Electrochemical and Stereochemical Investigation on the Mechanism of the Decay of 2-Halo Amide Anions. The Intermediacy of Aziridinones

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Abstract: 2-Halo amide anions can be generated by electroreduction of the corresponding NH-protic 2-halo amides through the self-protonation mechanism. Such anions are labile species whose decay, in the case of 2-bromo amide anions, competes with their electroreduction in the voltammetric time scale. Using the appropriate voltammetric treatment, the first-order rate constant of the decay has been determined for a series of representative 2-bromo amides. The lability orders point to an S_N2-type intramolecular substitution of bromine and thus to the formation of a three-membered ring. Stereochemical information on the decay has been gained using a chiral nonracemic 2-bromopropanamide, an amine nucleophile, and DMF as the solvent. The direct substitution by the amine proceeds by an S_N2 reaction, as witnessed by inversion of configuration at the α-carbon and voltammetric analysis. Conversely, when the reaction is triggered by electroreduction, the decay of the 2-bromo amide anion eventually leads to the formation of the retention product 2-amino amide together with other optically active products, namely two diastereomeric oxazolidin-4-ones, arising by cyclocondensation with DMF, and *cis*-2,5-dioxopiperazine. Analysis of the electrochemical and stereochemical results indicates that the mechanism of the base-promoted reactions of 2-halo amides proceeds through the transient formation of the corresponding aziridinone, independently of the fact that the latter is isolable or not. The formation of the aziridinone takes place by concerted intramolecular nucleophilic substitution of bromide ion within the 2-halo amide anion. The transient aziridinone behaves not only as the product-determining intermediate but also as a species capable of reacting with suitable partners under remarkable enantioselectivity control.

Introduction

In the presence of bases[1-3] or electrogenerated bases[4,5] 2-halo amides can be transformed into a variety of heterocyclic or 2-substituted derivatives. When the starting compound is a NH-protic 2-halo amide, the initial step to be considered in the reaction sequence is the formation of the corresponding conjugate base. The 2-halo amide anions are labile species that *decay*, eventually losing the halide ion and affording products which depend on the structure of the starting material and/or the reaction medium. Different species can be formulated to arise upon loss of halide ion within the 2-halo amide anion, in particular the aziridinone **3**, the iminooxirane **4**, and the dipolar ion **5**,[6] as shown in Scheme I for 2-bromo amides **1** and conjugate bases **2**.[7]

The hypothesis concerning the intermediacy of **3** is essentially based on the fact that some aziridinones have been isolated under special stabilizing conditions.[1,8] Stable aziridinones were also reacted with neutral or anionic nucleophiles, and the mechanisms of such reactions were often proposed to involve the intermediate formation of open species such as **5**[9] or that of elusive iminooxirane **4**;[1,8] on the other hand, very recent stereochemical data provided evidence for direct reactions of a stable aziridinone with

(1) See: Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25, and references therein.

(2) (a) Zanotti, G.; Filira, F.; Del Pra, A.; Cavicchioni, G.; Veronese, A. C.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2249. (b) Cavicchioni, G.; Scrimin, P.; Veronese, A. C.; D'Angeli, F. *J. Chem. Soc., Chem. Commun.* **1981**, 416. (c) Cavicchioni, G.; Scrimin, P.; Veronese, A. C.; Balboni, G.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2969. (d) Scrimin, P.; D'Angeli, F.; Cavicchioni, G. *Synthesis* **1982**, 1092. (e) Scrimin, P.; D'Angeli, F.; Baioni, V.; Cavicchioni, G. *J. Chem. Res.* **1983**, (*S*) 248,, (*M*) 2237. (f) Scrimin, P.; D'Angeli, F.; Veronese, A. C.; Baioni, V. *Tetrahedron Lett.* **1983**, *24*, 4473. (g) Scrimin, P.; Cavicchioni, G.; D'Angeli, F.; Goldblum, A.; Maran, F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 43.

(3) (a) Baumgarten, H. E.; McMahan, D. G.; Elia, V. J.; Gold, B. I.; Day, V. W.; Day, R. O. *J. Org. Chem.* **1976**, *41*, 3798. (b) Kakimoto, M.; Kajigaeshi, S.; Kanemasa, S. *Chem. Lett.* **1976**, 47. (c) Talaty, E. R.; Clague, A. R.; Agho, M. O.; Deshpande, M. N.; Courtney, P. M.; Burger, D. H.; Roberts, E. F. *J. Chem. Soc., Chem. Commun.* **1980**, 889. (d) Lai, J. T. *Tetrahedron Lett.* **1982**, 423, 595. (e) Okawara, T.; Matsuda, T.; Furukawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 1225. (f) Shiner, C. S.; Fisher, A. M.; Yacoby, F. *Tetrahedron Lett.* **1983**, *24*, 5687. (g) Baumgarten, H. E.; Chiang, N.-C. R.; Elia, V. J.; Beum, P. V. *J. Org. Chem.* **1985**, *50*, 5507. (h) Legrel, P.; Baudy-Floc'h, M.; Robert, A. *Tetrahedron* **1988**, *44*, 4805. (i) Coutts, I. G. C.; Southcott, M. K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 767.

(4) (a) Maran, F.; Vianello, E.; Cavicchioni, G.; D'Angeli, F. *J. Chem. Soc., Chem. Commun.* **1985**, 660. (b) Maran, F.; Vianello, E.; D'Angeli, F.; Cavicchioni, G.; Vecchiati, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 33. (c) D'Angeli, F.; Cavicchioni, G.; Catelani, G.; Marchetti, P.; Maran, F. *Gazz. Chim. Ital.* **1989**, *119*, 471. (d) Maran, F.; Fabrizio, M.; D'Angeli, F.; Vianello, E. *Tetrahedron* **1988**, *44*, 2351.

(5) See, also: (a) Carelli, I.; Inesi, A.; Carelli, V.; Casadei, M. A.; Liberatore, F.; Micheletti Moracci, F. *Synthesis* **1986**, 591. (b) Casadei, M. A.; Di Rienzo, B.; Inesi, A.; Micheletti Moracci, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 375. (c) Casadei, M. A.; Di Rienzo, B.; Inesi, A.; Micheletti Moracci, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 379.

(6) Other isomeric species have been sometimes considered as possible intermediates, namely oxaziridine[6a] and open species such as a Favorskii-type intermediate[6b] and a diradical.[6c] (a) Baumgarten, H. E.; Fuerholzer, J. F.; Clark, R. D.; Thompson, R. D. *J. Am. Chem. Soc.* **1963**, *85*, 3303. Liebman, J. F.; Greenberg, A. *J. Org. Chem.* **1974**, *39*, 123. (b) Sheehan, J. C.; Beeson, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 366. (c) Quast, H.; Meichsner, G.; Seiferling, B. *Chem. Ber.* **1987**, *120*, 217 and 225.

(7) The transient formation of intermediates **3–5** was postulated also in reactions of starting materials different from 2-halo amides. See, for example: (a) Reference 1. (b) Ohshiro, Y.; Minami, T.; Yasuda, K.; Agawa, T. *Tetrahedron Lett.* **1969**, 263. (c) Ikeda, K.; L'abbé, G.; Smets, G. *Chem. Ind. (London)* **1973**, 327. (d) Komatsu, M.; Ohshiro, Y.; Hotta, H.; Sato, M.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 948. (e) Schutyser, J. A.; De Schryver, F. C. *Tetrahedron* **1976**, *32*, 251. (f) Del'tsova, D. P.; Gambaryan, N. P.; Lur'e, É. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 1788. (g) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2483. (h) Bladon, C. M.; Kirby, G. W. *J. Chem. Soc., Chem. Commun.* **1982**, 1402. (i) Quast, H.; Seiferling, B. *Tetrahedron Lett.* **1982**, *23*, 4681. (j) Reference 2f. (k) Reference 3f. (l) Geffken, D.; Strohauer, K. *Z. Naturforsch.* **1985**, *40b*, 398. (m) Reference 6c. (n) Fulton, J. B.; Warkentin, J. *Can. J. Chem.* **1987**, *65*, 1177. (o) De Kimpe, N.; De Corte, B. *Tetrahedron* **1992**, *48*, 7345. (p) Hoffman, R. V.; Nayyar, N. K.; Klinekole, B. W. *J. Am. Chem. Soc.* **1992**, *114*, 6262. (q) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1992**, *57*, 5700.

