Analytica Chimica Acta, 257 (1992) 257–273
Elsevier Science Publishers B.V., Amsterdam

Electrochemistry of potentially bioreductive alkylating quinones

Part 3. Quantitative structure–electrochemistry relationships of aziridinylquinones

R.J. Driebergen [1,*], E.E. Moret, L.H.M. Janssen, J.S. Blauw and J.J.M. Holthuis [1]

Faculty of Pharmacy, University of Utrecht, Sorbonnelaan 16, 3584 CA Utrecht (Netherlands)

S.J. Postma Kelder, W. Verboom, D.N. Reinhoudt and W.E. van der Linden

Department of Chemical Technology, University of Twente, P.O. Box 217, 7500 AE Enschede (Netherlands)

(Received 8th July 1991)

Abstract

The concept of bioreductive alkylation as a mechanism of action of aziridinylquinoid anticancer agents has been investigated by the use of electrochemical techniques. Properly substituted aziridinylquinones are activated by an electrochemical step (reduction of the quinone function), followed by protonation of the aziridinyl moiety to the alkylating species. The influence of substitution on quinone reduction, on protonation and on subsequent opening of the aziridines (prior to and after quinone reduction) has been examined. A series of mono- and poly(1-aziridinyl)-quinones has been synthesized and analyzed by direct current (d.c.) polarography. The half-wave potential ($E_{1/2}$ value) of the quinone reduction and the pK_{red} and pK_{red2} (reflecting the ease of protonation at the mercury electrode of one and two aziridinyl rings, respectively) were used in a Hammett type QSAR analysis. A linear relationship between $E_{1/2}$ and the electronic substituent constant σ_p was obtained for simple quinones. Deviations from linearity were observed, due to steric and/or resonance interactions which influence quinone reduction, with amino- and halogen-substituted quinones. Unknown σ_p values could be calculated. Relationships between pK_{red2} and some physical-chemical parameters show that electronic and steric properties of quinone substituents affect pK_{red2}. In addition, the formation of a hydrogen bond between the quinone substituent and the adjacent aziridinyl ring (which may thwart aziridine protonation) and the presence of a methyl substituent at position 2 of the aziridine (which facilitates protonation) are of importance. Results of this study have lead to a better knowledge of the individual substituents with respect to their electronic and steric influences on quinone reduction and aziridine protonation, which may be of importance if these processes play a decisive role in cytostatic activity as well as toxicity.

Keywords: D.c. polarography; Aziridinylquinones; Benzoquinones; Electronic substituent constants; Naphthoquinones; Quantitative structure–electrochemistry relationships

The concept of bioreductive alkylation as a mechanism of action of aziridinylquinoid anticancer agents can be investigated by the use of electrochemical techniques [1,2]; a comprehensive description of this matter was given in the previous papers of this series [1,2]. The main points can be summarized as follows: according to the concept of bioreductive alkylation, properly substituted quinones are activated by an electrochemical step (reduction of the quinone func-

[1] Present address: Analytical Laboratories, EuroCetus B.V., P.O. Box 23023, 1100 DM Amsterdam, Netherlands.

0003-2670/92/$05.00 © 1992 – Elsevier Science Publishers B.V. All rights reserved

tion), followed by one or more chemical steps which lead to the formation of the alkylating species, generally a quinone methide structure or, in the case of an aziridinylquinone, an aziridinium ion, which is known to be unstable and to open rapidly upon nucleophilic attack. Hence it can be hypothesized that reduction of the quinone function facilitates protonation of the aziridinyl ring. However, it has also been reported that reduction decreases the reactivity of the aziridinyl rings and thus deactivates the compound.

For a better understanding of the mechanism of action of these compounds, a detailed electrochemical and chemical stability study of a series of aziridinylquinones has been made. The influence of substitution on quinone reduction, on protonation and on subsequent opening of the aziridines (prior to and after quinone reduction) has been examined.

Theoretically, quinone reduction is favoured by electron-withdrawing substituents, which, however, make subsequent protonation of the aziridines more difficult; electron-donating groups cause opposite effects and an optimum composition of the quinone substituents is required to give a maximum efficacy of activation. It also implies that a more negative half-wave potential ($E_{1/2}$ value), indicating a thwarted quinone reduction, is generally accompanied by an increase in the pK_a of the aziridinyl ring(s), which indicates facilitation of aziridine protonation in the hydroquinone. As a measure of these pK_as, the pK_{red} and pK_{red2} values (reflecting the ease of protonation at the mercury electrode of one and two aziridinyl rings, respectively [2]), of a series of mono- and poly(1-aziridinyl)quinones have been determined by direct current (d.c.) polarography. As both quinone reduction and aziridine protonation seemed to correlate qualitatively with the electronic properties of the quinone substituents, a quantitative structure–activity relationship (QSAR) study was made.

The objective of nearly all QSAR studies is to find a mathematical form of a relationship between a particular physical, chemical and/or biological property of the compound. This relationship can then be used to predict that feature for other compounds in the series. The theoretical treatment of substituent effects in chemical and/or biological reactivity is extensively described in the literature (e.g., [3–6]). Many parameters describing electronic (e.g., sigma constants such as σ_o, σ_m, σ_p, σ^*, σ^- and σ^+ and the Swain and Lupton parameters F and R) and steric properties (e.g., the Taft constant E_s and the Verloop parameters L and B_{1-4}) of substituents have been defined. Generally, equations describing the influence of electronic substituent effects on a particular chemical reaction in relation to the unsubstituted parent compound are of the type of the Hammett equation:

$$\log(k/k_0) = \rho\sigma \qquad (1)$$

where k is a rate or equilibrium constant of the particular reaction of the substituted compound and k_0 that of a reference compound, σ is an electronic parameter of the substituent of interest and the reaction constant ρ indicates the sensitivity of the reaction to electronic effects.

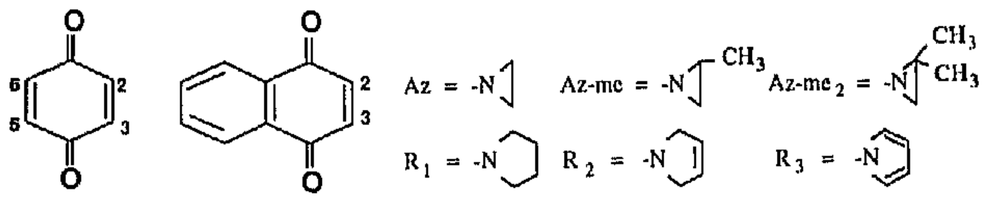
The theoretical aspects of substituent effects in aqueous organic polarography have been extensively studied by Zuman [7]. The half-wave potential of the unsubstituted compound, $(E_{1/2})_H$, is shifted to a new value, $(E_{1/2})_X$, by introducing a substituent X. This shift is influenced by both electronic and steric effects of the particular substituents and can be given by

$$\delta E_{1/2} = (E_{1/2})_X - (E_{1/2})_H = \rho_R \sigma_X \qquad (2)$$

when steric interactions are excluded [7]. Equation 2 is a modified form of the Hammett Eqn. 1. In Eqn. 2, σ_X is the electronic substituent constant of substituent X. The constant ρ_R is the reaction constant, which reflects the susceptibility of the reaction to the electronic properties of the substituents. Its value depends on the type of the electroactive group R, on the temperature and on the composition of the electrolyte, but is independent of the kind and position of the substituents [7]. It appeared that, within a series of structurally related quinones, good linear relationships can be obtained when $\delta E_{1/2}$ is correlated with σ_p [7]. Deviations from such a linear relationship may occur when steric and/or resonance interactions influence quinone reduction. This is particularly the case with polysubstitution of the quinone

TABLE 1

Structures of 1,4-benzoquinones and 1,4-naphthoquinones [a]



