Formation of Radical Anions by Electrochemical Reduction of Nitroimidazoles in Aprotic Solvents and Mixed Solvent

E. Norambuena[a]; C. Olea-Azar[b]

[a] Facultad de Ciencìas Básicas, Departamento de Química, Universidad Metroplitana de Ciencias de la Educación, Santiago, Chile [b] Facultad de Ciencias Quimicas, Departamento de Quimica Inorgánica y Analítica, Universidad de Chile, Santiago, Chile

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FORMATION OF RADICAL ANIONS BY ELECTROCHEMICAL REDUCTION OF NITROIMIDAZOLES IN APROTIC SOLVENTS AND MIXED SOLVENT

E. Norambuena * (1) and C.Olea-Azar (2).

(1).- Facultad de Ciencias Básicas, Departamento de Química, Universidad Metroplitana de Ciencias de la Educación. Casilla 147. Santiago. Chile.

(2).- Facultad de Ciencias Químicas, Departamento de Química Inorgánica y Analítica, Universidad de Chile. Casilla 653. Santiago. Chile.

ABSTRACT

The EPR spectra of radicals obtained by electrolytical reduction of 2-nitroimidazole and 4-nitroimidazole were measured in mixed solvents. The behavior of the nitrogen coupling constants with the solvent composition is discussed in terms of equilibria between radicals in different solvents. The equilibrium constants of the DMSO/water system were determinated. Molecular orbital calculations in the frame of LCAO-HMO method account correctly for the spin distribution of both compounds investigated.

INTRODUCTION

In this paper we report an EPR spectroscopy study for searching and identifying the radical species postulated as intermediates in the reduction mechanisms of 2- and 4-nitroimidazoles in aprotic solvents and in mixed aqueous aprotic solvents. Systematic studies of the solvent composition effect in the generation of the one-electron reduction product

were carried out means of EPR and cyclic voltammetry. The electrochemical behavior of several nitroimidazoles has been studied in aqueous media and in aprotic solvent (1,2). However, the radical intermediates have been poorly charecterizated, the corresponding EPR spectra present low resolution (3, 4).

In the DMSO-H_2O mixtures, we have calculated the equilibrium constant for the reorganization of the solvent around the radical anion. AM1 calculations were carried out to obtain the most stable conformations of the radical and neutral forms. In addition, we have performed INDO-SCF calculations to estimate the hyperfine coupling constants, which are compared with the available experimental values.

EXPERIMENTAL SECTION AND THEORETICAL METHODS

MATERIALS

Dimethysulfoxide (DMSO), Dimethyformamide (DMF), Acetonitrile (ACN), 2-nitroimidazole (2IM) and 4-nitroimidazole (4IM) were obtained from Aldrich Chemical Co. Inc. Tetraethylammonium perchlorate (TEAP), used as the supporting electrolyte, was obtained from. G. Frederick Smith and purified by several recrystallizations.

ELECTROCHEMICAL AND EPR MEASUREMENTS

Cyclic voltammetry was carried out in a Princeton Applied Research (PAR) 175 equipment and in a PAR Model 173 potentiostat, in the same solvents (ca 1.0 x10^{-2} moles dm^{-3}) under nitrogen atmosphere, using TEAP (ca 0.1 moles dm^{-3}) as supporting electrolyte, in a glass cell with a glassy carbon working electrode, a platinum-wire auxiliary electrode and an aqueous saturated calomel reference electrode (s.c.e)

The radicals were generated by electrolytic reduction *in situ* at room temperature. EPR measurements were caried out in a Variant Associated V 4520 X-band spectrometer, employing a 100 KHz magnetic field modulation, and V-1530 Klystron. The hyperfine splitting constants were calibrated by using a Varian E-500 gaussimeter. They were estimated to be accurate within 0.05 G.

QUANTUM CHEMICAL CALCULATIONS

Full geometry optimizations of 2IM and 4IM in neutral and radicals forms were carried out by the AM1 (5) method. INDO calculations were done employing the open shell UHF option.