(8) L'abbé, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 276.

(9) Although dipolar ion **5** is the acyclic intermediate most frequently hypothesized for the reactions of aziridinones, other open species have been invoked.[6b,c,9a] (a) Talaty, E. R.; Dypuy, A. E., Jr.; Utermoehlen, C. M.; Stekoll, L. H. *J. Chem. Soc., Chem. Commun.* **1973**, 48.

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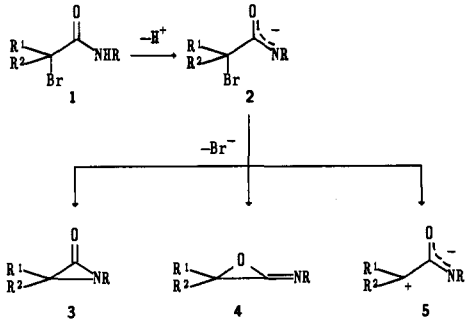
Scheme I



nucleophiles.[10] However, the synthesis or the reactions of the limited number of stable aziridinones so far isolated cannot be considered *a priori* as necessarily representative of the general mechanism of the base-promoted reactions of 2-halo amides. In fact, whenever the substituents are not liable to stabilize the aziridinone ring, dipolar ion **5** constituted and still constitutes an attractive alternative,[1,2d,f,3b,d,5b,7g,l,n,p,q,11] also in view of the existing evidence for the formation of α-carbonyl cations.[12] A mechanistic role of **5** must be taken into consideration also in the hypothesis of the intermediacy of **3** because the formation of an open intermediate might precede and/or follow that of **3**. In this framework, the stereochemical tracing of the overall reaction should provide a valuable tool. Few studies, however, have been carried out on this topic. Some chiral 2-halo amides were transformed into aziridinones of uncertain configuration[6b,13] or substitution products with considerable racemization,[14] and different stereochemical outcomes were observed upon solvolysis of a chiral 2-substituted amide.[15] The results obtained upon a study on the synthesis of stable, chiral aziridinones from 2-halo amides were not too promising.[16] Very recently, the formation of an isolable chiral aziridinone form a chiral 2-chloro amide, with inversion, has been reported.[17] We studied the reaction of chiral 2-bromopropanamides with amines and found[18] that the substitution at the α-carbon can be performed either with inversion or, in the presence of silver(I) oxide,[19] with retention of configuration. Stereochemical studies concerning the cyclocondensation reactions of 2-halo amides[20] are still lacking. Therefore, inspection of the existing stereochemical results provides useful but also controversial information.

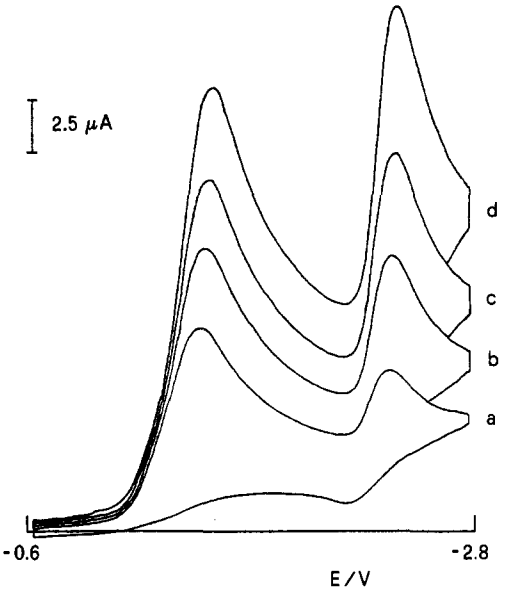


Figure 1. Cyclic voltammetries for the reduction of 1.2 mM 2-bromo-2-methyl-*N*-cyclohexylpropanamide in DMF–0.1 M TEAP at different scan rates: Curve a, 1 V s^{-1}; b, 2 V s^{-1}, c, 3.16 V s^{-1}; d, 5 V s^{-1}. T = 25 °C.

In conclusion, no definitive mechanistic analysis of the base-promoted reactions of 2-halo amides has been performed to date, in spite of the synthetic potentialities of such compounds. The main questions that emerge and that are common also to reactions of different starting materials[7] are (i) which is (are) the actual intermediate(s) when **3** is not stabilized and (ii) whether an open species such as dipolar ion **5** takes part in the mechanism. In recent years, different aspects of the electroreduction of 2-halo amides have been investigated.[4,21,22] Such studies together with related research[2] pointed to a relevant role of the 2-halo amide anions in most reactions of 2-halo amides.[23] On such grounds, the study of the mechanism of the base-promoted reactions of 2-halo amides has been addressed starting from the analysis of the decay of their conjugate bases. In this paper, the results concerning the voltammetric analysis of the decay of anions **2** will be described. Complementary and conclusive information on the decay was provided by the results obtained with a chiral nonracemic substrate. Once analyzed on a mechanistic ground, the reaction of **1** with DMF[2f,3i,4a–c] or amines[2d,3d,18,19d] proved to be a useful tool to ascertain the mechanism of the decay and therefore of the base-promoted reactions of 2-halo amides.

Results and Discussion

Electrochemistry of 2-Bromo Amide Anions. The voltammetric pattern for the reduction of 2-bromo amides **1** in a dipolar nonprotogenic solvent such as DMF is characterized by two irreversible voltammetric peaks (Figure 1). Equations 1–3 resume the previously established electrochemistry of **1**.[4,21] An enolate-

(10) (a) Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 2105. (b) Quast, H.; Leybach, H.; Würthwein, E.-U. *Chem. Ber.* **1992**, *125*, 1249.

(11) As a matter of consideration, the reduction of α,α'-dibromo ketones and the base-promoted reactions of α-bromo ketones are believed to proceed through open cationic intermediates[11a] in spite of the fact that some cyclopropanones can be isolated.[11b] (a) Noyori, R.; Hayakawa, Y.; Takaya, H.; Murai, S.; Kobayashi, R.; Sonoda, N. *J. Am. Chem. Soc.* **1978**, *100*, 1759. Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25.

(12) For a comprehensive review, see: Creary, X. *Chem. Rev.* **1991**, *91*, 1625. There are reports[12a,b] concerning reactions of protic 2-bromo amides in which carbocationic intermediates eventually form. Such reactions, however, are silver(I) ion-promoted and therefore cannot be taken as representative of the base-promoted reaction mechanism. (a) Sheehan, J. C.; Beeson, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 362. (b) Bégué, J. P.; Charpentier-Morize, M.; Pardo, C. *Tetrahedron* **1975**, *31*, 1919.

(13) Sarel, S.; Weissman, B. A.; Stein, Y. *Tetrahedron Lett.* **1971**, 373.

(14) El-Abadelah, M. M. *Tetrahedron* **1973**, *29*, 589.

(15) Creary, X.; McDonald, S. R.; Eggers, M. D. *Tetrahedron Lett.* **1985**, *26*, 811.

(16) Marren, T. J. Doctoral Dissertation, Nebraska University, 1986.