Compound	1,4-Benzoquinones				$E_{1/2}$ (V)	pK_{red2}
	Substituents					
	2	3	5	6		
1	H	H	H	H	0.055	
2	CH_3	H	H	H	0.000	
3	CH_3	H	CH_3	H	−0.050	
4	CH_3	H	H	CH_3	−0.055	
5	CH_3	CH_3	CH_3	CH_3	−0.160	
6	CH_3	CH_3	CH_3	OH	−0.247	
7	OH	H	OH	H	−0.379	
8	OCH_3	H	H	H	−0.043	
9	OCH_3	H	OCH_3	H	−0.183	
10	CH_3	H	CH_2CH_3	H	−0.041	
11	Br	H	CH_3	H	0.025	
12	Br	H	CH_2CH_3	H	0.027	
13	Br	H	$CH_2CH_2OCONH_2$	H	0.042	
14	CH_3	H	$CH_2CH_2OCONH_2$	H	−0.035	
15	NH_2	H	NH_2	H	−0.395	
16	$NHCH_3$	H	$NHCH_3$	H	−0.511	
17	$N(CH_3)_2$	H	$N(CH_3)_2$	H	−0.319	
18	$NHCOCH_3$	H	H	H	0.001	
19	$NHCOCH_3$	H	$NHCOCH_3$	H	−0.071	
20	$NHCO_2CH_2CH_3$	H	$NHCO_2CH_2CH_3$	H	–	
21	$NHCH_2CH_2OH$	H	$NHCH_2CH_2OH$	H	−0.500	
22	CH_3	CH_3	R_1	H	−0.303	
23	CH_3	CH_3	R_2	H	−0.311	
24	OCH_3	CH_3	R_1	H	−0.315	
25	R_1	H	R_1	H	−0.439	
26	R_2	H	R_2	H	–	
27	Az	H	Az	H	−0.105	7.5
28	Az-me	H	Az-me	H	−0.115	8.1
29	Az	Br	Az	Br	–	–
30	Az-me	Br	Az-me	Br	–	–
31	Az	Cl	Az	Cl	−0.113	–
32	Az-me	Cl	Az-me	Cl	−0.125	–
33	Az	F	Az	F	−0.087	7.2
34	Az-me	F	Az-me	F	−0.093	7.9
35	Az	OCH_3	Az	OCH_3	−0.179	8.0
36	Az-me	OCH_3	Az-me	OCH_3	−0.187	8.6
37	Az	NH_2	Az	NH_2	–	–
38	Az	$NHCH_3$	Az	$NHCH_3$	−0.415	8.5
39	Az-me	$NHCH_3$	Az-me	$NHCH_3$	−0.400	9.3
40	Az	$NHCH_2CH_2OH$	Az	$NHCH_2CH_2OH$	−0.385	9.5
41	Az	$NHCO_2CH_2CH_3$	Az	$NHCO_2CH_2CH_3$	−0.149	8.3
42	Az-me	$NHCO_2CH_2CH_3$	Az-me	$NHCO_2CH_2CH_3$	−0.145	8.5
43	Az	$N(CH_3)CH_2CH_2OH$	Az	$N(CH_3)CH_2CH_2OH$	−0.225	9.7
44	Az	R_1	Az	R_1	−0.315	10.6
45	Az-me	R_1	Az-me	R_1	−0.303	11.1
46	Az	C_6H_5	Az	C_6H_5	–	–
47	Az	CH_3	Az	CH_2CH_3	−0.227	8.7

TABLE 1 (continued)

Compound	1,4-Benzoquinones					
	Substituents				$E_{1/2}$ (V)	pK_{red2}
	2	3	5	6		
48	Az	CH_3	Az	CH_2CH_2OH	−0.209	8.6
49	Az	CH_3	Az	$CH_2CH_2OCONH_2$	−0.213	8.9
50	Az-me	CH_3	Az-me	$CH_2CH_2OCONH_2$	−0.235	9.7
51	Az	CH_3	Az	$CH(OCH_3)CH_2OCONH_2$	−0.182	8.6
52	Az	Br	Az	CH_3	−0.185	8.7
53	Az-me	Br	Az-me	CH_3	−0.194	9.2
54	Az-me_2	Br	Az-me_2	CH_3	–	–
55	Az	Br	Az	CH_2CH_3	−0.210	8.8
56	Az	Br	Az	$CH_2CH_2OCONH_2$	−0.201	8.9
57	Az	Cl	Az	CH_3	−0.197	8.5
58	Az	Az	Az	H	−0.171	8.0
59	Az	Az	Az	F	−0.171	7.8
60	Az-me	Az-me	Az-me	F	−0.195	8.2
61	Az	Az	Az	Az	−0.245	7.7
	1,4-Naphthoquinones				$E_{1/2}$ (V)	pK_{red}
	2	3				
62	H	H			−0.145	
63	OH	H			−0.360	
64	CH_3	H			−0.186	
65	CH_2CH_3	H			−0.247	
66	Br	H			−0.165	
67	Cl	H			−0.172	
68	NH_2	H			−0.377	
69	$NHCH_3$	H			−0.431	
70	$N(CH_3)_2$	H			−0.374	
71	$NHCH_2CH_3$	H			−0.425	
72	$NHCH_2CH_2OH$	H			−0.429	
73	$NHCO_2CH_2CH_3$	H			–	
74	$N(CH_3)COCH_3$	H			−0.147	
75	R_1	H			−0.435	
76	R_2	H			−0.439	
77	NH_2	Cl			−0.394	
78	$NHCOCH_2Cl$	Cl			−0.157	
79	$NHCO_2CH_2CH_3$	Cl			−0.175	
80	$NHCO_2CH_2CH_3$	R_2			−0.377	
81	$NHCO_2CH_2CH_3$	R_3			−0.209	
82	Az	H			−0.259	8.0
83	Az-me	H			−0.252	8.3
84	Az	Cl			−0.287	8.0
85	Az	NH_2			−0.414	8.0
86	Az	$NHCOCH_3$			−0.285	8.2
87	Az	$NHCOCH_2Cl$			−0.269	9.1
88	Az	$NHCO_2CH_2CH_3$			−0.285	8.3
89	Az-me	$NHCO_2CH_2CH_3$			−0.261	8.1
90	Az	$N(CH_3)CO_2CH_2CH_3$			−0.288	8.0
91	Az-me	$N(CH_3)CO_2CH_2CH_3$			−0.283	8.0
92	Az	$CH_2NHCO_2CH_2CH_3$			−0.317	9.0

[a] Half-wave potentials ($E_{1/2}$) at pH 7.0 and, in the case of mono(1-aziridinyl)-1,4-naphthoquinones, their pK_{red} values, in case of bis-, tris- and tetrakis(1-aziridinyl)-1,4-benzoquinones, their pK_{red2} values, all obtained by d.c. polarography.

moiety, as steric interactions between adjacent substituents and/or the quinone carbonyl function readily occur. Substituents which may be expected to cause such deviations from a linear relationship include halogens and amino functions [7–10].

In a first attempt to correlate the electrochemical data obtained with electronic substituent constants, it was decided to use σ_p in a Hammett-type correlation study, in analogy with [7]. In addition, the Swain and Lupton parameters F (describing the inductive-field component) and R (describing the resonance component) were used as electronic parameters. In this paper, results of these Hammett-type regression analyses are presented for a series of 54 benzoquinones and 30 naphthoquinones (Table 1). An attempt has also been made to describe the pK_{red2} values of a series of bis(1-aziridinyl)benzoquinones quantitatively via a Hammett-type approach, using electronic (σ_p) and steric (MR) substituent constants, combined with a parameter which describes the ability to form hydrogen bonds (HB_1) (see *Procedures*, MR = molar refractivity, as a measure for the molar volume).

It is expected that the results of this study will lead to a better knowledge of the individual substituents with respect to their electronic and steric influences on quinone reduction. Predictions about $E_{1/2}$ and/or pK_{red2} values may be of importance for the biological activity of aziridinylquinones when quinone reduction and/or aziridine protonation play a decisive role in cytostatic activity and toxicity.

