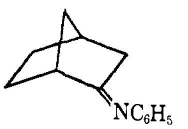
The Electrochemical Reduction of Imines in Dimethylformamide

Albert J. Fry and Roberta Gable Reed

Contribution from the Chemistry Department, Wesleyan University, Middletown, Connecticut 06457. *Received April 19, 1969*

Abstract: The mechanism of electrochemical reduction of several imines (Schiff bases) has been investigated in dimethylformamide containing tetraethylammonium bromide, using polarography, cyclic voltammetry, coulometry, and comparison of the stereochemistry of the amines produced in preparative-scale electrolysis, catalytic hydrogenation, and sodium–alcohol reduction. Polarography and cyclic voltammetry indicate an irreversible two-electron reduction. It is suggested that a radical anion is formed initially. With the species examined in this investigation, proton abstraction and a second electron transfer are both rapid. This behavior contrasts with the stability of ketyl ions in dimethylformamide; the higher basicity of the nitrogen species presumably enhances proton abstraction rates. A mechanism for sodium–alcohol reductions is suggested, based upon the electrochemical and stereochemical results.

There have been reported many studies on the mechanism of electrochemical reduction of carbonyl compounds.[1] As a result of both polarographic and preparative scale electrochemical studies and other investigations into changes of electrochemical behavior as a function of solvents, added proton donors, etc., the electrode processes involved in reduction of carbonyl compounds are known in substantial detail.[1] Relatively few studies, on the other hand, have concerned themselves with the electrochemical behavior of imines, or Schiff bases, which are the nitrogen analogs of carbonyl compounds. A number of reports[2] have indicated that amines are the products of reduction of imines in protic solvents such as ethanol, but there has been reported only one study[3] of the electrochemical reduction of imines in an aprotic solvent, dimethylformamide (DMF). The focus of attention in that study, however, was upon attempts to correlate polarographic half-wave potentials with Hückel molecular orbital energies, and a detailed mechanistic examination was not made. In view of the considerable success achieved by others in clarifying the mechanisms of reduction of aromatic hydrocarbons and carbonyl compounds through investigations in aprotic solvents, and because it was of interest to learn the stereochemical features of the reaction for possible future synthetic applications, a study of the stereochemistry and mechanism of electrochemical reduction of Schiff bases in DMF was undertaken. This paper reports the results of studies by polarography, cyclic voltammetry, coulometry, and preparative-scale controlled potential electrolysis, as well as catalytic hydrogenation and sodium–alcohol reduction. Significant differences from the electrochemical behavior of carbonyl compounds in DMF have been observed. In addition, the electrochemical and stereochemical results suggest a mechanism for sodium–alcohol reductions somewhat different from that recently proposed.[4] The imines investigated were the Schiff bases (anils) of aniline with norcamphor and camphor (**1** and **2**, respectively), and α-methylbenzylidene-α-methylbenzylamine (**3**).



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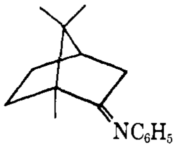

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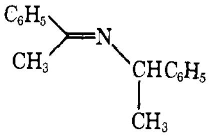

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Synthesis of Imines. Norcamphor anil (**1**) was prepared by azeotropic distillation of water from a benzene solution containing the ketone, amine, and a trace of methanesulfonic acid.[5] Imine **2** was prepared by condensing camphor with the amine using titanium tetrachloride.[6] Schiff base **3** was prepared according to a published procedure.[7]

Results

Polarography at the Dme. Each of the Schiff bases **1–3** possesses a single well-developed wave in DMF (0.1 *M* Et_4NBr as background electrolyte) (Table I).[8]

Table I. Electrochemical Data for the Reduction of Imines (Schiff Bases)[a]

Compd	$-E_{1/2}$[b]	I_d[c]	Slope[d]	$n_{(\mathrm{coul})}$[e]	$E_{1/4} - E_{3/4}$, mV
1	1.98	4.37	87	2 (2.07)	82
2	2.14	4.40	88	2 (1.98)	83
3	1.75	4.35	80	2 (1.82)	75

[a] Imines were 1 m*M* in a 0.1 *M* solution of TEAB in DMF. [b] Potentials are in volts relative to Ag–AgBr. [c] $I_d = i_d/Cm^{2/3}t^{1/6}$, where i_d is the diffusion current measured at the maximum of the instantaneous current. [d] Slope, in millivolts, of a plot of E *vs.* $\log i/(i_d - i)$. [e] The first value is the rounded-off coulometric *n* value; that within parentheses is the observed *n* value.