(17) Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 849.

(18) D'Angeli, F.; Marchetti, P.; Cavicchioni, G.; Bertolasi, V.; Maran, F. *Tetrahedron: Asymm.* **1991**, *2*, 1111.

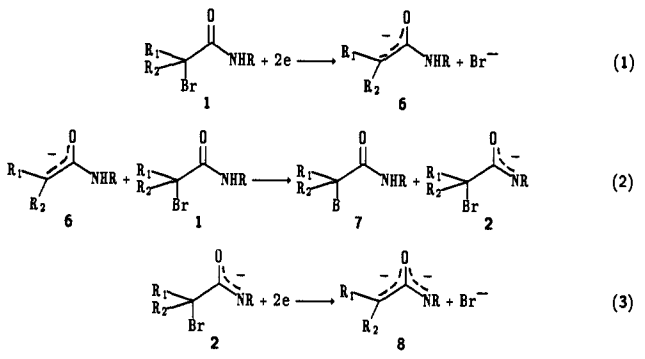
(19) The mechanisms of the silver(I)-promoted reactions of 2-bromo amides are under investigation,[19a] in particular for the synthetic relevance of such reactions.[19b–f] (a) D'Angeli, F.; Maran, F.; Marchetti, P., work in progress. (b) Cavicchioni, G. *Tetrahedron Lett.* **1987**, *28*, 2427. (c) Cavicchioni, G.; D'Angeli, F.; Casolari, A.; Orlandini, P. *Synthesis* **1988**, 947. (d) D'Angeli, F.; Marchetti, P.; Cavicchioni, G.; Catelani, G.; Moftakhari Kamrani Nejad, F. *Tetrahedron: Asymm.* **1990**, *1*, 155. (e) Catelani, G.; Moftakhari Kamrani Nejad, F.; D'Angeli, F.; Cavicchioni, G.; Marchetti, P. *Gazz. Chim. Ital.* **1992**, *122*, 51. (f) D'Angeli, F.; Marchetti, P.; Salvadori, S.; Balboni, G. *J. Chem. Soc., Chem. Commun.* **1993**, 304.

(20) The formation of five-membered heterocycles though the base-promoted condensation of 2-halo amides onto the C=X function (X = C, N, O, S) of suitable partners is well documented.[2a–c,e–g,3b,i,4a–c] Analogous products have been obtained also from stable aziridinones[2f,3b,6c,10b,20a,b] or other precursors.[2f,6c,7b–d,20c] (a) L'abbé, G.; Van Asch, A.; Toppet, S. *Bull. Soc. Chim. Belg.* **1978**, *87*, 929. (b) Del'tsova, D. P.; Gambaryan, N. P.; Mysov, E. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 2343. (c) Toppet, S.; L'abbé, G.; Smets, G. *Chem. Ind. (London)* **1973**, 1110.

(21) Maran, F.; Roffia, S.; Severin, M. G.; Vianello, E. *Electrochim. Acta* **1990**, *35*, 81.

(22) (a) Maran, F.; Severin, M. G.; Vianello, E. *Tetrahedron Lett.* **1990**, *31*, 7523. (b) Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320.

(23) Although the equilibrium acidity of 2-halo amides can vary by many pK_a units, in particular depending on the nitrogen substituent,[23a] the formation of 2-bromo amide anions is to be expected also when not very strong bases are employed. (a) In DMF, the pK_a's of *N*-*p*-cyanophenyl-, *N*-phenyl-, and *N*-benzyl-2-bromoisobutyramide, for example, are 16.4, 18.9, and 22.2, respectively.[22b]



type carbanion **6** is electrogenerated by reductive cleavage of the C–Br bond (eq 1).[24] The electrogenerated base **6** then undergoes self-protonation[25] to yield the reduced amide **7** together with the conjugate base **2** of the starting compound (eq 2). Such a proton transfer reaction is fast and irreversible[26] so that, although carbanion **6** arises upon a two-electron reduction, one electron per molecule is *apparently* consumed at the first peak up to high scan rates.[27] Of particular concern to the present study are the characteristics of the second peak, which is due to the dissociative electrode reduction of anion **2** (eq 3).

Taking into account both the electron consumption at the first peak and eq 3, the apparent number n of exchanged electrons should be 1 at the second peak as it is at the first peak. For a variety of 2-bromo amides, however, the height of the second peak, relative to that of the first one, depends on both the structure of the substrate and the potential scan rate v, which establishes the time scale of the experiment. For example, this is shown by the series of voltammetries reported in Figure 1 which depicts the relative increase of the second peak upon increasing v. This effect is ascribed to the lability of some of the bromo amide anions in the time scale of low scan rate voltammetry. The particular voltammetric pattern at the second peak derives from the competition between the rate of diffusion, and consequently of reduction of **2**, and the chemical decay. The relative rate of such processes is controlled by v and efficiently monitored by the current at the second peak. At low scan rates, labile bromo amide anions decay losing their electroactive C–Br function, and thus the current at the second peak is lower than expected. On increasing v, the time scale of the experiment decreases, the decomposition reaction becomes less competitive with electrode reduction and the height of the second peak increases. When the scan rate is high enough, the decay becomes too slow compared to the diffusion rate and hence the bromo amide anion is detected quantitatively at the second peak (one-electron process). These observations are of particular relevance because, as will be shown below, the study of the above competition provided a valuable tool to obtain information on the mechanism of the decay of anions **2**. Also, preliminary observations indicated that such a voltammetric behavior was independent of the substrate concentration and consequently that the process causing the disappearance of the bromo amide anion could be described as in eq 4, k being an apparent first-order rate constant.

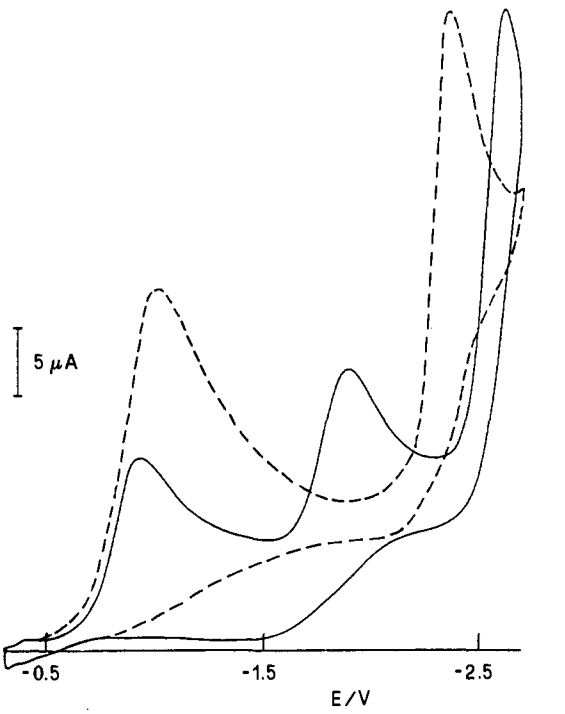
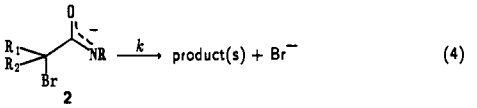


Figure 2. Cyclic voltammetries for the reduction of 3.3 mM 2-bromo-2-methyl-*N*-*p*-bromophenylpropanamide in DMF–0.1 M TEAP obtained in the absence (solid curve) or presence of 4 mM acetic acid (dashed curve): T = 25 °C, v = 0.2 V s^{-1}.