EXPERIMENTAL

Chemicals

Compounds **1**, **4**, **5**, **7**, **62**, **63**, **64** and **67** (Table 1) were obtained from Aldrich Europe (Janssen Chimica), **2** from Merck (Darmstadt) and **3** from ICN Pharmaceuticals (New York). Compound **6** was prepared according to [11], **8** and **9** according to [12], **10**, **13**, **14**, **46–49**, **52**, **55** and **56** as described in [13], **11** and **12** as in [14], the aminoquinones **15**, **16**, **17** and **68** analogously as reported in [15], [16], [17] and [18], respectively, **69**, **70** and **71** as reported in [19] and **18** and **19** as described in [20] and [21], respectively. The syntheses of **20**, **22**, **23**, **26**, **53**, **54**, **57**, **74**, **76**, **80**, **81**, **90**, **91** and **92** have been described in [22], and are available from the author on request. Compounds **21**, **24** and **25** were prepared according to [23], [24] and [25], respectively, the aziridinylquinones **27–32** and **82–84** as described in [26], **33**, **34**, **38**, **39**, **44**, **45**, **59** and **60** as described in [27], **35** and **36** as described in [28], **42** as described in [29], **50** as described in [30], **61** as reported in [31], **65**, **66** and **72** according to [32], [33] and [34], respectively, **73** and **75** as described in [35] and [36], respectively, **77** and **78** according to [37], **79** and **89** according to [38], **85** and **87** as reported in [39] and **86** according to [40]. The synthesis of **88** has been described previously [2].

Compounds **37** and **43** were a gift from Dr. J.S. Driscoll (Drug Research and Development Division of Cancer Treatment, National Institutes of Health, Bethesda, MD), **40** (BZQ) from Dr. E.V. Wilman (Institute of Cancer Research, Cancer Research Campaign Laboratory, Sutton), **41** (AZQ) from Dr. J.A. Kelley and Dr. V.L. Narayanan (Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD), **51** (carboquone) from Dr. H. Nakao (Chemical Research Laboratories, Sankyo, Tokyo) and **58** from Dr. K. Brandau and Dr. E. Muller (Bayer, Pharma Research Centre, Wuppertal).

Apparatus

The apparatus used for the determination of the electrochemical parameters of interest, viz., the half-wave potential of the quinone reduction ($E_{1/2}$) for all compounds and the pK_{red} and pK_{red2} values of the subsequent protonation of the aziridinyl ring(s) of the aziridinylquinones, was as reported previously [1,2]. Multiple linear regression analysis was done by means of the HP 98820A Statistical Library program on an HP 310 microcomputer, equipped with an HP 7475 A3 plotter (all from Hewlett-Packard).

Procedures

Small structural changes can lead not only to a shift in $E_{1/2}$, but also to changes in the number of waves observed, the pH dependence of $E_{1/2}$,

the number of electrons consumed and the character of the waves. This has been clearly demonstrated by electrochemical studies of simple amino- and aziridinylquinones [1,2]. For an adequate comparison of half-wave potentials within a series of structurally related compounds, the reduction mechanism has to be identical, i.e., the overall electrode reaction, the structure of the electroactive species, the number of electrons transferred, the type of electrode process (reversible, irreversible), similarity in pH dependence of the half-wave potential, etc. When these conditions are fulfilled, structural effects on shifts of the half-wave potential can be treated quantitatively [7].

To obtain well developed waves that permit an accurate determination of the half-wave potential ($\pm$2–5 mV), a concentration of the compound of ca. 0.1 mM and a slow scan rate (2 mV s^{-1}) are required. Further, the current and the half-wave potential should be measured under the same experimental conditions and the potential of the reference electrode should be calibrated (e.g., by measuring the half-wave potential of the thallium ion, which is -0.455 V, almost independent of pH and composition of the supporting electrolyte, and by introduction of a correction value when required).

It is preferable for structural correlation studies to compare half-wave potentials of quinones that are determined under conditions at which they are all independent of pH. Usually this will be the case under extremely acidic conditions (at $pH < pK_1^Q$ [1]), where protonation of the quinone function in the buffered solution occurs, or under extremely alkaline conditions (at $pH > pK_2^{HQ}$), where the product of reduction is no longer protonated and, in the case of reduction of quinones in aqueous media, an ee mechanism occurs [1]. Experimentally, this condition cannot be fulfilled, owing to decomposition of the quinoid compound or interference by oxidation of mercury [1,2]. Consequently, a pH value must be selected at which half-wave potentials of the whole series of compounds may be compared. However, compounds containing substituents that may participate in acid–base equilibria, e.g., amino and hydroxy groups, may influence the number of protons involved in the electrode reaction and consequently affect the pH dependence of $E_{1/2}$. As a result, a pH value must be chosen at which the plots of $E_{1/2}$ vs. pH of all compounds show parallelism. For this reason, pH 7.0 was selected. The procedures used for the verification of parallelism in the $E_{1/2}$ vs. pH plot, the measurement of $E_{1/2}$ at pH 7.0 of all quinones and for the determination of pK_{red} and pK_{red2} of the aziridinylquinones were as reported previously [1,2].

The physico-chemical parameters used were the electronic parameters σ_m and σ_p and the corresponding Swain and Lupton parameters F and R:

$$F = 1.3696\sigma_m - 0.373\sigma_p - 0.009 \quad (3)$$

$$R = \sigma_p - F \quad (4)$$

the steric parameter MR and a parameter describing the ability to form hydrogen bonds, HB_1 (includes both the H-acceptor and the H-donor).

Values of substituent constants are given in Table 3 for all relevant substituents. Values of well known substituents are tabulated in [5], with the exception of HB_1 values, which were obtained from [41] and electronic parameters of OCH_3 and $N(CH_3)_2$ functions, which were obtained from [4] (marked [b] in Table 3). Non-tabulated values are estimated (marked [c], mainly HB_1 and MR values), or calculated (marked [d], some σ_p, σ_m, F and R values) for less common substituents. Unknown σ_p and σ_m values were determined from regression Eqns. 5 and 6 and Eqns. 7 and 8, respectively, which relate $E_{1/2}$ of several well established benzoquinones with σ_p and σ_m constants (see Results). From these σ_p and σ_m values, F and R values can be calculated by Eqns. 3 and 4 [5].

In a first approach to estimate the ability to form hydrogen bonds, the method developed by Yang et al. [41] was employed for this series of compounds. Only the possible ability of the first two atoms of the substituent(s) to form hydrogen bond(s) with the carbonyl function of the quinone, with the hydroxy group of the hydroquinone and/or with other (viz., aziridine) substituents (as donor or as acceptor) was taken into account,

without considering the strength of the hydrogen bond formed. Each possible hydrogen bond formed increases the HB_1 value by 1. For equiscalarity reasons, MR values were divided by 10 in the correlation studies. Values listed in Table 3, however, are the original data. Occasionally an indicator variable I is used, which discriminates between a 1-aziridinyl ($I = 0$) and a 2-methyl-1-aziridinyl substituent ($I = 1$).

Regression analysis of the data results in a statistical evaluation of the fit. Relevant statistical data given with the regression equations in the text are the number of compounds used (n), the square of the correlation coefficient (r^2), the standard deviation (S.D.) and the distribution of variance ratio (F). The last parameter should not be confused with the Swain and Lupton F value.

RESULTS

The structures of the 1,4-benzo- and 1,4-naphthoquinones that were examined in this study, their half-wave potentials ($E_{1/2}$) at pH 7.0 and for mono(1-aziridinyl)-1,4-benzoquinones their pK_{red} values and for bis-, tris- and tetrakis(1-aziridinyl)-1,4-benzoquinones their pK_{red2} values are presented in Table 1.