The limiting current for each wave varies linearly with the square root of the height of the mercury column, indicating diffusion control. The diffusion current

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(1) For an excellent summary of concepts and results in this area, see M. J. Peover in "Electroanalytical Chemistry," Vol. 2, A. J. Bard, Ed., Marcel Dekker, New York, N. Y., 1967.

(2) (a) H. Lund, *Acta Chem. Scand.*, 13, 249 (1959); (b) P. Zuman and O. Exner, *Collect. Czech. Chem. Commun.*, 30, 1832 (1965); (c) H. D. Law, *J. Chem. Soc.*, 101, 154 (1912).

(3) J. M. W. Scott and W. H. Jura, *Can. J. Chem.*, 45, 2375 (1967).

(4) J. W. Huffman and J. T. Charles, *J. Am. Chem. Soc.*, 90, 6486 (1968).

(5) R. W. Layer, *Chem. Rev.*, 63, 489 (1963).

(6) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, 32, 3246 (1967).

(7) C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Am. Chem. Soc.*, 83, 1374 (1961).

(8) The Schiff bases of camphor and norcamphor with cyclohexylamine were not polarographically reducible under these conditions; at least one aromatic substituent is apparently necessary in order for the imine to be reducible.

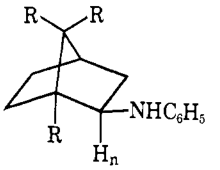
constants I_d show each wave to represent a two-electron process. The reductions are irreversible: this is clear from the observations that (a) by Tomes' criterion,[9] $E_{1/4} - E_{3/4}$ is always greater than $56/n$ mV, and (b) the slope of a plot of E *vs.* log $i/(i_d - i)$ is greater than $59/n$ mV in all cases. The value of Tomes' criterion is generally close, in fact, to the value of 84 mV calculated by Hoijtink for the case of a reversible one-electron transfer followed by rapid protonation,[10] and actually observed, for example, for the second polarographic wave of aromatic hydrocarbons in 96% dioxane.[10]

Cyclic Voltammetry at the Hmde. The cyclic voltammetric behavior of all of the Schiff bases investigated was the same. No evidence of an anodic reoxidation peak following scan reversal past the cathodic peak was observed even at high scan rates (100 V sec^{-1}). Significantly, a mixture of acetophenone and **3** *did* show an anodic peak due to oxidation of acetophenone ketyl upon scan reversal past the cathodic peak. (A separate polarographic experiment showed that acetophenone and **3** are reduced at the same potential.) These data indicate that the initial intermediate in the reduction of **3**, and presumably also the other Schiff bases **1** and **2**,[11] is considerably more reactive than the ketyl formed by reduction of acetophenone.

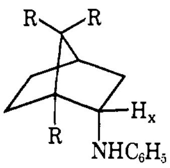
In all cases a new redox couple appeared at a position considerably *anodic* of the peak due to reduction of the amine. This couple was diminished or absent at low sweep rates. This behavior, indicative of formation of a reactive intermediate upon two-electron reduction, has been observed previously, *e.g.*, in the electrochemical reduction of benzophenone in pyridine.[12]

Chemical Reductions and Stereochemical Assignments. Schiff bases **1** and **2** were each subjected to reduction by two chemical methods, catalytic hydrogenation over platinum and sodium–alcohol reduction, and the stereochemical course of each reduction was determined.