The main chemistry triggered by the reduction of **2** was studied using 2-bromo-*N*-*p*-bromophenylisobutyramide which contains the *p*-bromo function and thus a further breakable bond. In the presence of an acid stronger than the bromo amide, the electrogenerated base **6** is protonated quantitatively to give **7** (Figure 2, dashed curve) and thus the reduction peak of the bromoamide anion **2** is absent. The most negative peak is due to the reduction of the *p*-bromo function of the so-formed amide **7**, as checked by comparison with the voltammetry of an authentic sample. On the other hand, whereas in the absence of the added acid (Figure 2, solid curve) the first two peaks are accounted for by reactions 1–3, the most negative peak is ascribed to the reduction of the conjugate base **9** of amide **7**. In fact, upon gradual addition of a base either to the acidified solution of **1** or to the authentic solution of **7**, the peak of **7** decreases and the most negative peak appears and grows. Therefore, the main fate of the highly reactive dianion **8** formed by reduction of **2**[28] is to undergo protonation by the reduced amide, which is the only acidic species accumulating in the solution layer close to the electrode surface.

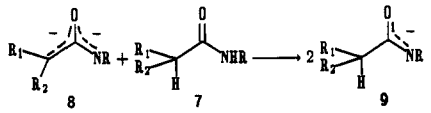
(24) The overall reduction 1 is a multistep process. The slow uptake of the first electron is associated with the breaking of the C–Br bond and the resulting radical is then reduced to **6** as soon as it is produced. Such a process is typical of organic substrates containing breakable σ-bonds, such as halides,[24a] sulfides,[24b] or ethers.[24c] (a) See, for example: Savéant, J.-M. *Adv. Phys. Org. Chem.* **1990**, *26*, 1. (b) Severin, M. G.; Arévalo, M. C.; Maran, F.; Vianello, E. *J. Phys. Chem.* **1993**, *97*, 150. (c) Thornton, T. A.; Ross, G. A.; Patil, D.; Mukaida, K.; Warwick, J. O.; Woolsey, N. F.; Bartak, D. E. *J. Am. Chem. Soc.* **1989**, *111*, 2434, and references therein.

(25) The term self-protonation is used by electrochemists to call the proton-transfer reaction between an electrogenerated base and the starting compound. Detailed kinetic studies on self-protonation reactions have been reported only recently on the basis of the appropriate voltammetric treatments. See: Roffia, S.; Concialini, V.; Paradisi, C.; Maran, F.; Vianello, E. *J. Electroanal. Chem.* **1991**, *302*, 115 and references cited therein.

(26) The rate constants for the self-protonation of 2-bromo amides are in the range 10^7–10^8 M^{-1} s^{-1}, depending on the nitrogen substituent.[26a] Taking into account the available estimates of the α-CH-acidity of tertiary amides[26b] and the pK_a of 2-bromo amides,[22b] the equilibrium constants for the self-protonation reaction 2 is not less than 10^9. (a) The reduction mechanism of 2-bromoacetamides and 2-bromopropanamides and corresponding self-protonation rates are analogous to those described in detail for 2-bromoisobutyramides.[4,21,22,26c] (b) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305. (c) Maran, F.; Vianello, E. *Stud. Org. Chem. (Amsterdam)* **1987**, *30*, 231.

(27) At 25 °C, this is verified up to scan rates of 20–100 V/s, depending on the selected 2-bromo amide and the concentration. In shorter time scales, the self-protonation rate is not high enough to permit quantitative formation of anion **2** and accordingly the apparent number of electrons n becomes larger than 1.

(28) α,α'-Dianions **8** have been obtained also by reaction of amides **7** with very strong bases. For recent references, see: Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223.



(5)

Once the number and type of significant species was defined, a kinetic scheme recently analyzed in this laboratory[29,30] was used to study quantitatively by voltammetry the first-order decay of anions **2**. In such theoretical treatment the pattern at the second peak was shown to depend on the potential difference between the two peaks, the transfer coefficients of the first and second peak, α_1 and α_2, and, most important, the ratio between the rate constant k of reaction 4 and scan rate v. The apparent number of electrons n is particularly affected by the variation of such a ratio. At low values of k/v, $n = 1$ because the chemical reaction 4 does not compete with diffusion and thus with electrode reduction 3. For increasing values of k/v, n gradually decreases up to the point at which the rate of the decay becomes much faster than the diffusion rate and the second peak appears as just a small wave due to the reduction of a steady-state concentration of the labile intermediate.[31]

The kinetic analysis of the decay of anions **2** was carried out at a mercury electrode in dry DMF containing 0.1 M tetraethylammonium perchlorate (TEAP), at 25 °C. A series of substrates was selected in order to study the substituent effect at both the nitrogen and α-carbon atom. For all compounds, n was found to increase by increasing log v, till reaching a plateau for $n = 1$. Figure 3 shows typical plots. The first-order character of reaction 4 was checked on a quantitative ground by running experiments at different substrate concentration in the range 0.7–4 mM, under otherwise identical conditions. For each compound and v value, the n data obtained by such measurements were coincident within experimental error, thus confirming the independence of n on the concentration (see for example the different sets of data used in Figure 3). Comparison of the experimental n data with the corresponding theoretical curves finally led to the calculation of the first-order rate constants k that are shown, together with the relevant electrochemical data, in Table I. To verify possible effects caused by bromide ions on the bromo amide anion decay, some runs were carried out using tetraethylammonium bromide (TEAB) and a series of such data is also reported in Table I. Comparison of the kinetic data obtained with the two salts shows that the decay of the bromo amide anions is slightly affected by the anion of the electrolyte; using TEAP the observed rate constants are 1.2–1.5 times higher than those obtained working in the presence of TEAB. Using mixed electrolytes, however, it was verified that once the concentration of bromide ion was decreased from 0.1 M by about one order of magnitude, the k values became the same within experimental error of those obtained with the perchlorate salt, therefore supporting the irreversibility of decay 4 in DMF + 0.1 M TEAP.

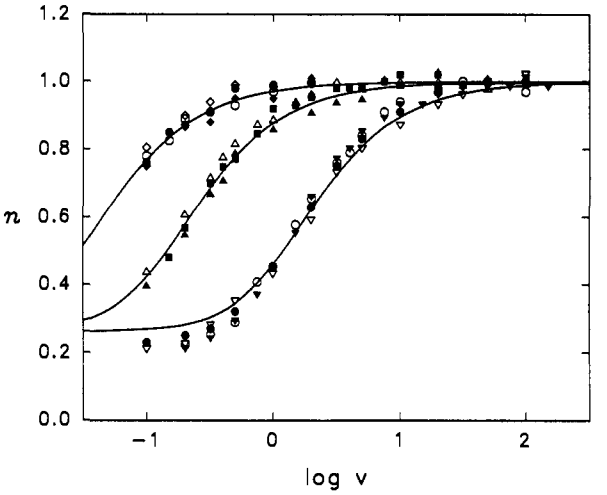


Figure 3. Scan rate dependences of the apparent number of electrons n for the reduction of the conjugate bases of the following 2-bromo amides (from left to right): 2-bromo-2-methyl-*N*-phenylpropanamide (◆, 0.7 mM; ●, 1.0 mM; ○, 1.1 mM; ◇, 2.4 mM. For clarity, only those data obtained at $v \leq 2$ V/s are reported in the plot), 2-bromo-2-methyl-*N*-benzylpropanamide (▲, 0.8 mM; ■, 1.5 mM; △, 3.5 mM), and 2-bromo-2-methyl-*N*-cyclohexylpropanamide (○, 0.9 mM; ▽, 1.2 mM; ●, 3.3 mM; ▼, 3.6 mM). DMF–0.1 M TEAP, $T = 25$ °C. For each 2-bromo amide anion, the experimental n values have been fitted onto the corresponding computed variation of n vs log v (solid curves).

