

An Electrochemical Determination of Relative pK_a of Weak Acids in *N,N*-Dimethylformamide

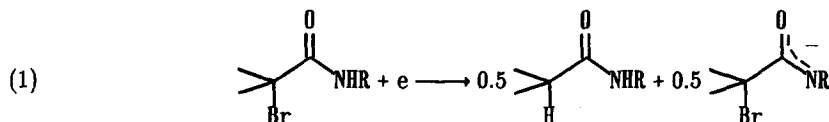
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Abstract – The self-protonation reaction undergone by α -bromoamides upon electroreduction in *N,N*-dimethylformamide is employed to get relative pK_a data on a series of *N*-H acids. The results are compared with the pK_a 's of the same acids in dimethylsulfoxide.

The electrochemical reduction of organic compounds is usually associated with the generation of basic species, such as carbanions, radical anions, and dianions. An interesting mode of reaction of electrogenerated bases in dry dipolar aprotic solvents is featured by the *self-protonation* reaction, in which the electrogenerated base undergoes protonation by the starting compound itself.¹ From a theoretical point of view the self-protonation reaction has noticeable relevance to the study of electroreduction processes in that it may explain apparently confusing experimental data, such as for instance an electron consumption lower than expected and partial recovery of the starting material after macro-electrolysis. However, since some of the starting compound is transformed into its conjugate base which is a species no longer reducible at the working potentials, the occurrence of the self-protonation reaction is usually of no practical utility. A possible exception is when the product determining intermediate is or derives from the conjugate base of the starting compound.² In this communication we will report an original application of self-protonation in the framework of the general problem of acidity determination in dipolar aprotic solvents.

The electroreduction of secondary α -bromoamides in *N,N*-dimethylformamide (DMF) affords two irreversible voltammetric peaks. The reduction stoichiometry at the first peak is:³

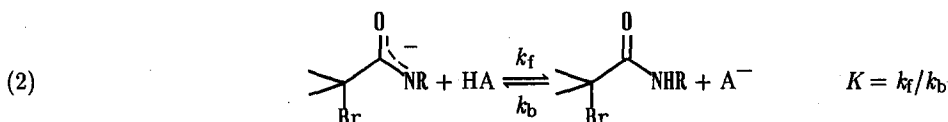


Two-electron reduction causes the breaking of the C-Br bond and leads to the formation of the carbanion⁴ which is quickly protonated by the parent molecule (rate constants are in the 10^7 – 10^8 $M^{-1}s^{-1}$ range)³ to yield the reduced amide and the conjugate base of the bromoamide. As a consequence, one-electron per molecule is apparently consumed in the process. The bromoamide anion undergoes two-electron C-Br bond cleavage at the second peak, so that, taking into account stoichiometry (1), an apparent one-electron process should be observed also at the second peak. This

anion, however, is a labile species releasing bromide ion in a concerted intramolecular nucleophilic substitution⁵ and thus a one-electron peak is observed only when the bromoamide anion is stable in the time scale of the experiment. From the scan rate (v) dependent competition between reduction and decay, the kinetics of the latter reaction can be determined.⁵

The calculation of the rate constant of both the self-protonation reaction and bromoamide anion decay allows one to define the v range and thus the time window in which the bromoamide anion is quantitatively formed (total efficiency of the self-protonation reaction) and is stable (no time enough for the chemical decay to take place). In this time window, we have the opportunity to provoke and study other reactions involving the bromoamide anion.

If the solution is added up with a relatively strong acid, the self-protonation step is hampered due to the quantitative protonation of the carbanion by the exogenous acid. As a consequence, whereas the current of the first peak doubles, featuring an actual two-electron process, the second peak disappears.³ On the contrary, when an acid weaker than the bromoamide is used, the self-protonation reaction is still operative and thus the first peak is unaffected. The second peak, however, decreases and a third, broad peak appears in the region in between the two main peaks.⁷ Such effects, which are magnified by an increase of the exogenous acid concentration and minimized by an increase of v , were expected to be caused by the regeneration of the starting bromoamide through equilibrium



where HA and A^- denote the exogenous acid and its conjugate base, respectively. It is worth noting that equilibrium (2) represents the difference in thermodynamic acidity (ΔpK_a) between the bromoamide and the exogenous acid HA. Therefore, proper analysis *via* voltammetric simulation of the reduction sequence (1,2) appeared to be an original method for calculating relative acidities.