Reduction of **1** or **2** may lead in each case to either *exo* (**4a** and **5a**) or *endo* (**4b** and **5b**) amine products. No vapor phase chromatographic (vpc) conditions could be found which would separate the respective *exo–endo* isomers of **4** and **5**, but an analysis was possible by nmr spectroscopy. It is well-established that *exo* protons (H_x) appear at lower field than the corresponding *endo* protons (H_n) for isomeric compounds in the bicyclo[2.2.1]heptane series,[13] and in addition, the band shapes for *exo* and *endo* protons are quite distinctive—*exo* protons appearing as a doublet of doublets and *endo* protons appearing as a triplet or near triplet.[13] In each chemical reduction of the imines **1** and **2**, the mixture of *exo* and *endo* isomers was collected by preparative-scale vpc and shaken with deuterium oxide to remove the interfering N-H proton by exchange. The ratio of *exo* and *endo* protons in the amine mixture was then measured by integration, where both isomers were present, of the two multiplets in the >C*H*N< region (*ca.* τ 6–7).[14] Results, presented in Table II, indicate that, as expected, catalytic hydrogenations afford the isomer (**4b** and **5a**) resulting from hydrogenation of the imine from the least hindered side. Surprisingly, the *endo* isomer predominates in sodium–alcohol reductions of both **1** and **2**. This result has a recent parallel in the report[4] by Huffman and Charles that the *endo* alcohol predominates in sodium–alcohol reductions of the ketones camphor and norcamphor. We shall return to this point in the Discussion.



4a, R = H
5a, R = CH$_3$



4b, R = H
5b, R = CH$_3$

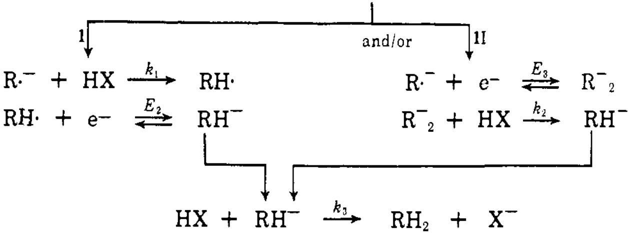
Table II. Stereochemistry of Reduction of Bicyclic Imines

Compd	Mode of reduction	Relative % products *exo*-Amine	 *endo*-Amine
1	Na–EtOH	33	67
2	Na–EtOH	0	100
1	H$_2$–Pt	0	100
2	H$_2$–Pt	100	0
1	Mercury cathode	20	80
2	Mercury cathode	0	100

Coulometry and Controlled-Potential Electrolysis. The electrochemical reduction of imines **1–3** on a preparative scale at the mercury pool electrode consumed in each case two electrons per molecule (Table I), in accord with the *n* value determined polarographically. Stereochemical and other data are presented in Table II. The isomeric amines are the only observable products by vpc analysis, and are formed in ratios which generally correspond to those formed in sodium–alcohol reductions of the imines. The significance of this stereochemical result to the mechanism of sodium–alcohol reductions will be discussed later.

Discussion

Reduction Mechanism. A generally accepted mechanistic scheme[1,15] for the electrochemical reduction of species (R) such as aromatic ketones and hydrocarbons



is as follows. This scheme illustrates the substantial ef-

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(9) J. Tomes, *Collect. Czech. Chem. Commun.*, 9, 12 (1937).

(10) G. J. Hoijtink, J. van Schooten, E. de Boer, and W. Y. Aalbersberg, *Rec. Trav. Chim.*, 73, 355 (1954).

(11) There is evidence that Schiff bases heavily substituted by stabilizing phenyl groups, *e.g.*, benzophenone anil **6**, form stable radical ions upon reversible one-electron reduction: A. J. Bard, private communication, and footnote 3.

(12) R. F. Michielli and P. J. Elving, *J. Am. Chem. Soc.*, 90, 1989 (1968).

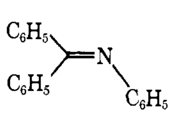
(13) (a) T. J. Flautt and W. F. Erman, *ibid.*, 85, 3212 (1963); (b) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, and T. E. Dye, *ibid.*, 88, 5350 (1966).