Table I. Electrochemical Data for the Reduction of 2-Bromo Amides **1** in DMF at 25 °C and First-Order Rate Constants for the Decay of Anions **2**

R	R_1	R_2	$-E_{p1}$[a] (V)	α_1	$-E_{p2}$[a] (V)	α_2	k[b] (s^{-1})	X^-[c]	pK_a
Ph	Me	Me	1.01[d]	0.30[d]	1.97[d]	0.31[d]	0.060	ClO_4^-	18.9[e]
$CHPh_2$	Me	Me	1.12	0.25[e]	2.21	0.34	0.15	ClO_4^-	21.2[e]
CH_2Ph	Me	Me	1.22[d]	0.28[d]	2.19[d]	0.34[d]	0.29	ClO_4^-	22.2[e]
Me	Me	Me	1.30[d]	0.32[d]	2.22[d]	0.35[d]	0.97	ClO_4^-	23.4[f]
C_6H_{11}	Me	Me	1.35[d]	0.28[d]	2.28[d]	0.34[d]	2.4	ClO_4^-	24.4[f]
t-Bu	Me	Me	1.43[d]	0.31[d]	2.31[d]	0.33[d]	9.0	ClO_4^-	25.6[f]
Ph	Me	H	1.04	0.36	2.02	0.32	0.16	ClO_4^-	
CH_2Ph	Me	H	1.26	0.29	2.31	0.36	0.50	ClO_4^-	
Ph	H	H	1.04	0.40	1.94	0.26	0.20	ClO_4^-	
CH_2Ph	Me	Me	1.21	0.28	2.18	0.33	0.21	Br^-	
Me	Me	Me	1.29	0.31[g]	2.20	0.32[g]	0.65[g]	Br^-	
C_6H_{11}	Me	Me	1.34	0.30	2.25	0.33	2.0	Br^-	
t-Bu	Me	Me	1.41	0.30	2.27	0.31	5.8	Br^-	

[a] E_p values are given for $v = 0.2$ V/s relative to SCE and have been directly measured (E_{p1}) or extrapolated (E_{p2}) from high scan rates (see Experimental Section). [b] The values are reproducible to ±7% or less. [c] X^- is the anion of the Et_4NX supporting electrolyte (0.1 M). [d] Reference 21. [e] Reference 22b. [f] See ref 33. [g] Reference 29.

Inspection of the kinetic data in Table I indicates that the rate of the decay of 2-bromo amide anions increases when the electron withdrawing character of the R substituent at nitrogen (and thus the NH-acidity) decreases. Moreover, the character of the halide affects the decay rate in the order tertiary < secondary < primary.[32] Such results support the idea that loss of bromide ion in reaction 4 is more in agreement with an S_N2-type reaction than with an S_N1-type ionization. A further observation is that most compounds reported in Table I were previously studied under macroelectrolysis conditions in DMF.[4a–c] In each investigated case, a large fraction of the resulting bromo amide anion was found to decay affording a cyclocondensation product with DMF,

(29) Maran, F.; Severin, M. G.; Vianello, E.; D'Angeli, F. *J. Electroanal. Chem.*, in press.

(30) The generalized form of the kinetic scheme describing the decay of bromo amide anions can be represented[29] as

$$2A + 2e^- \rightarrow B$$

$$B + 2e^- \rightarrow C$$

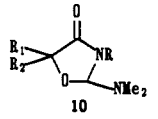
$$B \rightarrow D$$

The first two equations represent the irreversible electrode processes taking place at the first and second peak. The first equation derives from the assumption that the self-protonation reaction is fast in the time scale of the experiment[27] so as to occur in the very proximity of the electrode.[30a] The formation of reduced amide **7** can be neglected. Species C and D are neither chemically reactive toward A and B[30b] nor electroactive in the potential range of interest. (a) The validity of such an approximation was tested previously on studying the mechanism of the disappearance of anions **2** through proton transfer by added acids.[22] (b) C represents dianion **8** whose chemistry is unimportant for the present kinetic analysis because in such reaction we have the deprotonation of **7** to yield **9** (eq 5), i.e., the formation of another species which can be neglected in the scheme. Concerning D, it will be shown that its reactivity is not linked to any of the above species.

(31) A limiting situation of this type was also proposed to be responsible for the small reduction wave of butyl radicals which were generated at less negative potentials by voltammetric reduction of the corresponding iodides: Andrieux, C. P.; Gallardo, I.; Savéant, J.-M. *J. Am. Chem. Soc.* **1989**, *111*, 1620.

(32) The voltammetric pattern for the reduction of 2-bromoacetamides and 2-bromopropanamides is sometimes less reproducible than found with 2-bromoisobutyramides, in particular when *N*-alkylamides are considered. However, a semi-quantitative determination of the decay rate of both 2-bromo-*N*-benzylacetamide and 2-bromo-*N*-*tert*-butylpropanamide was also in line with the trend tertiary < secondary < primary.

oxazolidin-4-one **10**, often in quantitative yield. Such cyclocondensation could involve, in principle, either the bromo amide



10

anion **2** or any of the intermediates **3**–**5**[6b,c] arising upon loss of bromide ion. Although the kinetic experiments suggest that a concerted substitution reaction is causing the disappearance of **2**, the measured rate constants k are apparent first-order rate constants and thus either an intramolecular reaction, or a pseudo-first-order reaction with DMF, or even a mixture of both would be in agreement with the experimental results. In this context, the results obtained with the series of 2-bromo-*N*-alkylisobutyramides provide further mechanistic arguments. In fact, a Brønsted-type analysis of the rate-equilibrium data permits to calculate a slope of 0.4.[33] Although the variation of the R substituent at nitrogen could affect to some degree also the electrophilicity of the α-carbon, the rate data can be considered to reflect essentially the variation of the nucleophile. Under such reasonable hypothesis, the observed Brønsted slope provides an input[34] in favor of an intramolecular substitution reaction instead of a bimolecular reaction of **2** with DMF and, furthermore, decreases the relevance of a possible intramolecular electron transfer leading to a transient diradical species.

Stereochemistry. Substrates carrying a chiral nonracemic α-carbon are appropriate candidates to provide further insight into the mechanism of the decay. With respect to other 2-halo amides, 2-bromo amides **1** are the best suited substrates owing to the convenient time scale of the decay of their conjugate bases **2**. A further useful feature is a high NH-acidity, to check possible acid–base equilibria with nucleophiles. On such grounds, (*S*)-(–)-2-bromopropananilide was selected as an appropriate substrate to follow the stereochemical evolution of the decay.

The reaction of *tert*-butylamine with (*S*)-2-bromopropananilide was studied as representative of the substitution reactions. In the absence of strong bases, about 2 days are required at room temperature to carry out the substitution up to 90% conversion, in either toluene[18] or DMF. The inversion product (*R*)-(+)-2-*tert*-butylaminopropananilide ((*R*)-**11**) was obtained in quantitative enantiomeric excess. The observed net inversion points to an S_N2 reaction involving either the neutral bromo amide **1** or its conjugate base **2** and excludes all possible intermediates arising upon bromide loss from **2**. A reaction of the amine with **2** is based on the hypothesis of a mechanism in which an initial proton transfer between **1** and the amine takes place; although such a proton transfer is unfavored,[35] the overall process could be driven by the substitution reaction onto bromo amide anion **2**. For this purpose, the effect of the amine on the voltammetric pattern of the 2-bromo amide was studied. For $v < 5$ V/s, the peak of the 2-bromopropananilide anion is lower than its one-electron level; for example, about $^1/_4$ of the bromo amide anion generated by self-protonation at 0.2 V/s decays in the reaction layer before being electroreduced. In the presence of a reagent able to react with the bromo amide anion in a time scale equal or shorter than that typical of the decay of anion **2**, the new competitive reaction would lower the current of the second peak as a function of both the concentration and v. Addition to the solution of up to 20 equiv of the amine, however, did not affect at any v value either the first or second reduction peak, and, in particular, the absence of effects on the second peak showed that the amine is unable to interfere with the decay of bromo amide anion. Therefore, both the stereochemical and kinetic information indicate that the amine must react by an S_N2 reaction with the neutral 2-bromo amide, since it is unable to react directly with the bromo amide anion. Such considerations hold even more when 2-bromo amides less acidic than an anilide[22b] are used.

