[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Reduction Potentials of Various Naphthoquinones

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In continuation of previous studies of the effect of substituents on the oxido-reduction potentials of various quinone–hydroquinone systems, an examination has been made of a number of naphthoquinones, with the results recorded in Tables I, II and III. The potential values given represent averages of at least three closely agreeing determinations (1 mv.). In every case a solution of the reductant was prepared by hydrogenation and titrated with a suitable oxidizing agent, following for the most part the procedure recently outlined.[1] The solvent was selected according to the solubility and the stability of the oxidant in question and with consideration for the providing of conditions under which neither the oxidant nor reductant would be appreciably ionized. The values found in solvents B, C and D are approximately if not rigidly comparable.

TABLE I

REDUCTION POTENTIALS OF α-NAPHTHOQUINONES (25°)

Solvents: B, 50% Alcohol, 0.1 *N* in HCl and 0.2 *N* in LiCl; C, 37% Alcohol, 0.047 *M* in KH_2PO_4 and 0.047 *M* in Na_2HPO_4; D, 70% Alcohol, 0.2 *N* in HCl and 0.2 *N* in LiCl; E, Borate buffer, *p*H 8.02. Titrating agents: KF = $K_3Fe(CN)_6$; KM = $K_3Mo(CN)_8$; TB = Tetrabromo-*o*-benzoquinone.

1,4-naphthoquinone	Solvent	Titrated with	Normal potential, E_0 (av.), v.
1,4-Naphthoquinone	B		0.4839[1]
2-Methyl-[2]	D	KF	.4080
2,3-Dimethyl-[3]	D	KF	.3399
2,6-Dimethyl-[4]	B	KF	.4051
2,7-Dimethyl-[4]	B	KF	.4069
6-Methyl-2-hydroxy-[5]	D	KF	.3357
2,6-Dimethyl-3-hydroxy-[6]	D	KF	.2775
2-Phenyl-[7]	D	KF	.4515
2-Acetoxy-	B	KF	.4750
5-Benzoyl-[8]	D	TB	.5031
2-Diphenylmethyl-[9]	D	KF	.4328
2-Amino-[1]	C	KF	.2742
2-Methylamino-	C	KF	.2318
2-Dimethylamino-	E	KM	.2889
2-Acetylamino-[1]	B	KF	.4165
2-Anilino-	D	KF	.2858

(1) Fieser and Fieser, THIS JOURNAL, **56**, 1565 (1934).
(2) Anderson and Newman, *J. Biol. Chem.*, **103**, 406 (1933).
(3) Kruber, *Ber.*, **62**, 3044 (1929).
(4) Weissgerber and Kruber, *ibid.*, **52**, 346 (1919).
(5) Fieser and Seligman, unpublished results.
(6) Fieser and Seligman, THIS JOURNAL, **56**, 2690 (1934).
(7) Kvalnes, *ibid.*, **56**, 2478 (1934).
(8) Kegel, *Ann.*, **247**, 182 (1888).
(9) Möhlau and Klopfer, *Ber.*, **32**, 2146 (1899).

TABLE II

REDUCTION POTENTIALS OF β-NAPHTHOQUINONES (25°)

1,2-Naphthoquinone	Solvent[10]	Titrated with[10]	Normal potential, E_0 (av.), v.
1,2-Naphthoquinone	D		0.5760[11]
4-Methyl-[12]	D	KM	.5315
6-Methyl-[13]	C	KM	.5536
3,7-Dimethyl-[4]	B	KM	.5350
Dicarbethoxymethyl-[14]	D	TB	.5976
4-Amino-[1]	C	KF	.3249
4-Methylamino-	C	KF	.2933
4-Ethylamino-	C	KF	.2966
4-*n*-Butylamino-	C	KF	.2952
4-Benzylamino-	C	KF	.2997
3-Acetylamino-[15]	B	TB	.5545
4-Acetylamino-	B	TB	.5461

TABLE III[16]

SYSTEM FROM 1,2-DIHYDROXY-4-METHYLAMINONAPHTHALENE (25°)

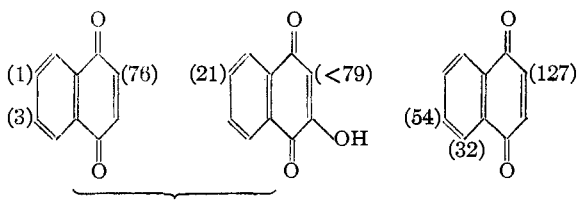
Constants of the reductant: $K_r^b = 5.80 \times 10^{-5}$. $K_r^a = 3.47 \times 10^{-10}$. β-Oxidant, 4-methylamino-1,2-naphthoquinone (*p*H 0–11): $E_0^\beta = 0.2899$ v. $K_\beta^b = 8.13 \times 10^{-2}$

