

Electroorganic Preparations

XXI. Polarography and Reduction of Imidazole-2-carboxylic Acid and Related Compounds

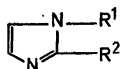
PALLE E. IVERSEN and HENNING LUND

Department of Chemistry, University of Aarhus, Aarhus C, Denmark

The polarographic behaviour of derivatives of imidazole-2-carboxylic acid and of imidazole-2-carbaldehyde is reported. The carbaldehyde group of the latter is found to be strongly hydrated in acid solution. The aldehyde is the main product from the controlled potential reduction of the acid and the amide. The *N*-benzylimidazole derivatives behave similarly.

It has previously been found¹ that several derivatives of the pyridine carboxylic acids are reduced polarographically in acid solution to the aldehydes which in this medium are protected against further reduction by hydration of the carbaldehyde group to the non-reducible *gem*-diol. This investigation has now been extended to derivatives of imidazole-2-carboxylic acid.

The polarographic behaviour of imidazole-2-carbaldehyde (Ia) is included in the investigation as a knowledge of that is necessary for an understanding of the reduction of the acid derivatives.



I	a	R ¹ = H	R ² = CHO	g	R ¹ = CH ₂ C ₆ H ₅	R ² = CH ₂ NHC ₆ H ₅
	b	R ¹ = H	R ² = COOH	h	R ¹ = CH ₃	R ² = CHO
	c	R ¹ = CH ₂ C ₆ H ₅	R ² = COOH	i	R ¹ = CH ₂ C ₆ H ₅	R ² = CHO
	d	R ¹ = H	R ² = CONH ₂	j	R ¹ = CH ₂ C ₆ H ₅	R ² = CH(OC ₂ H ₅) ₂
	e	R ¹ = CH ₂ C ₆ H ₅	R ² = CONH ₂	k	R ¹ = H	R ² = CH ₂ OH
	f	R ¹ = CH ₂ C ₆ H ₅	R ² = CONHC ₆ H ₅			

POLAROGRAPHIC INVESTIGATION

Imidazole-2-carbaldehyde (Ia). The dependence of the half-wave potentials (*vs.* S.C.E.) and limiting current on pH of the cathodic wave of this compound is shown in Fig. 1; in strongly acid solution H₊ is used as a measure of the acidity.

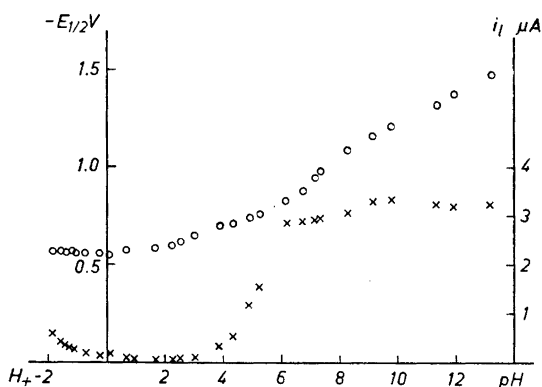


Fig. 1. Dependence on pH (H_+) of the limiting current (μA) \times and half-wave potentials O (S.C.E.) of the cathodic wave of imidazole-2-carbaldehyde. Concentration 40 mg/l.

The wave height is in the acid region only a few per cent of the wave height in neutral solution. In the acid region the wave height is independent of the mercury column height which suggests that the wave height here is kinetically controlled.

The height of the cathodic wave in neutral solution corresponds to a two-electron reduction to the carbinol. The anodic wave found in strongly alkaline solution is slightly smaller, but the electrode reaction is probably an oxidation to the acid as in the case of pyridine-4-carbaldehyde.¹

Imidazole-2-carbaldehyde and its *N*-benzyl derivative can be determined polarographically in a phosphate buffer (pH 7.2). Linear dependence of the limiting current on concentration was found in the interval 4×10^{-5} to 3×10^{-3} M.

Imidazole-2-carboxylic acid (Ib). Whereas imidazole-4-carboxylic acid and its amide are not polarographically reducible, imidazole-2-carboxylic acid gives a wave in strongly acid solution and in a small region around pH 5. In slightly acid solution the wave is masked by the hydrogen wave and in alkaline solution the anion is not polarographically active. The dependence on pH of the wave height and the half-wave potentials are plotted in Fig. 2. In Fig. 2 are also included the corresponding parameters of 1-benzylimidazole-2-carboxylic acid (Ic). In Fig. 3 are plotted the half-wave potentials and wave-heights in dependence of pH for imidazole-2-carboxamide (Id), 1-benzylimidazole-2-carboxamide (Ie), and 1-benzylimidazole-2-carboxanilide (If).