The substitution by *tert*-butylamine was also performed under macroelectrolysis conditions, i.e., by promoting the reaction through the controlled generation of the homogeneous base **6** and thus making use of the self-protonation sequence. As in the kinetic experiments and in view of the reaction of 2-bromo amides with DMF, the reduction was carried out in this solvent. Upon electrolysis at the first peak, working in the presence of 20 equiv of *tert*-butylamine, (*S*)-(–)-2-bromopropananilide disappeared after consumption of 1.0 F/mol, as expected.[21] Product analysis revealed the presence of reduced amide **7** (propananilide, 50% yield), a diastereomeric mixture of the DMF adducts **10** (2-(dimethylamino)-5-methyl-3-phenyloxazolidin-4-ones, 9% overall yield, 1:1 ratio), (*S*)-(–)-2-*tert*-butylaminopropananilide **11** (26% yield), and an optically active *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine **12** (15% yield).

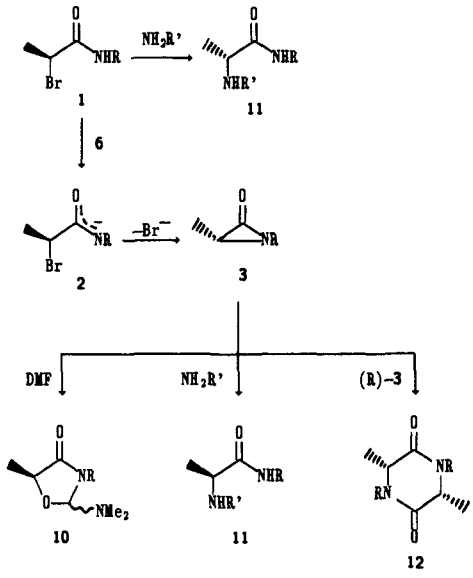
At variance with the net inversion observed in the unpromoted reaction, the formation of the (*S*)-2-amino amide, (*S*)-**11**, indicates that the reaction promoted by the electrogenerated base **6** goes through an apparent retention of configuration. The reduction of (*S*)-(–)-2-bromopropananilide was carried out also in the absence of the amine, under otherwise identical conditions. Macroelectrolysis again required 1.0 F/mol and led to the formation of propananilide (50%), diastereomeric oxazolidinones (28%, 1:1 ratio), and *cis*-dioxopiperazine (22%). The diastereomeric oxazolidinone mixture was hydrolyzed as previously described[4c] to afford 2-hydroxypropananilide which was identified as the (*S*)-(–)-enantiomer. Therefore, also the formation of the diastereomeric mixture of oxazolidinones (5*S*,2*SR*)-**10** points to retention of configuration in the overall reaction at the α-carbon. Finally, the same optically active dioxopiperazine that formed in the electrolyses was also obtained, 40% yield, in the reaction of (*S*)-(–)-2-bromopropananilide with sodium hydride in toluene.

Mechanism of the Decay and Conclusions. Some observations can be made on the experimental results obtained in DMF either in the presence or absence of the amine. First, the electrochemically induced formation of **10**, **11**, and **12** is not in competition with the unpromoted substitution reaction, which takes place in a much longer time scale. Under electrochemical conditions, the bromo amide anion **2** is formed in solution by the reduction/self-protonation sequence (1–2). The presence of both the (*S*)-amino amide and the (5*S*,2*SR*)-oxazolidinone mixture in the products indicates that the species reacting with either the amine or DMF is a transient intermediate arising from the bromo amide anion upon loss of bromide (eq 4). In fact, since it was verified that the observed products form irreversibly, the product ratios can be looked at as reflecting the competitive kinetics and therefore the reaction with the amine results much faster than that with DMF. Since, as shown above, the bromo amide anion does not react with the amine during its lifetime, even more so it cannot be directly involved in the slower reaction with DMF. The consequence is that the kinetics of the decay of the bromo amide anion is not due to a pseudo-first-order reaction of **2** with DMF but describes the rate of a preceding, first-order reaction in which the loss of bromide ion takes place. A further observation is that the yield of **12** is reduced when the electrolysis is performed in the presence of the amine, as it happens for the DMF-containing products **10**. Therefore, since also the formation of **12** is irreversible, the optically active **12** must arise in a further competitive reaction consuming the same reactive species that formed in reaction 4.

(33) The pK_a values for the least acidic 2-bromo amides were estimated from the correlation $pK_a^{DMF} = 2.1–15.8\,E_{pl}$ (0.2 V/s, DMF–0.1 M TEAP, 25 °C),[33a] $r = 0.995$: Maran, F. unpublished data. (a) The equation was obtained using E_{pl} values measured in the presence of a suitable strong acid or CO_2 in order to clear them from the effect of the self-protonation.[33b] (b) Maran, F.; Vianello, E. *Tetrahedron Lett.* **1990**, *31*, 5803.

(34) β_{nu} in the range 0.2–0.5 are typical of S_N2 reactions. See, for example: Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. In *Nucleophilicity. Advances in Chemistry Series 215*; Harris, J. M., McManus, S. P., Eds.; American Chemical Society: Washington, DC, 1987; p 137.

Scheme II



The stereochemistry of the products indicates that the loss of bromide ion must preserve the chiral center. Therefore, the product determining intermediate must be a closed species arising upon concerted intramolecular bromine substitution within anion **2**, in agreement with the outcome of the kinetic analysis. Only the aziridinone **3** and the iminooxirane **4** are actually in line with this observation but owing to the nature of the products, in particular oxazolidinones **10** and *cis*-dioxopiperazine **12**, the aziridinone **3** results to be the best description of the actual *product-determining and chirality-carrying intermediate*. Although only a relatively weak bond might form between nitrogen and α-carbon, it must be strong enough to hamper racemization at α-carbon in the time scale of the reactions of the transient intermediate **3** with the amine, or the DMF molecule, or itself. Scheme II summarizes the above findings.[36] The aziridinone **3** undergoes 1,3-ring opening through backside attack by the amine, with inversion at the α-carbon. Analogously, the DMF molecule opens the ring of **3** with inversion at the α-carbon by reacting as an oxygen nucleophile. The resulting dipolar open species eventually collapses to give **10** by C–N bond formation, a mechanism that accounts for the formation of a 1:1 diastereomeric mixture and which is in agreement with a similar result obtained very recently,[10b] starting however from a stable aziridinone. Concerning the formation of *cis*-**12** it appears that a four-center, head-to-tail reaction of two identical chiral aziridinones takes place,[37] although the actual mechanism of such a reaction would require further investigation.