*p*H	Hydrogen elec. potential, E_h, v.	Potential when [Ox.] = [Red.], E_n, v.	En (found-calcd.), mv.	Nature of slope $-\Delta E_n\Delta/p$H
0.33	−0.0194	0.3579	−3.6	0.06
1.02	.0611	.3131	−0.8	
1.41	.0835	.2837	−1.0	
2.10	.1243	.2285	0.9	0.09
2.63	.1555	.1820	.2	
3.29	.1945	.1259	1.2	
3.82	.2259	.0804	−0.1	
4.28	.2531	.0443	− .8	
4.91	.2901	−.0006	1.7	
5.48	.3241	.0357	−2.2	0.06
6.11	.3613	.0729	−1.7	
6.66	.3931	.1042	−1.2	
7.02	.4149	.1241	0.7	
7.57	.4479	.1563	1.5	
8.33	.4923	.2009	0.6	
9.23	.5456	.2519	2.1	
9.78	.5780	.2749	−1.3	0.03
10.42	.6157	.2951	1.0	
10.99	.6495	.3123	1.7	
11.45	.6769	.3283	...	
11.86	.7007	.3473	−0.9	0.06
12.35	.7300	.3756	0.1	
12.92	.7642	.4091	.8	

(10) See Table I.
(11) Fieser and Peters, THIS JOURNAL, **53**, 793 (1931).
(12) Fieser and Bradsher, unpublished results.
(13) Dziewoński, Schoenówna and Waldmann, *Ber.*, **58**, 1213 (1925).
(14) Sachs and Craveri, *ibid.*, **38**, 3687 (1905).
(15) Kehrmann and Zimmerli, *ibid.*, **31**, 2406 (1898).
(16) For an explanation of the symbols used see Ref. 1.

We had hoped to extend the observations[1] concerning the tautomerism of the aminonaphthoquinones, and several of the N-substituted derivatives of these compounds were prepared with this end in view. Most of these substances, however, proved to be either too sparingly soluble or too unstable for extended study in aqueous solution, and significant results were obtained only in the case of 4-methylamino-1,2-naphthoquinone (Table III). Although with this compound the potentials are decidedly lower than for the 4-amino derivative, the character of the E_n:pH curve and the relationship between the tautomeric forms are entirely similar and they require no further comment.

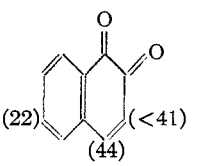
It is of interest to compare the effect produced by a given substituent when it is located in the various possible positions of the naphthoquinone nucleus, and an analysis of the significant results of this and earlier studies is given in the following chart for the para quinones



POTENTIAL-LOWERING EFFECT (MV.) OF SUBSTITUENT GROUPS

The figure opposite each position indicates the difference in the normal potentials of the substituted and unsubstituted quinones or, in the case of substituents in the 6 and 7 positions, the difference between the 2,6 or 2,7 derivative and the 2 derivative. The combined effect of the two methyl groups in 2,6-dimethyl-3-hydroxy-1,4-naphthoquinone is 79 mv., hence the effect of the methyl group at position 2 is somewhat, probably only slightly, less than this amount. Taking these results as a whole it may be said that the effect of substitution is considerably less in the benzenoid than in the quinonoid nucleus. Some effect is often transmitted, if weakly, through the benzenoid ring, and there is no distinct difference between α and β substitution in this ring. These positions are, of course, meta to one of the carbonyl groups and either ortho or para to the other.

The results for the ortho quinones are still less extensive and it may be inferred only that there is again an appreciable difference in the effect of the substitution of a methyl group in the two rings



It would seem that potentiometric data can be used only for the partial location of particularly effective substituents in naphthoquinones of unknown structure.