1-Benzyl-2-anilinomethylimidazole (Ig) which is a possible reduction product from (If) was found to be polarographically inactive. The corresponding derivatives of pyridine¹ and thiazole² are reducible in acid solution.

The waves of some of the derivatives of imidazole 2-carboxylic acid are rather close to the decomposition potential of the medium and the limiting currents are not well suited for quantitative work. The height of the wave of 2-carboxyimidazole corresponds approximately to a two-electron wave; in the preparative reductions n was found to be slightly higher (2.3–2.4). Some of the aldehyde is reduced further to the carbinol and some hydrogen ions may be reduced at the potential used; both factors will increase the measured value of n .

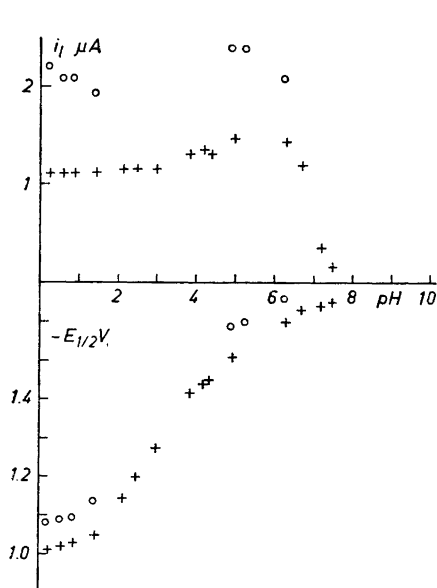


Fig. 2. Limiting currents (μA) and half-wave potentials (S.C.E.) in dependence of pH of 2-imidazolecarboxylic acid \circ and 1-benzyl-2-imidazolecarboxylic acid $+$. Concentration 40 mg/l.

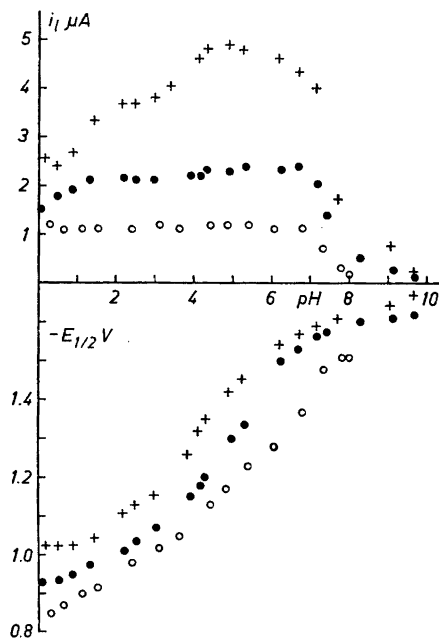
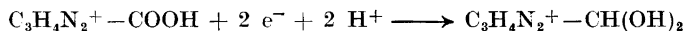


Fig. 3. Dependence on pH of the limiting currents (μA) and half-wave potentials (S.C.E.) of 2-imidazolecarboxamide (Id) $+$, 1-benzyl-2-imidazolecarboxamide (Ie) \bullet , and 1-benzyl-2-imidazolecarboxanilide (If) \circ . The medium of (If) contained 40% alcohol. Concentration 40 mg/ml.

PREPARATIVE REDUCTIONS

Controlled potential reductions in hydrochloric acid of imidazole-2-carboxylic acid (Ib), and carboxamide (Id), and the *N*-benzyl derivatives of both (Ic and Ie) showed that the main electrode reaction was a two-electron reduction to the aldehyde according to



The reductions were performed both at 0° and at 25° ; as in the case of the derivatives of 2-thiazolecarboxylic acid² better yields of aldehyde are obtained at low temperatures where the rate of dehydration of the hydrated aldehyde is lower. The results are summarized in Table 1.

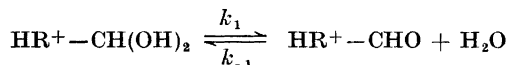
1-Benzyl-2-carboxanilide (If) was reduced in a four-electron reduction; the carbon-nitrogen bond of the anilide was preferably cleaved as a high yield of aniline (93%) was obtained and only traces (5–7%) of a secondary amine,³ presumably 1-benzyl-2-anilinomethylimidazole, was found.