In order to test the proposed mechanism and thus the method, the electroreduction of α -bromoisobutyranilide (BA) was studied in DMF + 0.1 M Et_4NClO_4 as a representative case. Experiments were driven in the absence and then in the presence of a series of N-H acids of known pK_a in dimethylsulfoxide (DMSO).⁸ Different v values (from 0.5 to 50 V/s, limits imposed by the rate of the bromoamide anion decay⁶ and the self-protonation reaction,³ respectively) and two concentration ratios, $\gamma = [\text{HA}]/[\text{BA}]$, were used. For each γ and K value, the system can be described⁹ by the kinetic parameter $\lambda = k_b RTC / \alpha F v$, where $C = [\text{BA}]$ and α is the electron transfer coefficient (for BA,³ $\alpha = 0.30$). For both γ 's and at all v values used, good overlapping of the experimental curves with the simulated voltammograms (*e.g.* Figure 1) was obtained by proper choice of the equilibrium constant K and the v dependent variation of the parameter λ , the error on K amounting to no more than $\pm 0.05 pK_a$ units.

Best fitting afforded the following ΔpK_a values (in brackets are reported the pK_a values in DMSO)¹⁰: formanilide, 1.42 (19.4),^{10b} N,N -diphenylurea, 1.73 (19.55); carbazole, 1.77 (19.9); phenylacetanilide, 2.68 (20.6); indole, 2.77 (20.95); acetanilide, 3.41 (21.45); isonicotinamide, 3.23 (21.5); phenoxazine, 3.46 (21.65); nicotinamide, 3.64 (22.0).^{10a} The validity of the method is supported

by the plot ΔpK_a^{DMF} vs. pK_a^{DMSO} reported in Figure 2. Least square analysis provides a slope of 0.865 and a correlation coefficient of 0.991. The correlation is considered satisfactory, in particular by considering that we are comparing results obtained in DMF with literature pK_a values in DMSO. Some differences are to be expected on passing from DMSO to DMF but on the other hand they should be rather small.¹¹

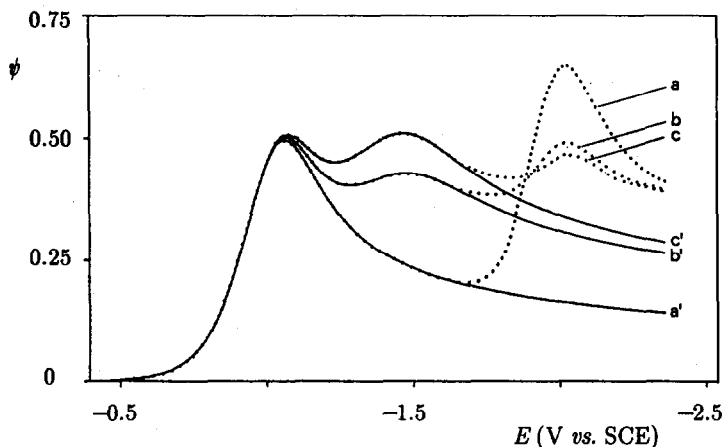


Figure 1. Voltammograms of 1 mM BA in DMF + 0.1 M Et_4NClO_4 at 0.5 V/s in the absence (curve a) and in the presence of acetanilide (curve b, $\gamma = 10$; curve c, $\gamma = 20$). The solid lines (curves a', b', c') are the corresponding simulated voltammograms (second peak not included in the calculations). ψ = dimensionless cathodic current.

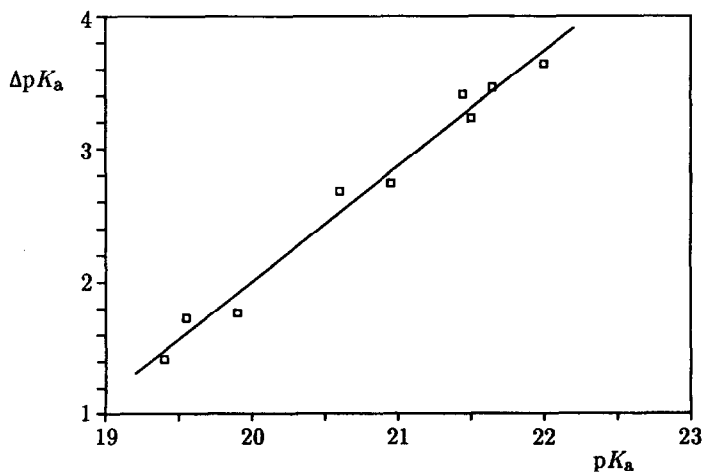


Figure 2. Correlation between $\Delta pK_a = pK_a(\text{HA}) - pK_a(\text{BA})$ obtained in DMF at 25 °C (this work) against $pK_a(\text{HA})$ in DMSO at 25 °C.¹⁰