Determination of unknown substituent constants

On the basis of compounds **1–5**, **10**, **11**, **15**, **16** and **17**, being simple quinones with well established and reliable σ values, regression equations were calculated using only the sum of σ_p of all substituents ($\sigma_{p,tot}$, Eqn. 5) and when σ_m was included as well (Eqn. 6):

$$E_{1/2} = 0.320(\pm 0.013)\sigma_{p,tot} + 0.049(\pm 0.011)$$

$$n = 10;\ r^2 = 0.987;\ \text{S.D.} = 0.024;\ F = 607.34;\ F_{1,8,0.999} = 25.42 \quad (5)$$

$$E_{1/2} = 0.356(\pm 0.025)\sigma_{p,tot} - 0.103(\pm 0.065)\sigma_{m,tot} + 0.053(\pm 0.010)$$

$$n = 10;\ r^2 = 0.990;\ \text{S.D.} = 0.022;\ F = 382.96;\ F_{2,7,0.999} = 21.69 \quad (6)$$

A plot of Eqn. 5 is given in Fig. 1 (line a). The value of the reaction constant ρ_{BQ} in Eqn. 5 of 0.320 corresponds fairly well with the values of 0.30 and 0.35, reported by Zuman [7] for similar

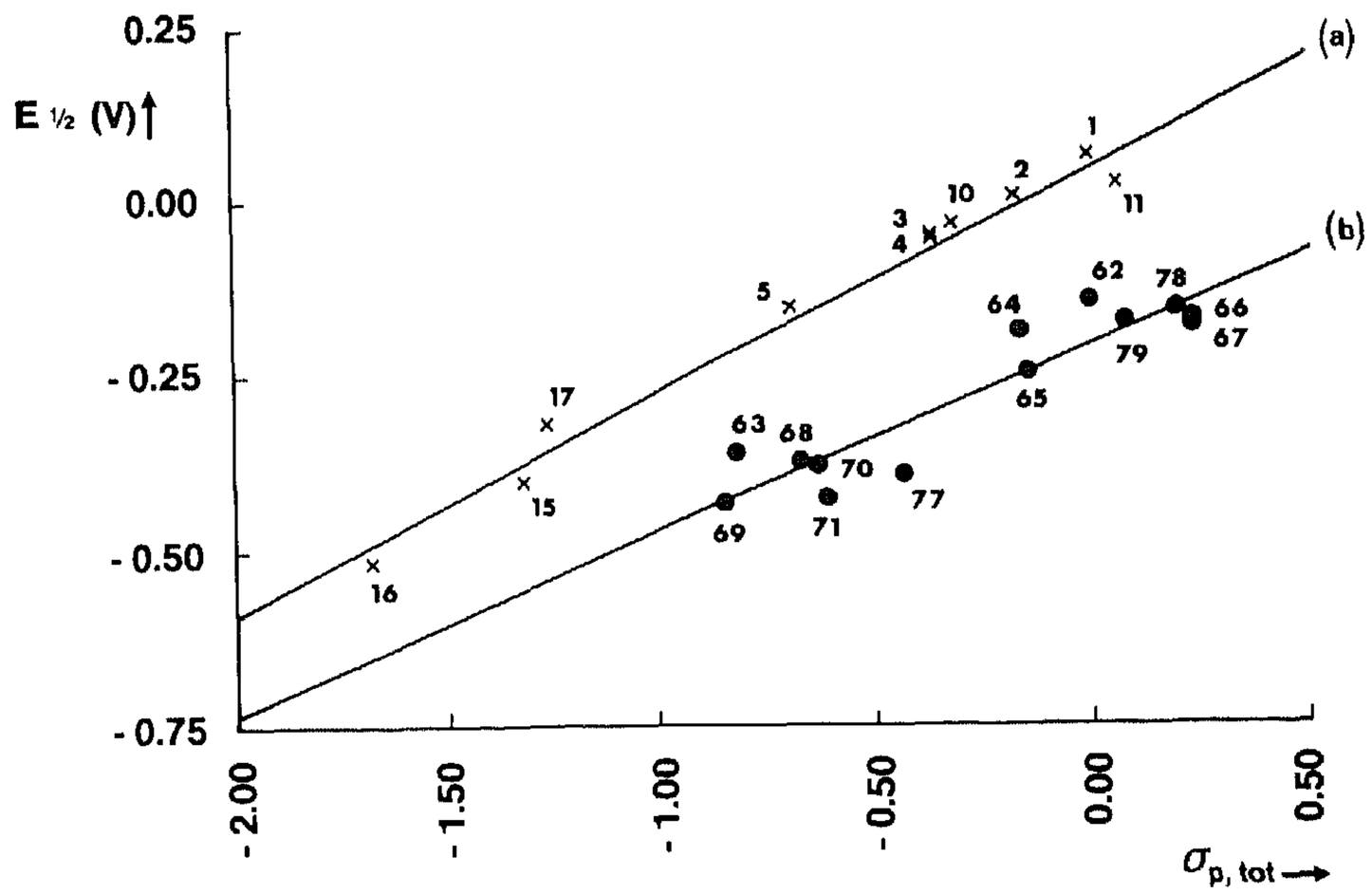


Fig. 1. (a) Plot of $E_{1/2}$ at pH 7.0 vs. $\sigma_{p,tot}$ of benzoquinones (×) **1–5**, **10**, **11** and **15–17**. Regression line corresponds to Eqn. 5. (b) Plot of $E_{1/2}$ at pH 7.0 vs. $\sigma_{p,tot}$ of naphthoquinones (●) **62–71** and **77–79**. Regression line corresponds to Eqn. 9. Numbers correspond to Table 1.

series of compounds, determined in acidic and alkaline aqueous solutions, respectively.

Combination of Eqn. 2 with Eqns. 5 and 6 results in

$$\delta E_{1/2} = (E_{1/2})_X - (E_{1/2})_H = 0.320\sigma_{p,tot} \quad (7)$$

$$\delta E_{1/2} = 0.356\sigma_{p,tot} - 0.103\sigma_{m,tot} \quad (8)$$

By analogy, Eqns. 9–12 were calculated for a series of thirteen naphthoquinones with well known σ_p and σ_m values (**62–71**, **77**, **78** and **79**):

$$E_{1/2} = 0.265(\pm 0.032)\sigma_{p,tot} - 0.205(\pm 0.015)$$

$$n = 13;\ r^2 = 0.865;\ \text{S.D.} = 0.044;\ F = 70.59;\ F_{1,11,0.999} = 19.69 \quad (9)$$

$$E_{1/2} = 0.381(\pm 0.053)\sigma_{p,tot} - 0.166(\pm 0.066)\sigma_{m,tot} - 0.167(\pm 0.020)$$

$$n = 13;\ r^2 = 0.917;\ \text{S.D.} = 0.036;\ F = 55.31;\ F_{2,10,0.999} = 14.91 \quad (10)$$

$$\delta E_{1/2} = (E_{1/2})_X - (E_{1/2})_H = 0.265\sigma_{p,tot} \quad (11)$$

$$\delta E_{1/2} = 0.381\sigma_{p,tot} - 0.166\sigma_{m,tot} \quad (12)$$

A plot of Eqn. 9 is given in Fig. 1 (line b). The value of the reaction constant ρ_{NQ} of 0.265 is in good agreement with the value of 0.29 determined for a series of naphthoquinones in ethanol–water mixtures [7].

Equations 5–12 make it possible to determine σ_m and σ_p values of other substituents X by measuring $E_{1/2}$. The Swain and Lupton constants F and R can then be calculated with Eqns. 3 and 4.

Substituents present only in the benzoquinone series

Reliable σ values can be calculated for substituents present only in the benzoquinone series by using Eqns. 7 and 8.

Substituents present only in the naphthoquinone series

It can be concluded from Fig. 1 that the correlations of the half-wave potentials with σ_p are better for the compounds in the benzoquinone series than in the naphthoquinone series. Therefore, when determined by Eqns. 11 and 12, values of substituents only present in the naphthoquinone series will be less reliable than and less comparable with those of other substituents obtained by Eqns. 7 and 8. Consequently, it was decided not to use Eqns. 11 and 12 to calculate the unknown σ value of a substituent. It was further assumed that the electronic effect of the "unknown" substituents on reduction of the quinone moiety may be approached by closely related substituents:

$-CH_2NHCO_2CH_2CH_3$ by $-CH_2NH_2$

$-N(CH_3)COCH_3$ by $-NHCOCH_3$

$-N(CH_3)CO_2CH_2CH_3$ by $-NHCO_2CH_2CH_3$

$-R_2$ by $-R_1$

TABLE 2

Electronic parameters of some substituents [a]

Substituent	σ_m [b]	σ_m [c]	σ_p [b]	σ_p [c]	F [b]	F [c]	R [b]	R [c]
$CH_2NHCO_2CH_2CH_3$	−0.03	−0.15	−0.11	−0.22	−0.01	−0.13	−0.10	−0.09
$NHCH_2CH_2OH$	−0.30	−0.79	−0.87	−1.07	−0.10	−0.69	−0.77	−0.38
$N(CH_3)COCH_3$	0.21	−0.01	0.00	−0.01	0.28	−0.02	−0.26	0.01
$N(CH_3)CO_2CH_2CH_3$	0.11	−0.08	−0.15	−0.11	0.14	−0.08	−0.28	−0.03
Az	−0.09	−0.30	−0.25	−0.43	−0.04	−0.26	−0.21	−0.17
Az-me	−0.09	−0.27	−0.27	−0.40	−0.03	−0.23	−0.24	−0.17
R_1	−0.26	−0.75	−0.77	−1.09	−0.08	−0.62	−0.69	−0.47
R_2	−0.26	−0.75	−0.77	−1.11	−0.08	−0.62	−0.69	−0.49

[a] Values calculated from $E_{1/2}$ values at pH 7.0 except where noted. [b] Eqns. 7 and 8 and Eqns. 3 and 4. [c] Eqns. 11 and 12 and Eqns. 3 and 4 (see text and Table 1).