2IM $^{2-\cdot}$ 4IM $^{2-\cdot}$
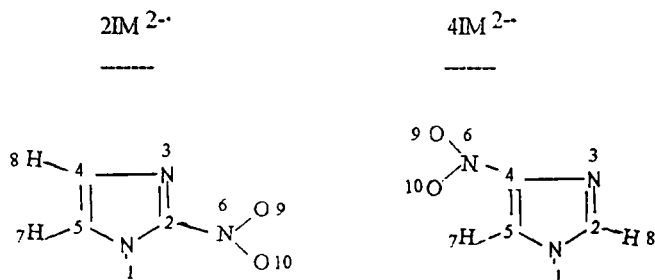
RESULTS AND DISCUSSION

CYCLIC VOLTAMMETRY

2IM and 4IM display comparable voltammetry behavior in all solvents used, showing two well-defined reduction waves (Figure 1). The first cathodic peak (I) was irreversible in the whole range of sweep rates used (20-500 V/s). When successive sweeps were recorded, the loss of this peak was detected. Vianello *et al* (1,6) have postulated that the irreversiblity is due to a fast selfprotonation reaction (a father-son type of reaction), with the formation of the hidroxylamino derivative, the necessary protons being supplied by the starting molecule.

According to standard reversible criteria (7) the second wave (II) corresponds to a reversible diffusion-controlled one-electron transfer (Figure 1B). It is attributable to the reduction of R-NO$_2^-$ to R-NO$_2^{2-\cdot}$, a stable dianion radical at room temperature. The potentials of the reduction peaks (Epc) in the first cyclic voltammogram for the solutions studied are summarized in Table 1.

With increasing concentration of water in the medium, the first reduction peaks of 2IM and 4IM were shifted to more positive potentials, indicating that the autoprotonation is favoured in all mixed solvent used. Also, it can be observed that the only anodic wave (III)
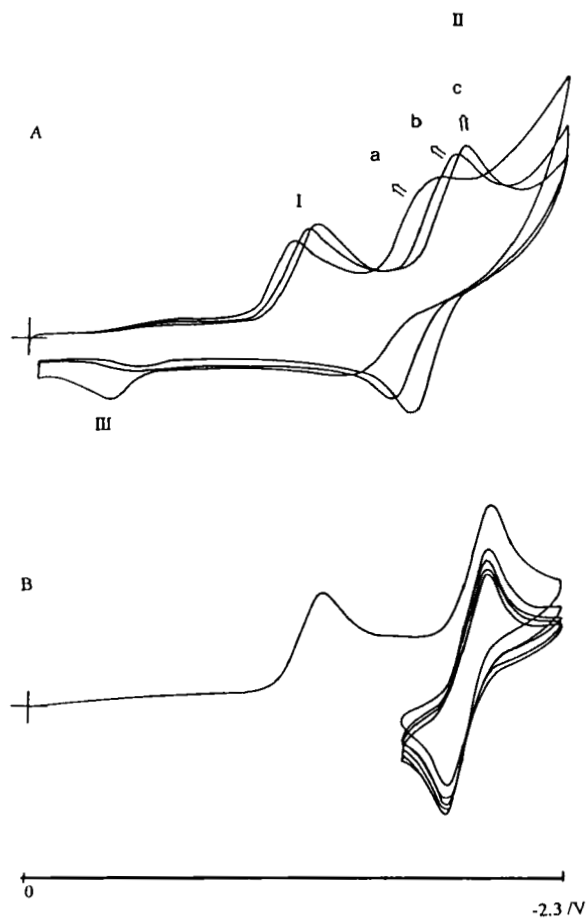
FIGURE 1
A.- Cyclic Voltammetry of 4IM in DMSO-Water. c, b, a increasing % water.
B.- Cyclic Voltammetry of 4IM in DMSO

TABLE 1
Cyclic voltammetry data for 2IM and 4IM vs saturated calomel electrode

2 IM

SOLVENT	WAVE	-Epc/V	ipa/ipc
DMSO	I	1.08	-
	II	2.07	0.89
DMF	I	1.14	-
	II	2.15	0.80
ACN	I	0.98	-
	II	1.96	0.68

4 IM

DMSO	I	1.28	-
	II	2.27	0.75
DMF	I	1.34	-
	II	2.30	0.65
ACN	I	1.24	-
	II	2.10	0.65

was increased. III can be attributed to a hydroxylamine derivative oxidation (1). The results on addition of water to DMSO solutions of 4IM are showed in Figure 1A.

The variation of the second potential reduction (Epc II of 2IM and 4IM) in DMSO versus water percentage is plotted in Figure 2. It can be noticed that the Epc II increases progressively until a potential constant value is attained.

EPR SPECTRA

The interpretation of the EPR spectra by means of a simulation process has led to the determination of the coupling constants for all magnetic nuclei (Table 2). In the case of nitrogen and hidrogen nuclei of the ring, the coupling constants were assigned on the basis of calculated spin densities.