Table 1. Polarographically determined yields of aldehyde in electrolytic reduction of 2-imidazolecarboxylic acid derivatives.

Temperature	N-Benzyl-2-imidazole		2-Imidazole	
	Acid	Amide	Acid	Amide
0°C	94 %	95 %	82 %	85 %
25°C	93 %	86 %	67 %	68 %

DISCUSSION

The most noticeable feature in the polarography of imidazole-2-carbaldehyde is the small limiting current in the acid region where the wave height is kinetically controlled. A similar decrease of the limiting current in acid solution is found for the pyridinecarbaldehydes,^{4,5} 2-thiazolecarbaldehyde,⁶ and to a much lesser degree for imidazole-4(5)-carbaldehyde.⁶ In all these cases the decrease in limiting current is explained by a more or less pronounced hydration of the carbaldehyde group to the *gem*-diol which is polarographically inactive. The height of the wave is in this region mainly determined by the rate of the dehydration of the *gem*-diol to the reducible carbaldehyde group



The product of the rate constant of the dehydration reaction k_1 and the equilibrium constant of the hydration equilibrium $K = (\text{R}-\text{CHO})(\text{H}_2\text{O})/(\text{R}-\text{CH}(\text{OH})_2)$ can be calculated from the polarographic data by means of the Koutecky equation.⁷ At higher pH both the hydrated and the anhydrous form are in equilibrium with their respective unprotonated forms, but at pH lower than 2 only the protonated forms need to be considered. The equilibrium constant K is not known; attempts to obtain K from UV-measurements were unsuccessful, possibly due to the low concentration of the anhydrous form. In Fig. 4 is plotted the dependence of the logarithm of the product k_1K on pH or H_+ .

In strongly acid solution, where H_+ has been used as a measure of the acidity as it reflects the ability of the medium to protonate a species carrying a positive charge, the curve approaches a straight line with the slope -1 .

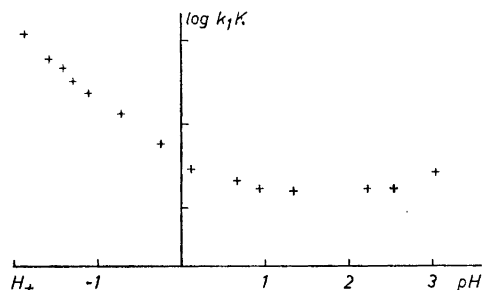


Fig. 4. Dependence on pH (H_+) of $\log k_1K$; k_1 is the rate constant and K the equilibrium constant of the dehydration reaction of imidazole-2-carbaldehyde.

The curve can be represented by assuming $k_1 = k_H(\text{H}^+) + k_0$,⁵ the dehydration thus consists of an acid catalyzed reaction competing with a "spontaneous" dehydration.

In strongly acid solution the protonated form exists in equilibrium with the doubly protonated species and the dehydration may be depicted as a rapid protonation of the positively charged imidazolmethanediol followed by a slow cleavage of the carbon-oxygen bond and a rapid deprotonation. The principle of microscopic reversibility indicates that the hydration in this medium starts with a protonation of the aldehyde group which then is attacked by a water molecule.

In less acid solution the hydration-dehydration proceeds mainly without acid catalysis. The protonated imidazole nucleus activates the carbonyl group sufficiently for the nucleophilic attack of water, whereas the unprotonated nucleus does not.

From Fig. 4 is seen that the rate constants k_H and k_0 are approximately equal. A similar result was found for the corresponding parameters of the pyridinecarbaldehydes.⁵

The equilibrium constant of the hydration equilibrium is not known, but imidazole-2-carbaldehyde is at least as strongly hydrated as pyridine-4-carbaldehyde⁵ and more strongly hydrated than 2-thiazolecarbaldehyde⁶ and imidazole-4-carbaldehyde.⁶ 1-Methyl- (Ih) and 1-benzylimidazole-2-carbaldehyde (Ii) are as strongly hydrated as their parent compound.