(14) H_x appears at τ 6.47 and 6.43, respectively, in **4b** and **5b**; H_n appears at τ 6.94 and 6.75, respectively, in **4a** and **5a**. The shapes of the bands are as expected.[13]

(15) J. Janata, J. Gendell, R. G. Lawton, and H. B. Mark, Jr., *J. Am. Chem. Soc.*, 90, 5226 (1968). The scheme as outlined by Mark, *et al.*, is used here, but the symbols are those in more common use, *e.g.*, ref 1.

fect of proton availability upon the course of reduction. In solvents of high proton donor concentration, *e.g.*, ethanol, 75% dioxane,[10] or dimethylformamide containing added phenol,[1,15] ions $R\cdot^-$ formed in the first reduction step will be protonated rapidly; since it is generally true that the potential E_2 for reduction of the radical $RH\cdot$ will be *less* cathodic than the potential E_1 for reduction of the parent species,[10] rapid transfer of a second electron will occur as soon as $RH\cdot$ is formed. This process—the so-called ece mechanism—is well-recognized in such solvents.[1,10,15] In solvents of low proton availability, such as alkaline solution or aprotic solvents, the lifetime of $R\cdot^-$ is long relative to the polarographic drop time, and a one-electron reversible reduction is usually observed in polarographic and cyclic voltammetric experiments. At a more negative potential E_3, a second one-electron reduction to R^{2-} takes place.

The data in the Results indicate that the Schiff bases examined in this study are reduced to a single over-all two-electron step in DMF containing tetraethylammonium bromide, *i.e.*, the ece mechanism, reaction manifold I in the above mechanistic scheme. This behavior contrasts with the two discrete one-electron transfers observed for aromatic ketones and hydrocarbons in this solvent. We believe, however, that the preceding mechanistic scheme accounts well for the reduction pattern observed for these Schiff bases. We first note that nitrogen bases are generally several orders of magnitude more basic than their oxygen counterparts (*cf.*, ammonia and water, or sodium amide and sodium hydroxide). Schiff bases are indeed much more basic than ketones.[5] The rate of protonation of $R\cdot^-$ governs whether pathway I or II is taken; this depends in turn upon the magnitude of the *product*[16] k_1[HX], and hence the reduction may be shifted toward pathway I just as readily by an increased value of k_1 as by a high concentration of proton donor. We suggest that the higher basicity of the $R\cdot^-$ derived from the Schiff bases does increase k_1 over that observed for aromatic ketones sufficiently to change the mechanism over to the ece type. Support for the contention that k_1 is much greater for Schiff bases than for ketones arises from the observation that a mixture of acetophenone and **3** shows in cyclic voltammetry only the anodic peak due to reoxidation of the ketyl ion. We predict further that highly phenylated radical ions, such as that formed by one-electron reduction of benzophenone anil (**6**), should be sufficiently resonance stabilized (and hence less basic) that k_1 should be smaller than for **1**–**3**. In fact, reduction of **6** does lead, *via* a reversible one-electron transfer, to a stable radical ion.[11] One ought in practice to expect a wide range of values for k_1, depending upon the basicity of the imine radical ion; such a range is implicit in the data of Scott and Jura, who observed considerable differences in stability of imine radical ions as measured by cyclic voltammetry and esr spectroscopy.[3]



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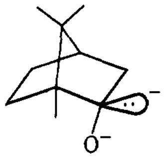
The new redox couple appearing in the cyclic voltammetric experiments at potentials anodic of the original reduction peak has not been investigated fully; it disappears at low sweep rates and is presumably the species RH^- formed in the second electron transfer, indicating k_3 to be smaller than k_1. Similar behavior has been observed for benzophenone in pyridine.[12]

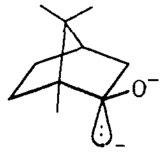
$$RH^- \equiv R_2\bar{C}NHR'$$

$E_{1/2}$**-Molecular Orbital Correlations.** These results bear considerable relevance to attempts to correlate the half-wave potentials for imine reduction with Hückel MO energy levels. A large number of such investigations have been reported for aromatic hydrocarbons, and correlations have often been remarkably good.[17] Recently, Mark[15,18] has sounded a warning with respect to such correlations, however, in experiments which indicate that measured $E_{1/2}$'s are sensitive to traces of proton donors and suggest that the success of such correlations may be because the anodic shift due to protonation is of the same magnitude for all members of the series. We have noted previously that k_1 is *not* of the same magnitude for all imines, and hence correlations $E_{1/2}$ with molecular orbital energy levels, if attempted, at all, should be restricted to those cases where k_1 is of comparable magnitude. A previous study[3] does not fulfill this criterion.