The *in situ* electrochemical reduction in DMSO of compound 2IM led to a detectable EPR spectrum (Figure 3). It is consistent with one quintet from two equivalent nitrogen (of
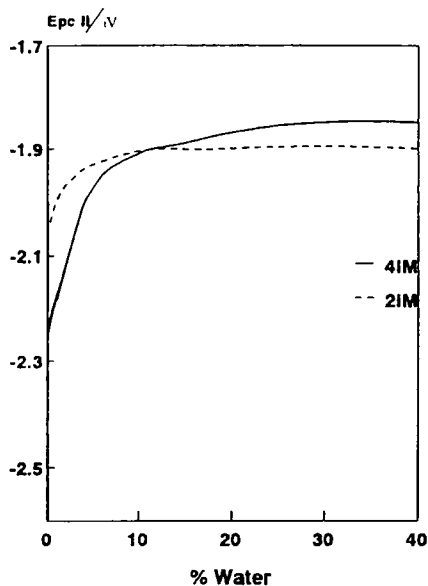
FIGURE 2
Variation of Epc II (peak potential of second wave of 2IM and 4IM) as a function of the %
Water.

Table 2
Experimental and calculated INDO hyperfine splitting (Gauss) for the dianion radical
investigate

2IM

SOLVENT	aN (NO$_2$)	aN (Ring1,3)	aH (7,8)
DMSO	13.9	1.28	0.86
DMF	14.0	1.28	0.84
INDO	10.5	1.29	0.64

4IM

SOLVENT	aN (NO$_2$)	aN (Ring1,3)	aH (7)	aH (8)
DMSO	14.5	0.68, 0.20	0.83	4.5
DMF	15.2	0.70, 0.22	1.00	5.0
INDO	10.6	1.11, 0.19	0.88	8.02

334,90   3393,90 / gauss
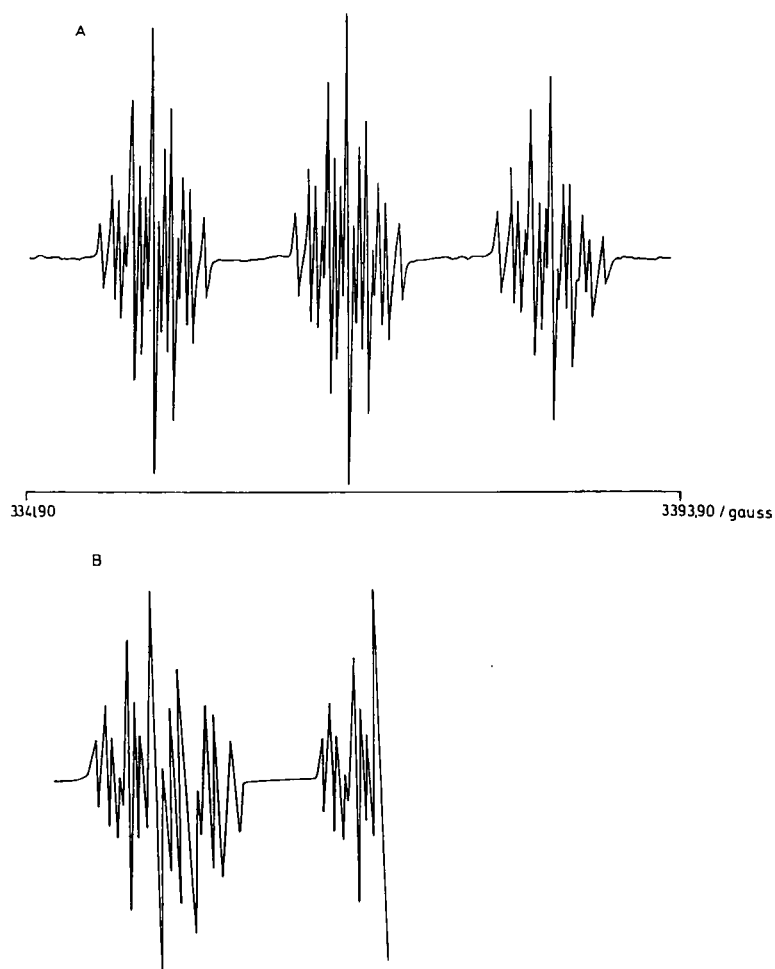
FIGURE 3
A.- EPR Experimental Spectrum of the Radical-Dianion of 2IM in DMSO
B.- Computer Simulation of the Same Spectrum

the ring), a nitrogen triplet from a nitro group and one triplet from C4 and C5 heterocyclic protons. The same hyperfine pattern is seen in the others solvents.