Substituents present in both the benzoquinone and the naphthoquinone series

The difference in ρ_{BQ} and ρ_{NQ} results in different values of σ for substituents present both in the benzoquinone and in the naphthoquinone series. Comparison of σ_p, σ_m, F and R values of several such groups, either calculated using Eqns. 7 and 8 (marked [b] in Table 2), 11 and 12 (marked [c]) and 3 and 4 or estimated (marked [b], of the functions described above) has been made and the data are given in Table 2. It can be concluded from Table 2 that all σ values determined from the benzoquinone regression line (marked [b]) or estimated based on reasonable assumptions, are less negative than those calculated from the naphthoquinone line (marked [c]). Consequently, F values obtained from the latter equation are more negative and R values more positive. These differences are a result of the lower value of ρ_{NQ} (0.265), as compared with ρ_{BQ} (0.320). It was decided to calculate the unknown σ values of a substituent present both in the benzoquinone and in the naphthoquinone series by using Eqns. 7 and 8, because of the quality of this fit and because of the reasonable conformity of the values of some substituents with values reported in the literature (e.g., σ_p for Az – 0.22 [4], σ_m for Az – 0.07 [4], σ_p for R_1 – 0.90 [5], σ_p

TABLE 3

Physico-chemical parameters of functional groups [a]

Substituent	σ_m	σ_p	F	R	HB_1	MR
H	0.00	0.00	0.00	0.00	0	1.03
Br	0.39	0.23	0.44	−0.17	0	8.88
Cl	0.37	0.23	0.41	−0.15	0	6.03
F	0.34	0.06	0.43	−0.34	0	0.92
O^-	−0.47	−0.81	−0.35	−0.49	1 [c]	1.82 [c]
OH	0.12	−0.37	0.29	−0.64	2	2.85
OCH_3	−0.10 [b]	−0.12 [b]	−0.10 [b]	−0.02 [b]	1	7.87
CH_3	−0.07	−0.17	−0.04	−0.13	0	5.65
CH_2CH_3	−0.07	−0.15	−0.05	−0.10	0	10.30
CH_2CH_2OH	−0.06 [d]	−0.16 [d]	−0.03 [d]	−0.13 [d]	0 [c]	11.84
$CH_2CH_2OCONH_2$	−0.04 [d]	−0.11 [d]	−0.02 [d]	−0.09 [d]	0 [c]	21.18 [c]
$CH(OCH_3)CH_2OCONH_2$	−0.01 [d]	−0.07 [d]	0.00 [d]	−0.07 [d]	1 [c]	28.02 [c]
$CH_2NHCO_2CH_2CH_3$	−0.03 [c]	−0.11 [c]	−0.01 [c]	−0.10 [c]	2 [c]	25.80 [c]
C_6H_5	0.06	−0.01	0.08	−0.08	0	25.36
NH_2	−0.16	−0.66	0.02	−0.68	3	5.42
$NHCH_3$	−0.30	−0.84	−0.11	−0.74	2	10.33
$NHCH_2CH_3$	−0.24	−0.61	−0.11	−0.51	2	14.98
$NHCH_2CH_2OH$	−0.30 [d]	−0.87 [d]	−0.10 [d]	−0.77 [d]	2 [c]	16.23 [c]
$NHCOCH_3$	0.21	0.00	0.28	−0.26	3	14.93
$NHCOCH_2Cl$	0.17	−0.03	0.23	−0.25	3 [c]	19.77
$NHCO_2CH_2CH_3$	0.11	−0.15	0.14	−0.28	3 [c]	21.18
$N(CH_3)_2$	−0.15 [b]	−0.63 [b]	0.03 [b]	−0.66 [b]	1	15.55
$N(CH_3)COCH_3$	0.21	0.00 [c]	0.28 [c]	−0.26 [c]	2 [c]	19.58
$N(CH_3)CH_2CH_2OH$	−0.06 [d]	−0.19 [d]	−0.02 [d]	−0.17 [d]	1 [c]	20.85 [c]
$N(CH_3)CO_2CH_2CH_3$	0.11 [c]	−0.15 [c]	0.14 [c]	−0.28 [c]	3 [c]	25.80 [c]
Az	−0.09 [d]	−0.25 [d]	−0.04 [d]	−0.21 [d]	1 [c]	13.53
Az-me	−0.09 [d]	−0.27 [d]	−0.03 [d]	−0.24 [d]	1 [c]	18.15 [c]
R_1	−0.26 [d]	−0.77 [d]	−0.08 [d]	−0.69 [d]	1 [c]	22.79 [c]
R_2	−0.26 [c]	−0.77 [c]	−0.08 [c]	−0.69 [c]	1 [c]	22.79 [c]
R_3	0.47	0.37	0.50	−0.09	1 [c]	19.51

[a] Values obtained from [5] except where noted; HB_1 values from ref. [41] except where noted. [b] From [4]. [c] Estimated values. [d] Calculated from Eqns. 7 and 8, resulting in calculated values of F and R from Eqns. 3 and 4 (see text and Table 1).

for CH_2CH_2OH − 0.06 [5]). All values used in the following regression analyses are those given in Table 3.

Relationships between $E_{1/2}$ and electronic substituent constants

Unfortunately, not all quinones could be analysed electrochemically in aqueous media. Addition of a virtually clear stock solution (5 mM in *N*,*N*-dimethylformamide) of quinones **20**, **26**, **37**, **46** and **73** to the aqueous phosphate buffer led to crystallization of the compound, resulting in no or only small currents, even when a 1 + 1 mixture of *N*,*N*-dimethylformamide and buffer was used. Compounds **29**, **30** and **54** show anomalous behaviour in the medium pH range, possibly owing to chemical decomposition. Consequently, 54 benzoquinones and 30 naphthoquinones remained for regression analysis. Parallelism in the $E_{1/2}$ vs. pH plots of these compounds at pH 7.0 was verified and observed for all quinones, except for **7** and **63**. The reduction mechanisms at pH 7.0 of these compounds differ from those of the other quinones because, owing to acid–base reactions of the hydroxy group(s), additional protons are involved. In the quinoid form, **7** and **63** are deprotonated at pH 7.0 to the di- and monoanion, respectively, as the pK_a values of the hydroxy groups are 2.71 and 5.18 for **7** and 4.00 for **63** [42]. When at pH 7.0 the $E_{1/2}$ values of these compounds must be compared with those of the other quinones, O^- must be considered to be the actual quinone substituent instead of OH and, consequently, parameters of O^- were used in the correlation studies.