(35) Although the acidity of 2-bromo anilides is high as NH-acids, the proton transfer here considered is unfavored by a factor 10^{-8}.[35a] (a) Methyl substitution at the α-carbon almost unaffects the NH-acidity of amides,[22b,35b] and thus the pK_a of 2-bromopropananilide in DMF should be around 18.9, that of 2-bromoisobutyranilide.[22b] The pK_a of *t*-$BuNH_3^+$ in DMF is unknown but should be similar[35c] to that of *n*-$BuNH_3^+$ which has been reported to be 10.5[35d] and 9.1.[35e] (b) Bordwell, F. G.; Fried, H. E. *Tetrahedron Lett.* **1977**, 1121. (c) As a matter of fact, the pK_a's of *n*-$BuNH_3^+$ and *t*-$BuNH_3^+$ differ in CH_3CN by only 0.1 pK_a unit: Coetzee, J. F.; Padmanabhan, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 5005. (d) Demange-Guerin, G. *Talanta* **1970**, *17*, 1075. (e) Kolthoff, I. M.; Chantooni, J. K., Jr.; Smagowski, H. *Anal. Chem.* **1970**, *42*, 1622.

(36) The independence of the decay rate in DMF–TEAP on the concentration of bromide ion, mentioned in the kinetic section, and thus the apparent irreversibility of reaction 4 is due to the reactions consuming **3** and leading to products **10** and **12**. Such result indicates that for the selected substrates and conditions the rate of the reaction with DMF is overwhelming that with bromide ion.[36a] (a) In fact, in the absence of other partners, stable aziridinones react with halide salts to yield 2-halo amides.[3a,10a]

(37) As depicted in Scheme II, the formation of (3*R*,6*R*)-**12** is hypothesized. This is also suggested by the outcome of analogous, preliminary reactions carried out with (*S*)-(–)-2-bromo-*N*-benzylpropanamide; whereas such compound yields optically active *cis*-**12** together with its trans isomer, in significantly lower amount, an enantiomeric excess for (3*R*,6*R*)-**12** is supported by comparison with an authentic sample of (3*S*,6*S*)-1,4-dibenzyl-3,6-dimethyl-2,5-dioxopiperazine.

The intermediacy of aziridinone **3** should be of rather general mechanistic value. First, the set of kinetic data given in Table I are relative to substrates in which the substituents at both nitrogen and α-carbon have been varied significantly; such data are in agreement as a whole with the mechanism of intramolecular nucleophilic substitution leading to **3** and in particular with an S_N2-type reaction, as supported by the Brønsted-type analysis. A second observation concerns the use of an anilide in the stereochemical investigation. Anilides provide a good chance of delocalizing the negative charge and in the meanwhile do not yield stable aziridinones.[1,8] Since both factors work in favor of dipolar ion **5**, the absence of racemic products observed with 2-bromopropananilide is worth noting. A final consideration regards the role of the solvent. Whereas the base-promoted reactions of 2-halo amides (or other precursors leading to analogous products) have been routinely carried out in weakly polar solvents,[1-3] the present results have been obtained in a dipolar solvent such as DMF that is particularly suitable to solvate cations.[38] As before, a good chance was provided to the decay to proceed via the dipolar ion **5**. Therefore, if a definite enantioselectivity is obtained with the selected system, the mechanism depicted in Scheme II should hold even more under less ionizing conditions, as witnessed for example by the formation of the same optically active **12** when the reaction is promoted either by the homogeneous electrogenerated base **6** in DMF or the heterogeneous base NaH in toluene.

Scheme II depicts the outcome of just a few trapping reactions of a transient aziridinone in which full transmission of chirality is observed. It can be expected, however, that other reaction partners, capable to react with **3** at least in a similar or shorter time scale, should yield products under enantioselectivity control.[39] It is also worth noting that the present mechanistic analysis provides strong evidence about the intermediacy of **3** although only one among the series of 2-bromo amides used in this work, 2-bromo-*N*-*tert*-butylisobutyramide, is liable to afford a relatively stable aziridinone.[40] A further conclusion is thus that there is no real need of looking for structural or environmental factors leading to the stabilization and/or isolation of aziridinones.[1,3b,i,8] This is particularly true when enantioselective results are sought, as witnessed by the results reported here. In this light and also in view of the growing interest on the base-promoted asymmetric syntheses involving amides carrying chiral auxiliaries,[41] chiral 2-halo amides, which are easily obtained from the chiral pool of natural amino acids,[42] emerge as convenient starting materials for straightforward enantioselective reactions at the α-carbon.

Experimental Section

N,*N*-Dimethylformamide (Aldrich) was purified as previously reported.[22b] Tetraethylammonium perchlorate (Fluka), tetraethylammonium bromide (Erba), and tetrabutylammonium perchlorate (Fluka) were recrystallized from ethanol, ethanol–diethyl ether, or ethanol–water, respectively. Each salt was dried under vacuum at 60 °C and then stored

(38) Gutmann, V. *The Donor–Acceptor Approach to Molecular Interactions*; Plenum: New York, 1978.

(39) Rigorously, since the rate of the reaction with the aziridinone intermediate **3** is a key point for enantioselectivity, the possibility that the available reagents might be unable to trap **3** within its lifetime should be considered. For example, this could be the case using dipolar nonprotogenic solvents of high donicity[38] and amides bearing powerful electron withdrawing substituent at nitrogen and cation-stabilizing substituents at the α-carbon. On the basis of previous results, obtained at room temperature with 2-bromoisobutyramides[4b] or stable aziridinones upon heating,[1,8] it must be also considered that in the absence of suitable partners the transient aziridinone either fragments or, whenever possible, rearranges to the α,β-unsaturated amide, probably via open species[6] and iminooxirane **4**.

(40) Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356.

(41) For several examples see the following papers and references cited therein: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011. Nerz-Stormes, M.; Thronton, E. R. *J. Org. Chem.* **1991**, *56*, 2489. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747.

(42) See references 18 and 19d, references cited therein, and: Koppenhoefer, B.; Schurig, V. In *Organic Synthesis*, Heathcock, C. H., Ed.; Wiley: New York, 1988; Vol. 66, p 151. Larcheveque, M.; Mambu, L.; Petit, Y. *Synth. Commun.* **1991**, *21*, 2295.

over P_2O_5. The syntheses and spectral data of each amide and 2-bromo amide used in this study have been already reported.[2a,c,4b,18,19d,21,22b]

Electrochemical Apparatus and Procedures. Electrochemical measurements were conducted in an all glass cell, thermostatted at 25 ± 0.2 °C. All glassware was predried overnight in an oven at 80 °C and assembled while still hot. In order to keep the water content at minimum, most experiments were carried out after treating the solvent–electrolyte system with alumina (Merck, activity grade 1), previously activated overnight at 350 °C under vacuum. The solution was deoxygenated with argon (SIAD, 99.9995%) and then a blanket of gas was maintained over the liquid. A mercury microelectrode, prepared and activated as previously described,[22b] and a magnetically stirred mercury pool served as the cathodes for voltammetric measurements and macroelectrolyses, respectively. The reference electrode (Ag/AgCl) and the counter-electrode have been also described previously.[43] After each voltammetric experiment, the potential of the reference electrode was calibrated against the KCl saturated calomel electrode (SCE). The electrochemical instrumentation was PAR 173/179 potentiostat-digital coulometer, PAR 175 universal programmer, Nicolet 3091 digital oscilloscope, and Amel 863 *X/Y* pen recorder.

Families of voltammetries were recorded at various scan rates in the range 0.1–100 V/s. Each voltammogram was then processed to obtain the values of the peak current i_p and peak potential E_p, for both the first and second peak. The measurement of the current of the second peak was made with reference to the *i* vs *time* curve recorded by stopping the scan at an appropriate potential between the first and second peak.[44] The typical separation of about 1 V between the two peaks was large enough to reduce at minimum possible errors. Plots of E_p and $i_p/v^{1/2}$ as functions of log *v* were constructed for both peak. The slope of the E_p vs log *v* plots was used[44] to calculate the transfer coefficients α_1 and α_2,[45] necessary to compute the *n* vs log λ curves and eventually the rate constant values. Since the occurrence of the chemical decay 4 affects both the shape and the position of the second peak,[29] the majority of α_2 data were obtained from E_{p2} values pertaining to relatively high scan rate ranges, i.e., where the E_{p2} vs log *v* plots are linear; this condition is roughly verified starting from *v* values at which $n > 0.5$.