From this analysis it comes out that the exogenous acid must be at least 1.4 pK_a units less acidic than the α -bromoamide. A limitation on the other side is that the acidity of the proton donor should not be much lower than that of the bromoamide, otherwise too high γ values would be required. It seems, however, that an overall variation of up to ca. 2.5 pK_a units can be covered. Since proper modulation of the R substituent at nitrogen allows one to vary the acidity of amides¹² and thus the pK_a range explored, we are planning to enlarge the present investigation to other α -bromoamides as well as to anchor the data with the low pK_a scale in DMF. In this framework, it is worth noting that, in spite of the relevance of DMF for both organic and electroorganic processes, the high pK_a region (say, $pK_a > 18$) in this solvent is almost¹³ unexplored with respect to e.g. DMSO.

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REFERENCES AND NOTES

- (a) Many investigations on the electroreduction of organic compounds provided evidence of such a mechanism. Detailed kinetic analysis, however, has been performed only recently^{1b} on the basis of pertinent theoretical treatments.^{1c-d} (b) For leading references see: Roffia, S.; Concialini, V.; Paradisi, C.; Maran, F.; Vianello, E., *J. Electroanal. Chem.*, in press. (c) Amatore, C.; Capobianco, G.; Farnia, G.; Sandonà, G.; Savéant, J.M.; Severin, M.G.; Vianello, E. *J. Am. Chem. Soc.* **1985**, *107*, 1815. (d) Arévalo, M.C.; Farnia, G.; Severin, M.G.; Vianello, E. *J. Electroanal. Chem.* **1987**, *220*, 201.
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- (a) In line with the general electroreduction behaviour of organic halides,^{4b} the overall reduction is actually a stepwise process controlled by the uptake of the first electron. The initial electron transfer, most likely concerted with the breaking of the C–Br bond for alkylic type halides,^{4c} affords a radical which is reduced to the carbanion as soon as it is produced. (b) see for instance: Hawley, M.D. In *Encyclopedia of Electrochemistry of the Elements*, Vol. XIV, Bard, A.J., Lund, H., Eds.; Dekker: New York, 1980. (c) Savéant, J.M. *J. Am. Chem. Soc.* **1987**, *109*, 6788.
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- The best solvent for testing the method would be DMSO, due to the impressive number of pK_a values reported in this medium.¹⁰ However, since most of the α -bromoamides suffer from adsorption phenomena at potentials of the first peak in DMSO, the voltammetric analysis would be seriously complicated in this solvent. In amide solvents, such as DMF, this problem practically vanishes.
- (a) The electrode mechanism was simulated following a standard approach^{9b} to obtain the variation of the current as a function of the potential, for different values of the three parameters γ , λ , and K . In the simulated mechanism, it is neglected the small current contribution to the third peak due to the formation (in small amounts) of the protic isobutyranilide (eq. 1). It was verified, however, that such an approximation is quite reasonable in front of the large third peak effects (high λ values) we studied. (b) See for instance: Britz, D. *Digital Simulation in Electrochemistry*, Springer-Verlag: Berlin, 1988.
- (a) Bordwell, F.G. *Acc. Chem. Res.* **1988**, *21*, 456. Bordwell, F.G.; Fried, H.E.; Hughes, D.L.; Lynch, T.-Y.; Satish, A.V.; Whang, Y.E. *J. Org. Chem.* **1990**, *55*, 3330. (b) Corrected pK_a value: Petrov, E.S. *Russ. Chem. Rev. (Engl. Transl.)* **1983**, *52*, 1144.
- (a) This is supported for instance by a comparative study on acidities in DMSO and *N*-methylpyrrolidinone,^{11b} a carboxamide solvent having similar properties to DMF. (b) Bordwell, F.G.; Branca, J.C.; Hughes, D.L.; Olmstead, W.N. *J. Org. Chem.* **1980**, *45*, 3305.
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