A linear relationship may be obtained within a series of structurally related quinones when $E_{1/2}$ is correlated with σ_p [7]. Deviations from a linear relationship may occur when steric and/or resonance interactions influence quinone reduction (e.g., [7–10]). In principle, steric interactions may be expected to occur with many of the polysubstituted quinones examined in this study (e.g., **29–61**, **77–81** and **84–92**). Excluding these compounds would leave only 28 benzoquinones and 17 naphthoquinones for a correlation study. In a first attempt to correlate half-wave potentials with electronic substituent constants, it was decided to

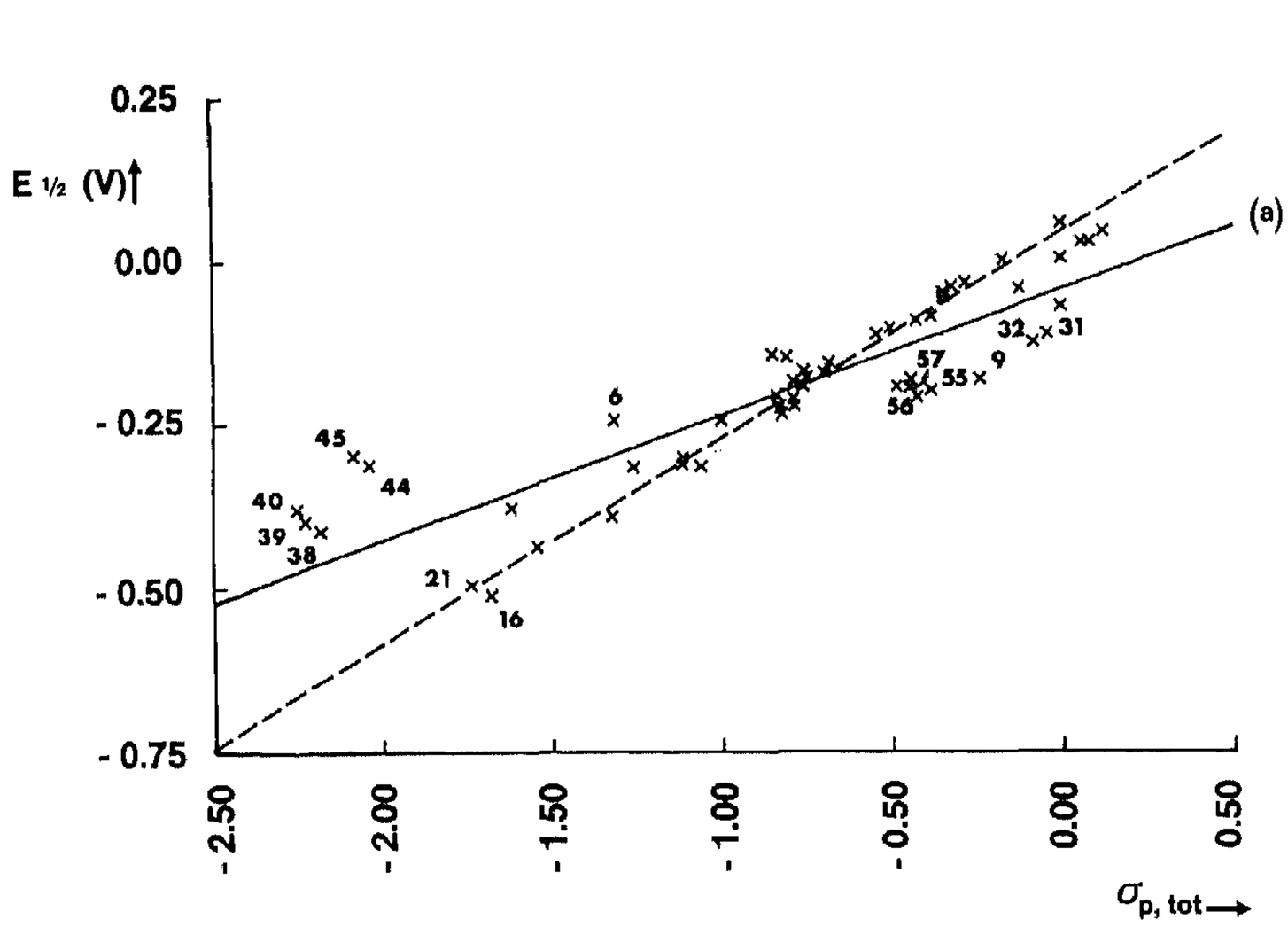


Fig. 2. Plot of $E_{1/2}$ at pH 7.0 vs. $\sigma_{p,tot}$ of 54 benzoquinones with corresponding regression line (Eqn. 13). Numbers correspond to code in Table 1 and indicate compounds for which the $E_{1/2}$ deviates significantly from the original regression line for ten benzoquinones (dashed line, Eqn. 5).

correlate $E_{1/2}$ values of all 54 benzoquinones and 30 naphthoquinones with σ_p or F and R. When the measured $E_{1/2}$ value of one of the 84 quinones examined in this study deviates significantly from that calculated by Eqn. 7 or 11, a steric interaction may be involved which is not covered by σ_p.

1,4-Benzoquinones. Results of correlations between $E_{1/2}$ and σ_p of ten simple benzoquinones as presented in Eqns. 5–8 were shown in Fig. 1 (line a). Regression analysis of the data of all 54 1,4-benzoquinones resulted in Eqns. 13 and 14. A plot of $E_{1/2}$ vs. $\sigma_{p,tot}$ of these compounds is given in Fig. 2.

$$E_{1/2} = 0.192(\pm 0.014)\sigma_{p,tot} - 0.043(\pm 0.014)$$

$$n = 54;\ r^2 = 0.786;\ \text{S.D.} = 0.065;\ F = 190.69;\ F_{1,40,0.999} = 12.61 \quad (13)$$

$$E_{1/2} = 0.158(\pm 0.028)F_{tot} + 0.201(\pm 0.018)R_{tot} - 0.036(\pm 0.017)$$

$$n = 54;\ r^2 = 0.789;\ \text{S.D.} = 0.065;\ F = 95.33;\ F_{2,40,0.999} = 8.25 \quad (14)$$

As mentioned previously, amino and halogen substituents may affect the half-wave potential of polysubstituted quinones through both electronic and steric interactions, which results in deviations from the linear relationship between $E_{1/2}$ and σ_p obtained for simple quinones [7–10]. Indeed, this can be observed in Fig. 2. It is clear from Fig. 2 that mainly **38–40**, **44** and **45** in the left part and **9**, **31**, **32** and **55–57** in the right part of the plot deviate strongly from the original regresssion line (Eqn. 5). Exclusion of the aminoquinones **38**, **39**, **40**, **44** and **45** leads to

$$E_{1/2} = 0.253(\pm 0.015)\sigma_{p,tot} - 0.014(\pm 0.012)$$

$$n = 49;\ r^2 = 0.854;\ \text{S.D.} = 0.051;\ F = 275.40;\ F_{1,40,0.999} = 12.61 \quad (15)$$

Exclusion of more amino- and/or halogen-containing compounds (**31**, **32**, **43**, **52**, **53** and **55–61**) results in Eqn. 16, which is a significant improvement over Eqns. 13 and 15:

$$E_{1/2} = 0.274(\pm 0.014)\sigma_{p,tot} + 0.014(\pm 0.012)$$

$$n = 37;\ r^2 = 0.921;\ \text{S.D.} = 0.043;\ F = 408.20;\ F_{1,30,0.999} = 13.29 \quad (16)$$