Imidazole-2-carboxylic acid (Ib) has two acidic functions with $\text{p}K_1 = 1.0$ and $\text{p}K_2 = 6.4$. The former was determined using the dependence of the maximum in the UV-spectrum about $250 \text{ m}\mu$ on pH. The maximum shifted from $250 \text{ m}\mu$ in 4 N hydrochloric acid to $239 \text{ m}\mu$ at pH 3. $\text{p}K_2$ was measured potentiometrically. $\text{p}K_1$ is connected with the dissociation of the carboxyl group whereas $\text{p}K_2$ is connected with the loss of a proton from the protonated imidazole ring. Between $\text{p}K_1$ and $\text{p}K_2$ the acid exists mainly as the zwitterion. $\text{p}K$ of imidazole-2-carboxamide (Id) was found to 3.5.

The reduction in aqueous solution of an acid to an aldehyde is unusual and it is noteworthy that in the reduction of the imidazole-2-carboxylic acids just as good yields of the aldehydes are obtained from the free acids as from the carboxamides. This is not so in the case of derivatives of isonicotinic acid¹ and 2-thiazole-carboxylic acid,² where side reactions take place in the reduction of the acids. The results are probably connected with the easier reducibility of the pyridine and especially the thiazole nucleus compared to that of the imidazole nucleus.

Imidazole-2-carbaldehyde (Ia) has recently become available through a reductive debenzoylation of *N*-benzylimidazole-2-carbaldehyde diethylacetal (Ij) followed by deacetalization⁸ or by oxidation of the carbinol (Ik) with activated manganese dioxide-B in anhydrous ether.⁹ The electrolytic reduction of the acid presents an alternative to the other routes.

EXPERIMENTAL

The polarographic and electrolytic equipment was the same as that used previously;¹ the capillary delivered 1.95 mg/sec of mercury at a corrected mercury column height of 48.5 cm. The drop time could be regulated to 3.0 sec with a Radiometer Drop Life Timer. IR-spectra were recorded on a Perkin-Elmer Infracord, and microanalysis were made by Ilse Beetz, Kronach, Strauss and Weiler, Oxford, and our Analytical Department. Melting points are uncorrected.

The preparation of the aldehydes has been described elsewhere.⁸

2-Imidazolecarboxylic acid (Ib), m.p. 165–166° (163–164°),¹⁰ was prepared in 63 % yield (0.1 mole) according to Jones.¹⁰

2-Imidazolecarboxamide (Id), m.p. 290–291° (closed tube, subl. 160–170°/0.1 mm) was prepared in 57 % yield by refluxing the acid (0.02 mole) with excess of purified thionyl chloride¹¹ for 6 h with occasional shaking, removing excess of thionyl chloride *in vacuo*, and adding excess of methanolic ammonia to the residue. (Found: C 43.93; H 4.61. Calc. for C₄H₅N₃O: C 43.24; H 4.54).

N-Benzyl-2-imidazolecarboxylic acid (Ic), m.p. 102° (decomp.), was prepared in 70–85 % yield (0.2 mole) according to Shirley and Alley.¹²

N-Benzyl-2-imidazolecarboxamide (Ie), m.p. 157–157.5° (benzene) (151–152.5°)¹² was prepared through the acid chloride in 90 % yield. The thionyl chloride must be pure,¹¹ otherwise a poor yield is obtained.

N-Benzyl-2-imidazolecarboxanilide (If), was prepared from the acid through the mixed anhydride with ethyl chloroformate.¹³ 0.01 mole of the acid (monohydrate) was dissolved in 100 ml of tetrahydrofuran and 0.02 mole of triethylamine. The mixture was cooled to –35° with stirring and 0.02 mole of ethyl chloroformate in 10 ml of tetrahydrofuran was added dropwise during 5–10 min. Stirring at –35° was continued for further 1 1/2 h and 0.01 mole of aniline was added dropwise. The mixture was stirred cold for further 1 h and left overnight at room temperature. The solution was filtered from triethylamine hydrochloride which was washed with hot tetrahydrofuran and the tetrahydrofuran evaporated *in vacuo*. The residue was recrystallized from ethanol yielding 58 % of *N*-benzyl-2-imidazolecarboxanilide, m.p. 111–112°. (Found: C 73.63; H 5.45). Calc. for C₁₇H₁₅N₃O: C 73.63; H 5.45).

