatory. In fact, the voltammetric curve taken just after the mixing indicates that a fast, quantitative transformation of the parent compound into anion (**12**) takes place, as revealed by the disappearance of the first peak. On the other hand, the rather slow decrease of the second peak, until its eventual disappearance, is due to the decay of anion (**12**) through non-electrochemical pathways.

As a general conclusion on the reduction of 2-bromo-2-methylpropanamides, self-protonation of the electrogenerated carbanion promotes a normal dehydrohalogenation of a parent aprotic amide, whereas it induces a proton abstraction from the N–H bond of a parent protic (secondary) amide. The latter proton transfer and the versatility of anion (**12**) are key points in the progress of the reactions. We shall investigate further some synthetic and mechanistic aspects.

Acknowledgements

The National Research Council (C.N.R.) and the Ministry of Education are gratefully acknowledged for financial support. We thank Drs. F. Coletta and G. Fantin for assistance with the ^1H n.m.r. spectra, and Mrs. N. Formenton for valuable help in the h.p.l.c. analysis.

References

1 (*a*) I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 25; (*b*) P. Scrimin, F. D'Angeli, and A. C. Veronese, *Synthesis*, 1982, 586.
2 G. Zanotti, F. Filira, A. Del Pra, G. Cavicchioni, A. C. Veronese, and F. D'Angeli, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2249.
3 A. Subbaraj, C. Ananthanarayanan, and V. T. Ramakrishnan, *Synth. Commun.*, 1977, **7**, 433; T. Okawara, Y. Noguchi, T. Matsuda, and M. Furukawa, *Chem. Lett.*, 1981, 185.
4 P. Scrimin, F. D'Angeli, V. Baioni, and G. Cavicchioni, *J. Chem. Res.*, 1983; (*S*) 248; (*M*) 2237.
5 (*a*) G. Cavicchioni, P. Scrimin, A. C. Veronese, and F. D'Angeli, *J. Chem. Soc., Chem. Commun.*, 1981, 416; (*b*) G. Cavicchioni, P. Scrimin, A. C. Veronese, G. Balboni, and F. D'Angeli, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2969.

6 P. Scrimin, F. D'Angeli, A. C. Veronese, and V. Baioni, *Tetrahedron Lett.*, 1983, **24**, 4473.
7 (*a*) Yu. V. Svetkin and L. N. Andreeva, *Zh. Obshch. Khim.*, 1965, **35**, 839; (*b*) D. Bérubé, J. Caza, F. M. Kimmerle, and J. Lessard, *Can. J. Chem.*, 1975, **53**, 3060; (*c*) I. Carelli, A. Inesi, M. A. Casadei, B. Di Rienzo, and F. Micheletti Moracci, *J. Chem. Soc., Perkin Trans. 2*, 1985, 179.
8 C. Amatore, G. Capobianco, G. Farnia, G. Sandonà, J. M. Savèant, M. G. Severin, and E. Vianello, *J. Am. Chem. Soc.*, 1985, **107**, 1815.
9 F. Maran, E. Vianello, G. Cavicchioni, and F. D'Angeli, *J. Chem. Soc., Chem. Commun.*, 1985, 660.
10 C. A. Bischoff, *Ber. Dtsch. Chem. Ces.*, 1897, **30**, 3174.
11 R. E. Carter, *Acta Chem. Scand.*, 1967, **21**, 75.
12 H. Staudinger, H. W. Klever, and P. Kober, *Justus Liebig's Ann. Chem.*, 1910, **374**, 1.
13 E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, 1950, **15**, 662.
14 T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.*, 1972, **37**, 3810.
15 K. Dietliker and H. Heimgartner, *Helv. Chim. Acta*, 1983, **66**, 262.
16 T. A. Sokolova, *Zh. Obshch. Khim.*, 1957, **27**, 2205.
17 V. D. Bezuglyi, T. A. Alekseeva, and L. P. Kruglyak, *Ukr. Khim. Zh.*, 1965, **31**, 500.
18 G. Farnia, F. Maran, G. Sandonà, and M. G. Severin, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1153.
19 R. Lines, B. S. Jensen, and V. D. Parker, *Acta Chem. Scand., Ser. B*, 1978, **32**, 510.
20 I. Ugi and R. Meyr, *Chem. Ber.*, 1960, **93**, 239.
21 F. D'Angeli and P. Scrimin, unpublished work.
22 J. F. Liebman and A. Greenberg, *J. Org. Chem.*, 1974, **39**, 123; G. L'abbé, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 276.

Received 6*th January* 1986; *Paper* 6/045