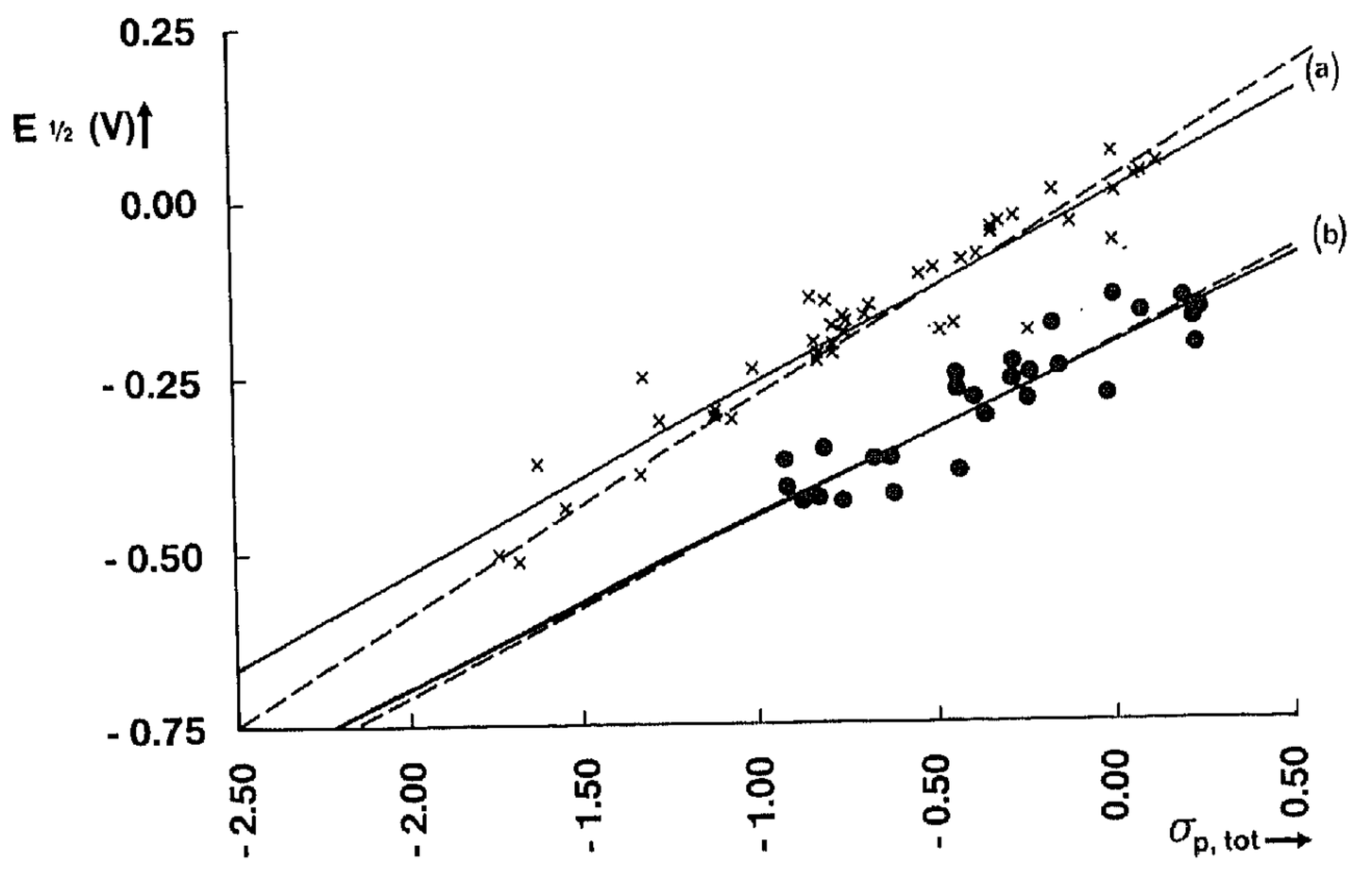


Fig. 3. (a) Plot of $E_{1/2}$ at pH 7.0 vs. $\sigma_{p,tot}$ of 37 benzoquinones (×) with corresponding regression line (Eqn. 16). Dashed line represents the original regression line for ten benzoquinones (Eqn. 5). (b) Plot of $E_{1/2}$ at pH 7.0 vs. $\sigma_{p,tot}$ of 30 naphthoquinones (●) with corresponding regression line (Eqn. 17). Dashed line represents the original regression line for thirteen naphthoquinones (Eqn. 9).

A plot of $E_{1/2}$ vs. $\sigma_{p,tot}$ is given in Fig. 3 (line a).

1,4-Naphthoquinones. Results of correlations between $E_{1/2}$ and σ_p of thirteen simple naphthoquinones as presented in Eqns. 9–12 were shown in Fig. 1 (line b). Regression analysis of the data of all 30 1,4-naphthoquinones resulted in Eqns. 17 and 18.

$$E_{1/2} = 0.243(\pm 0.021)\sigma_{p,tot} - 0.208(\pm 0.010)$$

$$n = 30;\ r^2 = 0.832;\ \text{S.D.} = 0.041;\ F = 138.58;$$

$$F_{1,28,0.999} = 13.50 \qquad (17)$$

$$E_{1/2} = 0.176(\pm 0.030)F_{tot} + 0.290(\pm 0.029)R_{tot} - 0.181(\pm 0.016)$$

$$n = 30;\ r^2 = 0.855;\ \text{S.D.} = 0.039;\ F = 79.85;$$

$$F_{2,27,0.999} = 9.02 \qquad (18)$$

Comparison of Eqns. 9 and 17 shows that no significant deviations occur on extension of the number of compounds from 13 to 30. A plot of $E_{1/2}$ vs. $\sigma_{p,tot}$ is given in Fig. 3 (line b).

Relationships between pK_{red}, pK_{red2} and some physico-chemical parameters

A second interesting electrochemical parameter which can be obtained from d.c. polarography of aziridinylquinones is their pK_{red} value, determined from the *i* vs. pH plot of the compound and reflecting the ease of protonation of the aziridine at the mercury electrode, after prior reduction of the quinone moiety [2]. In d.c. analysis of 3-substituted 2-(1-aziridinyl)- and 2-(2-methyl-1-aziridinyl)-1,4-naphthoquinones, no clear relationship between pK_{red} and the σ_p value of the 3-substituent can be observed, probably owing to the inaccuracy of the pK_{red} values determined (Table 1).

However, d.c. analysis of quinones having two, three or four aziridinyl rings shows, that in the intermediate pH range two aziridines are nearly simultaneously protonated at the mercury electrode. It can be concluded from the data in Table 1 that this process is influenced by the electronic properties of other substituents. A quantitative study on the influence of electronic effects on this process therefore seemed indicated.

Not all aziridinylquinones presented in Table 1 exhibit unambiguous *i* vs. pH plots. Especially the dibromo and dichloro derivatives **29–32** and compound **54** showed deviations from the regular pattern of waves. In addition, **46** could not be analysed, owing to solubility problems. Consequently, 28 compounds remained for which the pK_{red2} values were determined. The relationships between the pK_{red2} values of these compounds and $E_{1/2}$ of the quinone reduction process at pH 7.0, σ_p of the substituents at positions 3 and 6 ($\sigma_{p3,6}$) and *MR* of the substituents at positions 3 and 6 are demonstrated in Fig. 4 and can be described by Eqns. 19, 20 and 21, respectively (N.B.: read *MR*/10 for *MR* and HB_1 for *HB* in the following equations):

$$pK_{red2} = -6.337(\pm 1.601)E_{1/2} + 7.338(\pm 0.364)$$

$$n = 28;\ r^2 = 0.376;\ \text{S.D.} = 0.706;\ F = 15.66;$$

$$F_{1,26,0.999} = 13.74 \qquad (19)$$

$$pK_{red2} = -0.853(\pm 0.229)\sigma_{p3,6} + 8.328(\pm 0.166)$$

$$n = 28;\ r^2 = 0.348;\ \text{S.D.} = 0.721;\ F = 13.86 \qquad (20)$$

$$pK_{red2} = 0.449(\pm 0.092)MR_{3,6} + 7.688(\pm 0.237)$$

$$n = 28;\ r^2 = 0.478;\ \text{S.D.} = 0.645;\ F = 23.82 \qquad (21)$$

It is clear from these results that both electronic and steric properties of quinone substituents affect pK_{red2}. Combination of σ_p and *MR* leads to

$$pK_{red2} = -0.468(\pm 0.223)\sigma_{p3,6} + 0.343(\pm 0.100)MR_{3,6} + 7.728(\pm 0.224)$$

$$n = 28;\ r^2 = 0.556;\ \text{S.D.} = 0.607;\ F = 15.68;$$

$$F_{2,25,0.999} = 9.22 \qquad (22)$$

It can be hypothesized that the formation of a hydrogen bond between the quinone substituent and the adjacent aziridinyl ring may thwart aziridine protonation. Further, the presence of a methyl substituent at position 2 of the aziridine facilitates protonation [2]. As a consequence, the introduction of parameters describing these ef-