A comparison of the various different groups investigated in this and in earlier papers is given in Table IV, the potential differences given being for alcoholic solutions unless otherwise noted. The methylamino group is quite consistently more powerful than the amino group, and it is hence surprising to find that the dimethylamino group is slightly less effective than the parent group. There is, to be sure, only one value as yet available for comparison, for we did not succeed in preparing the dimethylamino derivative of β-naphthoquinone, the compound apparently undergoing hydrolysis to the secondary amine. The effect of substitution appears to be greater for the β-quinone than for the α-quinone with the amino,

TABLE IV

THE EFFECT OF SUBSTITUENT GROUPS ON THE POTENTIAL OF NAPHTHOQUINONES

2-Substituted 1,4-quinones

Substituent	Effect in mv.
$-NH_2$	−210 (−187, aq.)
$-NHCH_3$	−252
$-NHCOCH_3$	− 67
$-CH_3$	− 76
$-OCH_3$	−131
$-OC_4H_9$	−133
$-SO_3Na$	+ 69 (+63, aq.)
$-NHC_6H_5$	−198
$-N(CH_3)_2$	−181, aq.
$-CH(C_6H_5)_2$	− 51
$-C_6H_5$	− 32
$-OH$	−127 (−119, aq.)
$-OCOCH_3$	− 9
$-Cl$	+ 24
$-SO_2C_6H_4CH_3$	+121

4-Substituted 1,2-quinones

Substituent	Effect in mv.
$-NH_2$	−251 (−229, aq.)
$-NHCH_3$	−283 (−265, aq.)
$-NHCOCH_3$	− 30
$-CH_3$	− 44
$-OCH_3$	−143
$-OC_4H_9$	−154
$-SO_3Na$	+ 60 (+75, aq.)
$-NHC_2H_5$	−279
$-NHC_4H_9$	−281
$-NCH_2C_6H_5$	−276
$-CH(COOR)_2$	+ 22

methylamino and alkoxyl groups, but there is a curious reversal with the methyl and sulfonate groups. This perhaps only serves to indicate the limits within which such data are significant.

With regard to the order of effectiveness of different substituent groups, a generalization may be phrased which covers at least roughly all of the available potentiometric data bearing on the problem: the groups which lower the potential of the parent quinone are those which facilitate substitution in the benzene ring; those which produce an increase in the potential have the opposite effect and retard benzene-substitution. The rule is stated in this way rather than in terms of ortho–para and of meta orientation in order to take account of the well-known fact that halogen atoms, although they are ortho–para directing, retard rather than promote substitution in the benzene ring. They also have a potential-raising effect. A few illustrations will show how the rule operates. Groups such as $-NO_2$, $-CN$, $-SO_2Ar$, $-COAr$, $-COOR$, $-COOH$, $-SO_3H$, which are strongly unsaturated at the point of attachment (meta type), as well as halogens, have an effect upon the potential of a quinone which is in the positive direction; a negative effect is exerted by the following saturated or weakly unsaturated groups, all of which are of the ortho–para type: $-NHR$, $-NH_2$, $-OH$, $-OR$, $-CH_3$, $-CH_2Ar$, $-CH{=}CHR$, $-C_6H_5$, $-NHCOCH_3$, $-OCOCH_3$. These are arranged approximately (and provisionally) in order; the amino or alkylamine group surpasses all others, as is the case also for substitutions, and hydroxyl is intermediate between this and methyl. Acetylation of the active groups diminishes greatly their influence. The introduction of phenyl radicals modifies only slightly the effect of amino or methyl groups, but there is a reversal of type on substitution of two carbethoxy radicals into the methyl group.

Experimental Part

Improved procedures for preparing in a highly pure condition various naphthalene derivatives required as starting materials are indicated in the following notes.

1-Amino-2-naphthol Hydrochloride.[17]—A solution of 105 g. of sulfanilic acid dihydrate and 26.5 g. of anhydrous sodium carbonate in 500 cc. of water was treated at 15° with 37 g. of sodium nitrite in 100 cc. of water and poured onto 106 cc. of concd. hydrochloric acid and 600 g. of ice. After fifteen minutes the suspension was stirred into a solution of 72 g. of β-naphthol and 110 g. of sodium hydroxide in 600 cc. of water, cooled to 5° by the addition of 500 g. of ice. After one hour the suspension of dye was heated to 45° and one-tenth of 230 g. of sodium hydrosulfite was added cautiously, the remainder as soon as the froth subsided. The mixture was digested close to the boiling point, cooled to 25° and the washed product transferred to a solution at 30° of 2 g. of stannous chloride (anti-oxidant) and 53 cc. of concd. hydrochloric acid in 1 liter of water. The solution, warmed only in case crystals began to form, was stirred with 10 g. of Norite, filtered with suction, treated with 200 cc. of hydrochloric acid and heated to boiling (the color fades). After cooling to 0° the nearly colorless crystals were washed with cold 5% acid and dried at 35°; yield, 80–83 g. (82–85%). Recrystallizing from 1 liter of water with 2 g. of stannous chloride and 2 cc. of concd. hydrochloric acid, filtering the hot solution through a layer of Norite, adding more acid and reheating as above, the material was ash-free and could be stored in the dark for months without acquiring any appreciable color (loss 5–7 g.).