If compound 4IM was subemitted to electrochemical reduction in DMSO, the dianion-radical was obtained and rationalized in terms of the hyperfine splittings constants listed in Table 2 (Figure 4).

The nitrogen coupling constants of nitro group undergo variation in different solvents. This is clear through the formation of species in which there are solvent molecules bonded to the radical. The coupling constant relative to the N atom of nitro group, for both compounds, increased with the water concentration in the mixture DMSO-water, until this coupling constant reaches a constant value. (Figure 5).

In a mixture of two solvents, there is an equilibrium that can be represented as:

$$R-H_2O \quad + \quad DMSO \quad <======> \quad R-DMSO \quad + \quad H_2O \tag{1}$$
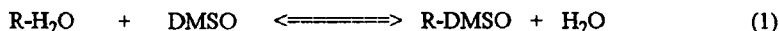
where R is a radical.

Only one spectrum is observed and this means that exchange for this stystem is fast. In the case of fast exchange (8), the relationship between the coupling constant and the ratio of the concentration of the solvents, $\alpha = [DMSO]/[H_2O]$ can be written in a linear form respect to α.

$$1 / (aN - a^{DMSO}) = [K / (a^{DMSO} - a^{H_2O})] \alpha + 1 / (a^{DMSO} - a^{H_2O}) \tag{2}$$

where $K = [R-DMSO] [H_2O] / [R-H_2O] [DMSO]$ and a^{H_2O}, a^{DMSO} are the coupling constant relative to a magnetic nucleus in water and pure DMSO respectively. a_N represents the coupling constant in several mixtures of DMSO/ H_2O.

The plot of $1/(aN - a^{DMSO})$, at room temperature, versus [DMSO]/[Water] for the two radicals presents a linear correlation, indicating a one to one interaction between the radical and solvent molecules (8).

The values of the equilibrium constant were 0.06 and 0.11 for 2IM and 4IM respectively. This means that the competition of the two solvents is maximum for 4IM. Therefore, the

A

3341   3393/
                                                                   gauss
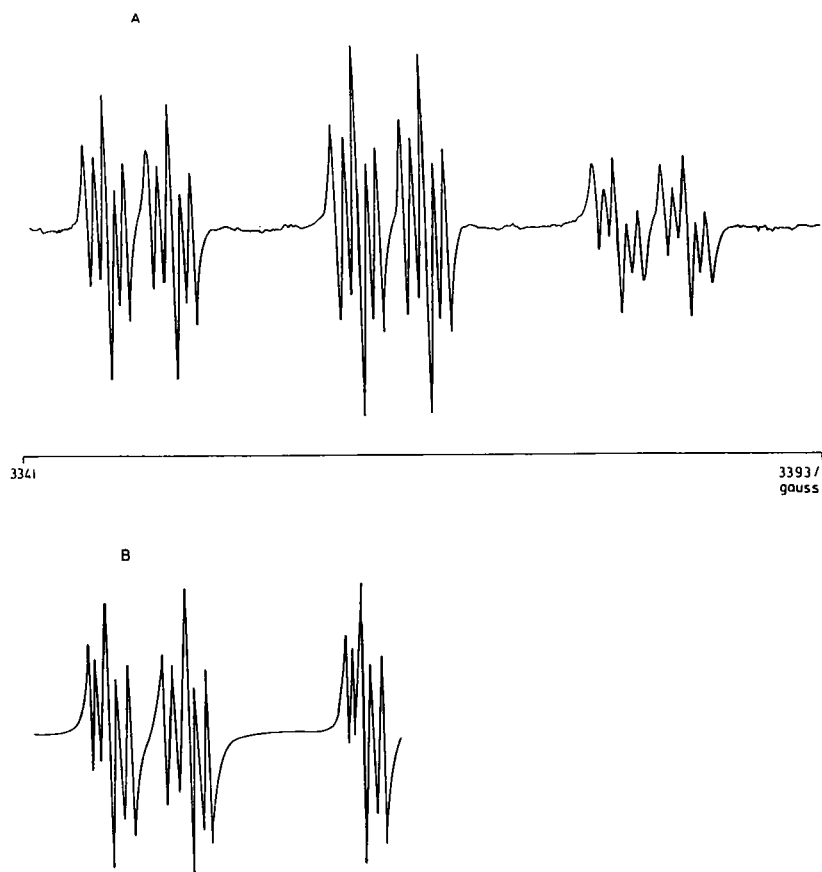
B