N-Benzyl-2-anilinomethylimidazole dihydrochloride (Ig), was prepared by the method of Zymalkovsky.¹⁴ 1 g of imidazole-2-carbaldehyde in 5 ml of aniline and 25 ml abs. ethanol was hydrogenated (1 atm) over 1 g of Pd/BaSO₄ at room temperature for two days. The mixture was filtered and the filtrate steam-distilled. The aqueous residue was extracted three times with 100 ml of ether which was then dried over potassium carbonate. Addition of dry hydrogen chloride precipitated 250 mg of a very hygroscopic crude dihydrochloride which was recrystallized from ethanolic hydrogen chloride. Yield 10–15 %, m.p. 156–157° (decomp., closed tube). The purity of the compound was ascertained by thin layer chromatography (silica gel, 1:1 butanol-methanol). (Found: C 60.73; H 5.92; Cl 20.78; N 12.78. Calc. for C₁₇H₁₉Cl₂N₃: C 60.71; H 5.70; Cl 21.09; N 12.50).

Reduction of N-benzyl-2-imidazolecarboxylic acid (Ic), 5.0 g of the acid (monohydrate) were reduced at –1.05 V vs. S.C.E. in 150 ml of prerduced 1.3 N hydrochloric acid with consumption of 2.4 electrons/molecule. The temperature was kept at about 10°C. An aliquot of the catholyte was polarographically analyzed for aldehyde (85 %) in phosphate buffer (pH 7.2), the rest was made alkaline with potassium carbonate and continuously extracted overnight (16 h) with chloroform which was then dried over potassium carbonate. Removal of the solvent and fractionation of the residue *in vacuo* gave 2.7 g (64 %) of *N-benzyl-2-imidazolecarbaldehyde (Ii)*, b.p._{0.07} 105–108°, *n*_D²⁵ 1.5948 (b.p._{0.1} 110°, *n*_D²⁵ 1.5935),⁸ 0.7 g of a higher boiling fraction, probably a mixture of aldehyde and carbinol, were also isolated.

In a similar reduction of the acid (0.5 g) a yield of aldehyde (92 %) was found polarographically. The aldehyde was isolated from sodium carbonate solution as the *N-benzyl-2-imidazolecarbaldehyde oxime* (70 %), identified by its m.p. 163–164° (166°)⁸ and IR-spectrum.

Reduction of N-benzyl-2-imidazolecarboxamide (Ie). 0.50 g of the amide was reduced at –1.05 V vs. S.C.E. in 150 ml of prerduced 0.8 N hydrochloric acid containing 40 % of ethanol with consumption of 2.3 electrons/molecule. Polarographic analysis of the catholyte showed the presence of 86 % aldehyde and 6 % amide. The aldehyde from half

of the catholyte was isolated as the *2,4-dinitrophenylhydrazone hydrochloride*. The yellow crystals (405 mg, 41 %) were filtered off, dried *in vacuo* over calcium chloride and identified from the m.p. 201–203° (202–204°)⁸ and IR-spectrum.

Reduction of 2-imidazolecarboxylic acid. 0.50 g of the acid was reduced at –1.15 V vs. S.C.E. in 150 ml of prereduced 0.8 N hydrochloric acid with a consumption of 2.4 electrons/molecule. Polarographic analysis in phosphate buffer (pH 7.2) showed the presence of 67 % aldehyde. After addition of excess of potassium carbonate to the catholyte the aldehyde was isolated by continuous extraction overnight (16 h) with chloroform which was afterwards dried over potassium carbonate. Evaporation of the solvent left 300 mg of a yellow substance, m.p. 175–180° (decomp., closed tube); purification by sublimation *in vacuo* (110°/0.1 mm) gave 150 mg (35 %) of pure *2-imidazolecarbaldehyde*, identified from the m.p. 194–195° (decomp.) (195°)⁸ and IR-spectrum.

Reduction of 2-imidazolecarboxamide. 0.50 g of the amide was reduced at –1.0 V vs. S.C.E. in 150 ml of prereduced 0.8 N hydrochloric acid with consumption of 2.1 electrons/molecule. Polarographic analysis showed the presence of 68 % aldehyde and 5 % amide; the same yield of aldehyde was found by precipitation of the *2,4-dinitrophenylhydrazone hydrochloride*, m.p. 305–307° (310–312°)⁸ from part of the solution. From the rest of the catholyte the free *2-imidazolecarbaldehyde* was isolated as above.

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Received September 8, 1966.