1-Amino-4-naphthol Hydrochloride.—Using pure α-naphthol the above procedure was followed with only a few changes. The suspension of aminonaphthol was not heated above 70° during the coagulation; the crude amine was washed with 1% hydrosulfite solution and dissolved by heating in 800 cc. of water, 2 g. of stannous chloride and 63 cc. of concd. hydrochloric acid. Treatment with carbon at this point was omitted, the color largely disappearing when the filtered solution was boiled with acid. For recrystallization 700 cc. of water was required; colorless needles, 70–73 g. (72–75%).

β-Naphthoquinone.—Material superior to any yet reported can be obtained by the careful oxidation of the above pure amine hydrochloride. If recrystallized salt is used filtration may be omitted. A solution of 80 g. of the hydrochloride prepared quickly by shaking with 3 liters of water and 5 cc. of concd. hydrochloric acid at 35° was rapidly filtered and transferred to a 5-liter flask. While rotating the flask vigorously there was added all at once a cold, filtered solution from 240 g. of ferric chloride crystals, 90 cc. of concd. hydrochloric acid and 500 cc. of water. The quinone separated at once and was washed on the funnel and by stirring with 2 liters of water and air-dried at 25°; yield, 61 g. (94%); microscopic needles, pure golden-yellow, softens at 140°, m. p. 145–147° (dec.), stable on storage.

α-Naphthoquinone.—Russig's method[18] of oxidizing the aminonaphthol was the best of any tried, 70 g. of the pure hydrochloride giving 54 g. of dull yellow quinone, m. p. 124–125°. It was purified with advantage as compared with previous methods[19] by shaking a solution of the material in 1.5 liters of ether with 10 g. of Norite for ten minutes, filtering and evaporating until crystals began to form. Further crops were obtained from the mother liquor after treatment with Norite and all of the material was pure yellow; m. p. 124–125°; 46.4 g. (82% recovery).

(17) Conant and Corson, "Organic Syntheses," **11**, 8 (1931); Witt, *Ber.*, **21**, 3472 (1888); Paul, *Z. angew. Chem.*, **10**, 48 (1897); Skita and Rohrmann, *Ber.*, **63**, 1482 (1930).

(18) Russig, *J. prakt. Chem.*, **62**, 31 (1900).

(19) Conant and Freeman, "Organic Syntheses," Coll. Vol. I, 375 (1932).

1-Amino-2-naphthol-4-sulfonic Acid.[19]—The procedure of Fieser[21] was improved as follows. The mixture of nitrosonaphthol (from 300 g. of β-naphthol) and bisulfite was stirred vigorously with a paddle so that the soluble product was brought into solution in three to four minutes and the filtration was conducted as rapidly as possible. Acid was added to the golden-yellow filtrate immediately, giving a light gray product. (If much time elapses the material is darker.) The product was washed with water, then with 1.5–2 liters of hot alcohol until this no longer extracted a dark red impurity, and then with ether. Dried to constant weight in the dark at 60–80°, 370–380 g. (75–78%) of pure white, dust-dry material was obtained.

1,2-Naphthoquinone-4-sulfonate.[20]—A 10-g. portion of pure 1-amino-2-naphthol-4-sulfonic acid was stirred into a mixture of 145 cc. of concd. nitric acid and 400 cc. of water at 30°, the solution was allowed to come to rest and 2 cc. of the concentrated acid was poured down the side of the beaker without stirring. The oxidation commenced in one to two minutes and the solution was maintained at 25–30° while stirring in 340 g. of material in 25-g. portions, adding 100 cc. of ether when the mixture began to froth (more later). Within a few minutes the reaction subsided; 175 cc. of saturated ammonium chloride solution was added and the thick paste cooled to 0°. The ammonium salt was washed with a cold mixture of 150 cc. of saturated ammonium chloride solution and 100 cc. of water, then with alcohol and ether. The clean, orange ammonium salt was dried at 40°; yield, 350–365 g. (94–98%).