The voltammetric behavior of the first peak was then studied to establish the maximum scan rate to be used in the kinetic measurements of the bromo amide anion decay. In particular, the constancy of the ratio $(i_p)_1/v^{1/2}$ within 2–3% was taken as the proof of working under kinetic self-protonation regime.[27] At any scan rate, *n* was obtained by normalizing the actual current function with respect to the one-electron value that, in turn, was easily calculated from the data obtained at high scan rates, in the plateau region. The *n* vs log λ working curves were obtained as previously described.[29] The rate constant *k* was finally obtained by a best fitting procedure in which the experimental values of *n* were compared with the pertinent working curve. For each compound, 30–50 *n* values, obtained at different scan rates and substrate concentrations, were used to calculate the corresponding *k* value.

Electrolysis and Analysis of the Products. Controlled potential electrolyses were carried out in the limiting current region of the first peak. In some experiments, a second sample of the 2-bromo amide was added to the electrolytic solution and the same procedure repeated. The electrolyzed solutions were then worked up as follows. The solvent was distilled off at low pressure, and the product mixture was extracted with diethyl ether (typically 3 × 10 mL), leaving the supporting electrolyte undissolved. The ethereal solution was then evaporated to yield the crude product mixture, usually as an oil, that was analyzed by ^{1}H NMR and HPLC. ^{1}H NMR spectra were recorded using a Bruker AC 200 spectrometer. Chemical shifts (δ) are reported as ppm downfield from tetramethylsilane. HPLC was performed using a Bruker LC 21-C liquid chromatograph, equipped with a Bruker LC 313 UV variable wavelength detector and a computer for chromatogram analysis. A 4.6 mm × 25 cm stainless steel column packed with Spherisorb 5 ODS2 C_{18}, 5 μm mean particle size, was employed. The eluting solution was usually 50% acetonitrile–50% water. Quantitative analysis was performed in comparison with authentic samples. Preparative HPLC separations were performed wtih a Waters Delta Prep 3000 system using a 3 mm × 30 cm column packed with Delta Pak C_{18} 3000 A, 15 μm mean particle size. The eluting solutions were mixtures acetonitrile–water, sometimes enriched with 0.1% trifluoroacetic acid. Column chromatography was performed using SiO_2 columns (Merck, KG-60). Melting points were measured with a Reichter-Kofler instrument and are uncorrected. Specific rotations [α] were measured using a Perkin-Elmer 241 polarimeter.

Electrolysis of (*S*)-(–)-2-Bromo-*N*-phenylpropanamide in DMF. A sample of (*S*)-(–)-2-bromopropananilide (144 mg, 0.63 mmol), $[\alpha]_{D^{20}} = -40.8°$, *c* 1.0, $CHCl_3$, was dissolved in DMF (60 mL) containing *n*-Bu_4NClO_4 (0.1 M). The bromo amide was exhaustively reduced at –1.4 V SCE. The current dropped to vanishing values after a charge consumption of 1.02 F/mol. The resulting solution was concentrated and then extracted to yield an oil (100 mg). ^{1}H NMR analysis revealed the presence of propananilide (50%), diastereomeric 2-(dimethylamino)-5-methyl-3-phenyloxazolidin-4-ones in a 1:1 ratio (28%, overall yield), and *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine (22%). The product mixture was then dissolved in THF (1 mL) and treated with 2 N HCl (0.25 mL). The colorless solution was magnetically stirred overnight and concentrated under vacuum to yield an oil. The products were finally separated by HPLC to yield the following colorless compounds: (*S*)-(–)-2-hydroxypropanamide[46] (18 mg, $[\alpha]_{D^{20}} = -15.6°$, *c* 1, $CHCl_3$); propananilide (33 mg); *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine (17 mg, $[\alpha]_{D^{20}} = -26.9°$, *c* 1, $CHCl_3$): mp 188–189 °C; ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 6 H, *J* = 7 Hz, $2CH_3$), 4.51 (q, 2 H, *J* = 7 Hz, 2CH), 7.38 (m, 10 H, 2Ph).

Electrolysis of (*S*)-(–)-2-Bromo-*N*-phenylpropanamide in DMF Containing *tert*-Butylamine. A typical experiment was performed as follows. A sample of (*S*)-(–)-2-bromopropananilide (134 mg, 0.59 mmol) was dissolved in DMF (60 mL) containing *n*-Bu_4NClO_4 (0.1 M) and *tert*-butylamine (1.24 mL, 11.8 mmol). The bromo amide was reduced at –1.4 V SCE, with consumption of 1.01 F/mol. The resulting solution was worked up to yield a colorless oil (116 mg): ^{1}H NMR analysis revealed propananilide (50%), diastereomeric 2-(dimethylamino)-5-methyl-3-phenyl-oxazolidin-4-ones in a 1:1 ratio (9% overall yield), *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine (15%), and 2-(*tert*-butylamino)propananilide (26%). The oil was chromatographed (esane–ethyl acetate 1:2) to yield propananilide, the partially hydrolyzed oxazolidinones,[4c] and (*S*)-(–)-2-(*tert*-butylamino)propananilide[18] (27 mg; $[\alpha]_{D^{20}} = -48.7°$, *c* 1, $CHCl_3$).

Reaction of (*S*)-(–)-2-Bromo-*N*-phenylpropanamide with *tert*-Butylamine in DMF. The reaction was performed as previously done in toluene.[18] (*S*)-(–)-2-Bromopropananilide (114 mg, 0.5 mmol) was treated with *tert*-butylamine (182 mg, 2.5 mmol) in DMF (5 mL) for 48 h at room temperature and then concentrated under vacuum. The resulting colorless oil (109 mg) revealed that about 90% of the 2-bromo amide had reacted with the amine. Chromatography (esane–ethyl acetate, 1:8) provided (*R*)-(+)-2-(*tert*-butylamino)-*N*-phenylpropanamide[18] (85 mg, $[\alpha]_{D^{20}} + 49.1°$, *c* 1.0, $CHCl_3$). The other enantiomer was undetected by ^{1}H NMR using the shift reagent Eu(tfc)$_3$.

Reaction of (*S*)-(–)-2-Bromo-*N*-phenylpropanamide with Sodium Hydride in Toluene. The reaction was performed as previously described for racemic 2-bromopropananilide in tetrahydrofuran[2c] and provided an analogous product mixture. At difference with the previous outcome which provided both the cis and trans isomer,[2c] only *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine (40% yield) was detected. Chromatography and recrystallization gave a sample having $[\alpha]_{D^{20}} = -27.5°$ (*c* 1, $CDCl_3$).

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(45) In principle, the potential dependence of the transfer coefficient α should be taken into account.[45a] Concerning reductive cleavages, the potential dependence of α has been found with alkyl,[45b] fluorenyl,[45c] and benzyl halides[45d] and a sulfide.[24b] However, the potential dependence of α for the reduction of 2-bromo amides is of the order of the experimental error on peak current measurements; α is thus considered to be constant all over the potential range explored by each peak on varying *v*. (a) See, for example: Savéant, J.-M.; Tessier, D. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 57 and references cited therein. (b) Andrieux, C. P.; Gallardo, I.; Savéant, J.-M. *J. Am. Chem. Soc.* **1986**, *108*, 638. (c) Maran, F. et al. work in progress. (d) Andrieux, C. P.; Le Gorande, A.; Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 6892.

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