Mechanism of Sodium–Alcohol Reductions. A recent study[4] of the stereochemistry obtained in sodium–alcohol reduction of cyclic ketones has demonstrated the fallacy of the common generalization that sodium–alcohol reductions give the more stable of a pair of epimeric products. Reduction of camphor and norcamphor afforded in each case a preponderance of the *endo* alcohol; we have observed in the present study that the *endo* amine also predominates in reduction of **1** and **2** by sodium in alcohol. Huffman and Charles suggested a dual mechanistic scheme for sodium–alcohol reductions similar to that outlined above for the electrochemical reduction of aromatic substrates. It was proposed[4] that reductions of unhindered ketones, such as norcamphor, follow pathway I, *i.e.*, an ece mechanism. It was suggested that steric hindrance to protonation of the initial intermediate $R\cdot^-$ in hindered ketones, such as camphor, would allow pathway II to compete successfully, resulting in a dianion R^{2-}. The observed stereochemistry was accounted for by assuming that the intermediate in pathway I is protonated from the least hindered side (giving *endo* product from norcamphor), but that the stereochemical fate of R^{2-}, formed from hindered ketones, is governed not by the preferred direction of protonation, but by the preferred geometry of the tetrahedral dianion R^{2-}. **7a** should be sterically



7a



7b

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[16] This is implicit in the analysis of Hoijtink, *et al.*[10] The proton donor HX may be traces of water in the solvent, but water is not an efficient proton donor in DMF: S. Wawzonek and A. Gunderson, *J. Electchem. Soc.*, 107, 537 (1960). We regard it as much more likely that HX is the tetraalkylammonium salt, acting in a Hofmann elimination. The latter reaction is extremely rapid in dimethylformamide: J. W. Sease and R. C. Reed, private communication.

[17] G. J. Hoijtink, *Rec. Trav. Chim.*, 74, 1525 (1955).

[18] H. B. Mark, Jr., *Rec. Chem. Progr.*, 29, 219 (1968).

more stable than **7b**, and protonation of **7a** would result in the *endo* product. This latter reduction scheme for camphor requires the questionable assumptions of slow protonation of $R\cdot^-$ *in a protic solvent*, and configurational stability for the dianion **7a**. Our results from polarography and cyclic voltammetry indicate that **1** and **2** are *both* reduced by the ece mechanism, pathway I above. In spite of this, the stereochemical result of electrochemical reduction is identical with that obtained in sodium–alcohol reductions of the Schiff bases and ketones. This indicates that a duality of mechanism[4] *need not be invoked* to account for the stereochemistry observed in sodium–alcohol reduction of the bicyclic ketones. It is more economical to assume that sodium–alcohol reductions of the ketones and imines also involve a common mechanism, and that this mechanism may be the same as that involved in electrochemical reduction of the imines. However, in this event, an alternate explanation for the stereochemical pattern is necessary. It may be due instead to the fact that protonation of intermediates in the camphor series from the less hindered side creates a sufficiently severe steric interaction with the bridge methyl at C-7 that protonation from the more hindered side, to afford *endo* product, can compete successfully.[23]

Experimental Section

Apparatus. Polarographic measurements were made with a Sargent Model XXI polarograph. Cyclic voltammetric experiments were carried out using a multipurpose electroanalytical instrument of the type described by Underkofler and Shain.[19] Controlled-potential coulometry was carried out using a potentiostat based upon a Kepco KS-120-2.5 programmable power supply;[20] to obtain coulometric data, the voltage drop across a standard resistor in series with the cell was measured with a Brown Elektronik recorder, and the area under the i–t curve was integrated.