FIGURE 4
A.- EPR Experimental Spectrum of the Radical-Dianion of 4IM in DMSO
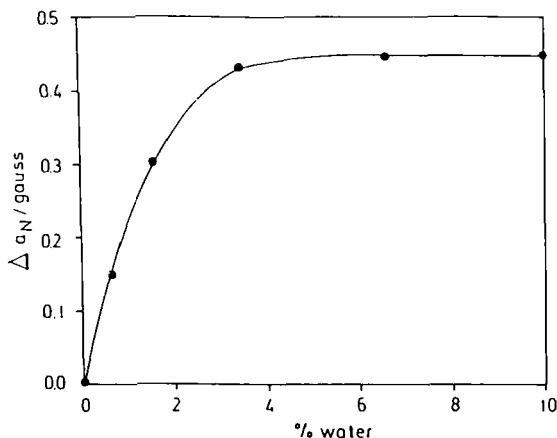B.- Computer Simulation of the Same Spectrum

FIGURE 5
Variation of a_N of 2IM in mixtures DMSO-water as a function of percentage of water

possibility of detecting the absorption lines corresponding to the two species of radicals R-H2O and R-DMSO at the same time, at room temperature, is maximum to 4IM

Because the radicals were unstable in DMF/Water and mixtures, their equilibrium constant were not calculated. In addition, other coupling constant showed no alterations upon increasing the water percentage.

THEORETICAL CALCULATIONS

AM1 calculations were carried out in vacuum, for both 2IM and 4IM in dianion radical and neutral forms. Complete optimization of all internal coordinates was performed. Table 3 shows the distances (D), angles (A) and total energies for the (neutral ans radical) most stable forms.

Whereas the nitro groups in neutral forms are in the ring plane, the nitro groups in the radical form are outside the ring plane, indicating that the electronic density is mainly located on this position. The 4IM presents an increased dihedral angle respect to 2IM. This result is

Table 3
AM1 molecular geometries and total energies of the neutral and dianion radicals forms to 2IM and 4IM

	2IM NEUTRO	4IM N1H	4IM N3H	2IM Radical	4IM Radical
D (N1-C2)	1.414	1.386	1.343	1.394	1.387
D (C2-N3)	1.372	1.363	1.409	1.395	1.380
D (N3-C4)	1.381	1.363	1.382	1.375	1.376
D (C4-C5)	1.419	1.423	1.420	1.425	1.440
D (C5-N6)	1.485	1.459	1.467	1.527	1.490
D (N6-O9)	1.193	1.199	1.206	1.243	1.248
D (N6-O10)	1.204	1.203	1.197	1.245	1.242
A(N1-C2-N3)	111.2	111.9	111.9	113.2	115.1
A(C2-N3-C4)	105.2	106.4	107.3	104.3	103.3
A(N3-C4-C5)	110.5	109.1	105.4	109.2	109.4
$\phi1$	0.16	-	-	10.59	-
$\phi2$	-	0.03	0.11	-	15
Total Energies	-38793.5	-38799.1	-38797.7	-38445.8	-38456.8

$\phi1$ = O10-N6-C2-N3
$\phi2$ = O9-N6-C4-N3
Total energies in Kcal/mol
Bond lengths (D) in Å

consistent with hyperfine coupling constant values, the coupling constant of the nitro group in 4IM is slightly higher than that of 2IM. The SOMO energy was similar for both radical and the examination of the MO coefficients indicated that the SOMO is mainly localized on the nitro group. The addition of one electron was partially localized on the N atom of the nitro group.

In order to obtain the theoretical hyperfine constant, INDO calculations were performed using standard geometries. The dihedral angles used here were those obtained from AM1 calculations. Table 2 shows both, the experimental and theoretical hyperfine constants. The comparison of the these results are in agreement with the assignement of the hyperfine constant.

CONCLUDING REMARKS

2IM and 4IM presented a comparable voltametric behavior in all the solvents used (pure and mixture). The first cathodic peak was atributed a fast selfprotonation reaction, which is favourated according to an increased percentage of water. The second wave corresponded to a reversible one electron transfer. The EPR spectrum to dianion radical for 2IM and 4IM presented a very good resolution. The equilibrium constants to the DMSO/water system were determinated.

The AM1 calculations indicated that the nitro group in neutral forms are in the plane, whereas in the radicals forms the nitro group are 14 degrees outside the ring plane, according with the nitro hyperfine constant for both radical. The theoretical hyperfine constant obtained by INDO calculations shows very good correlation with the experimentals ones.

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