For further purification of this very sensitive quinone 50 g. of the ammonium salt was dissolved quickly in 1.7 liters of water preheated to 50° and containing 0.3 cc. of bromine to destroy impurities, the solution was shaken with 3 g. of Norite, filtered by suction and treated with 400 cc. of saturated potassium chloride solution. After cooling to 0° the potassium salt was collected, washed with a dilute solution of the chloride, with alcohol and ether and dried at 45°; yield, 49 g. (91% recovery). A second crystallization from 1.7 liters of water with 0.2 cc. of bromine at 60°, using 300 cc. of the salt solution and omitting the clarification, gave 48 g. (66% yield from β-naphthol). The quinone was obtained as beautiful bright orange needles comparable in purity with the best material obtainable by the elaborate process of Folin,[22] as judged by the delicate tests of Folin and of Danielson.[23]

Potassium 1,4-Naphthoquinone-2-sulfonate.[24]—A new method of preparation is from α-naphthoquinone and bisulfite, both of which being of good quality (preliminary test). To a mechanically stirred solution of 36 g. of sodium bisulfite in 400 cc. of water at 20–25°, 32 g. of the finely powdered quinone was added in fifteen minutes and after one hour the dark yellow solution was filtered from a trace of gray residue, treated with 4 cc. of concd. sulfuric acid, boiled for fifteen minutes and treated at 25° with 24 g. of potassium dichromate and 18 cc. of concd. sulfuric acid in 70 cc. of water. On adding 200 cc. of saturated potassium chloride solution in portions the quinone sulfonate separated as glistening yellow plates. The brown solution of the collected material in 600 cc. of water at 55° became pure yellow on Norite treatment; on adding 300 cc. of saturated potassium chloride solution, both solutions being at 45°, the quinone salt separated as bright yellow plates of the monohydrate; yield, 47 g. (79%). At a higher temperature the salt separates in an anhydrous form (fine needles); the aqueous solution of the crude salt often decomposes badly above 55°.

2-Hydroxy-1,4-naphthoquinone.[20]—The second procedure (b) of a previous paper[25] is advantageously modified. To 1 liter of methyl alcohol and 80 cc. of concd. sulfuric acid at 0° 255 g. of ammonium 1,2-naphthoquinone-4-sulfonate was added and mixed to an even paste. In thirty minutes the mixture was warmed slowly with shaking and boiled gently for thirty minutes, adding 250 cc. more alcohol. The earlier procedure was then followed except that the alkaline solution of hydroxynaphthoquinone was acidified while hot and cooled for two hours at 0°, giving a nicely granular and a very pure product; yield 58–65%.

2-Alkylamino-1,4-naphthoquinones.—A preparation of the dimethylamino compound simpler than that of Plimpton[26] consists in boiling for five minutes a solution of 21 g. of 1,4-naphthoquinone-2-sulfonate and 10.5 cc. of 33% dimethylamine in 400 cc. of water, cooling the red solution and crystallizing the precipitate from 1 liter of water (Norite); brilliant red, hair-fine needles (2.1 g.), m. p. 120°. The methylaminoquinone can be obtained in much better yield by the same process but Plimpton's method is also more satisfactory in this case (m. p. 234°).

4-Alkylamino-1,2-naphthoquinones could not be obtained from β-naphthoquinone or its 4-sulfonate but were prepared readily as follows. To a filtered solution of 3 g. of 4-ethoxy-1,2-naphthoquinone in 50–60 cc. of alcohol at 45° a filtered mixture of 3 cc. each of 33% methylamine solution and alcohol was added. The methylaminoquinone slowly separated as bright red plates and in a pure condition (1.6 g.). Dimethylamine gave the identical compound. Ethylamine and *n*-butylamine reacted normally, giving pure products for which no crystallizing solvent was found. The benzylamino compound was accompanied by a green by-product removed by washing with alcohol and ether and the quinone crystallized well from alcohol. The four quinones all form bright red plates only slightly soluble in water, soluble in cold alkali.

TABLE V

4-SUBSTITUTED 1,2-NAPHTHOQUINONES

Substituent	Decompn., 0°		Calcd.	Found
Methylamino	247–249	C	70.57	70.61
		H	4.85	4.98
Ethylamino	248–250	N	6.97	6.97
n-Butylamino	228–230	N	6.11	6.12
Benzylamino	205–208	N	5.32	5.47

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(20) The work of Elmore L. Martin.
(21) Fieser, "Organic Syntheses," **11**, 12 (1931).
(22) Folin, *J. Biol. Chem.*, **51**, 386 (1922).
(23) Danielson, *ibid.*, **101**, 507 (1933).
(24) With H. Theron Thompson.
(25) Fieser, THIS JOURNAL, **48**, 2922 (1926).
(26) Plimpton, *J. Chem. Soc.*, **37**, 633 (1880).