Chemicals. Dimethylformamide was refluxed over calcium hydride, 70° (1 mm) for 1 hr, followed by distillation *in vacuo* through a 10 mm × 300 mm glass helix packed column. Tetraethylammonium bromide (Eastman) was recrystallized from an ethanol–ether mixture and dried *in vacuo*. Camphor anil (**2**) was prepared by the method of Weingarten, Chupp, and White.[6] α-Methylbenzylidene-α-methylbenzylamine (**3**) was prepared by the method of Overberger, Marullo, and Hiskey.[7]

Norcamphor Anil (1). A solution of 11.0 g of norcamphor, 9.5 g of freshly distilled aniline, and a catalytic amount (100 mg) of methanesulfonic acid in 100 ml of benzene was refluxed under a Dean–Stark trap until the calculated amount of water (1.8 ml) had been removed by azeotropic distillation. The solvent was then removed at the rotary evaporator. Distillation afforded 12 g (65%) of the anil **1**: bp 73° (0.1 mm); ir (CCl_4) 5.9 μ (C=N); nmr (CCl_4) multiplets from τ 2.7 to 3.4 and from 7.0 to 9.0, relative areas 1:2. Satisfactory microanalytical data could not be obtained, apparently due to slow hydrolysis of the imine in air. All electrochemical experiments were carried out on a sample freshly purified by preparative-scale vpc.

Catalytic hydrogenations were carried out using the Brown[2] hydrogenator[21] as supplied by Delmar Laboratories.

Sodium–alcohol reductions were carried out as follows. Approximately 0.4 g-atom of sodium was added in small pieces to a solution of 0.1 mole of imine in 100 ml of absolute ethanol, at a rate sufficient to maintain reflux. After addition was complete, the solution was refluxed for 3 hr, cooled, and poured into 100 ml of ice water. The amine was extracted with 100 ml of ether, and the ether extract, after three washings with water, was extracted with dilute hydrochloric acid. This extract was neutralized and reextracted with ether; the ether was washed with water and dried over magnesium sulfate. The ether was distilled, and the mixture of amines was separated from a trace of starting anil by vpc (1 ft alkaline[22] Carbowax 20M, 10% by weight on Fluoropak 80, 170°) and analyzed by nmr. Amine mixtures from sodium–alcohol reductions, catalytic hydrogenations, or preparative electrolyses were shaken with deuterium oxide, and the nmr methyne region was integrated. Results of duplicate reduction experiments agree to ±3%.

The hygroscopic, liquid amines were characterized by conversion into α-naphthylureas through reaction with α-naphthyl isocyanate (Table III).

Table III. Characterization Data of Amine α-Naphthylureas

Amine	Mp of urea, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
4b	123	80.87	6.79	81.13	6.84
5a	146	81.37	7.59	81.49	7.55
5b[23]	146	81.37	7.59	81.57	7.39

Acknowledgments. Financial support was provided by the Petroleum Research Fund of the American Chemical Society. We thank Dr. John Sease and Mr. Richard C. Reed for much helpful advice, and the latter for performing the cyclic voltammetric experiments.

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(19) W. L. Underkofler and I. Shain, *Anal. Chem.*, **35**, 1778 (1963).

(20) P. Birman, "Power Supply Handbook," Kepco Inc., Flushing, N. Y., 1965, p 129.

(21) C. A. Brown and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 2829 (1962).

(22) D. G. Hey, G. D. Meakins, and T. L. Whatley, *J. Chem. Soc., C*, 1509 (1967).

(23) *endo*-Amine **5b** is formed under *kinetic* control in sodium–alcohol reductions of **2**; this is demonstrated by the fact that **5a** is recovered unchanged after 8-hr reflux in an ethanol solution containing sodium ethoxide and 2 mole % of **2** as a potential hydride acceptor (for an equilibration pathway involving alternate Oppenauer oxidations and Meerwein–Ponndorf–Verley reductions).