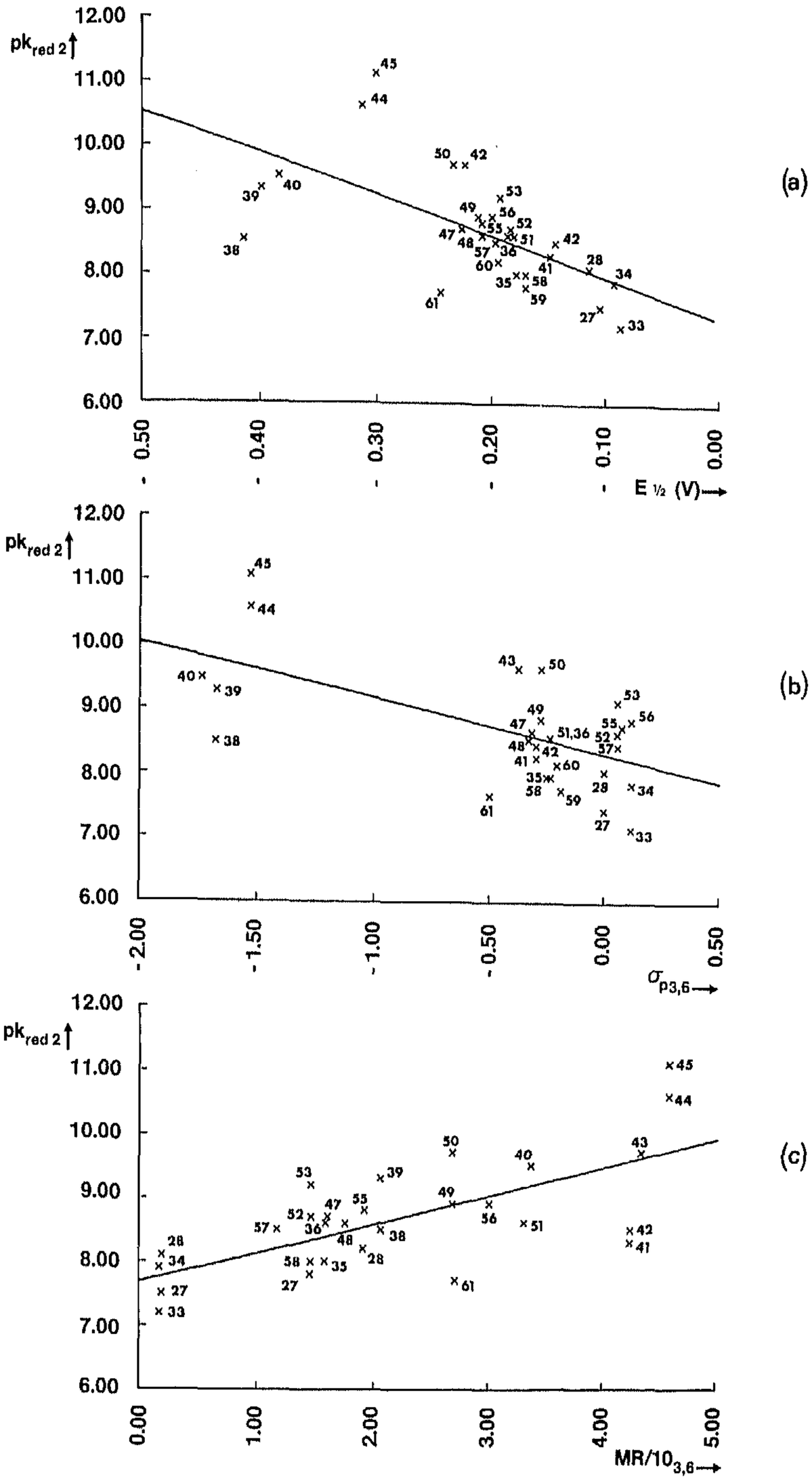


Fig. 4. Plots of pK_{red2} vs. (a) $E_{1/2}$ of quinone reduction at pH 7.0 and (b) σ_p and (c) $MR/10$ of substituents at positions 3 and 6 of a series of 28 aziridinylbenzoquinones. Data obtained by d.c. polarography. Numbers correspond to Table 1 and regression lines to Eqns. 19, 20 and 21, respectively.

fects into the correlation study (i.e., HB_1 and I) is expected to improve the regression equation. Indeed, this can be observed in Eqn. 23:

$$\begin{aligned} pK_{red2} = &-0.784(\pm 0.144)\sigma_{p3,6} \\ &+0.538(\pm 0.066)MR_{3,6} \\ &-0.320(\pm 0.051)HB_{3,6} \\ &+0.563(\pm 0.148)I + 7.441(\pm 0.145) \end{aligned}$$

$$n = 28;\ r^2 = 0.856;\ \text{S.D.} = 0.360;\ F = 34.22;\ F_{4,23,0.999} = 6.69 \quad (23)$$

The measured pK_{red2} values of **51**, **61** and **60** deviate significantly (> 2 S.D.) from those calculated with Eqn. 23. Exclusion of these compounds results in Eqn. 24:

$$\begin{aligned} pK_{red2} = &-0.737(\pm 0.096)\sigma_{p3,6} \\ &+0.575(\pm 0.045)MR_{3,6} \\ &-0.327(\pm 0.034)HB_{3,6} \\ &+0.571(\pm 0.104)I + 7.475(\pm 0.097) \end{aligned}$$

$$n = 25;\ r^2 = 0.941;\ \text{S.D.} = 0.239;\ F = 80.16;\ F_{4,21,0.999} = 6.95 \quad (24)$$

DISCUSSION

Substituent effects on quinone reduction

Substitution in quinoid compounds generally leads to linear shifts of $E_{1/2}$ with the electronic properties of the substituent [7]. The compounds in this study contain virtually all alkyl, amino and/or halogen substituents. Therefore, regression analysis was performed on ten benzoquinones and thirteen naphthoquinones containing simple alkyl, amino, alkylamino and halogen substituents with generally accepted σ_p values [5]. To avoid steric interactions, only mono- and 2,5-disubstitution was taken into account. For the benzoquinones a good linear fit was obtained between $\sigma_{p,tot}$ and $E_{1/2}$ values determined under standardized conditions (Fig. 1a, Eqns. 5 and 6, $r^2 = 0.99$). The correlation in the naphthoquinone series was less good (Fig. 1b, Eqns. 9 and 10, $r^2 = 0.87$). The σ_p values of substituents which were not available as yet were either calculated from Eqn. 7 using the half-wave potential of the simplest quinone containing the substituent of interest, or were estimated by comparison with electronically similar substituents. These values are in fact "optimum" values for electrochemical correlation studies of (poly)substituted 1,4-quinones when $E_{1/2}$ (and hence σ_p) has been influenced by additional effects (see below).

With σ_p, F and R values of all 54 benzoquinones, partly obtained from these experiments and partly from the literature, new regression equations were made (Eqns. 13 and 14). These equations show a reasonable correlation of $E_{1/2}$ with $\sigma_{p,tot}$ and with a combination of F_{tot} and R_{tot} ($r^2 = 0.79$), considering the number and type of compounds and substituents used. However, comparison of Eqns. 5 and 13 reveals a decrease in ρ_{BQ} from 0.320 to 0.192 on extension of the number of compounds from 10 to 54. It is clear from Fig. 2 that aziridinylquinones containing amino functions (e.g., $NHCH_3$, $NHCH_2CH_2OH$ or 1-pyrrolidinyl) or halogen substituents (Br, Cl) are responsible for this phenomenon. These compounds deviate strongly from the original linear relationship (Eqn. 5) obtained from simple mono- or disubstituted quinones. Deviations from a linear relationship between $\sigma_{p,tot}$ and $E_{1/2}$ are mainly caused by steric interactions, e.g., between the substituent and the carbonyl function of the quinone moiety [7]. This results in loss of coplanarity and, as a consequence, in a decrease in conjugation and thus in a more negative value of $E_{1/2}$. Analogously, steric hindrance of a substituent with resonance properties (e.g., NHR) by a vicinal substituent (e.g., aziridine) may prevent the resonance effect, which requires coplanarity of the substituent with the quinone moiety, from being exercised and consequently an $E_{1/2}$ value is found that is more positive than would be expected from the individual electronic properties of the substituents (e.g., [9]). Furthermore, halogen-substituted quinones may sometimes reveal anomalous, inexplicable behaviour during polarographic analysis in aqueous buffer solutions, in addition to the steric effects described above [7,8,10]. Exclusion of most of these compounds results in a good linear relationship (Eqn.

16), which corresponds much better with Eqn. 5 (Fig. 3a). It cannot be explained why **9** deviates from this relationship.

Extension of the number of naphthoquinones included in the regression analysis from 13 to 30 did not result in significant changes (compare Eqns. 9 and 17). Either steric interactions in the naphthoquinone series are less pronounced or they have already influenced the original linear relationship (Eqn. 9) obtained from simple substituted quinones. Other parameters used in regression analyses (e.g., σ_m, s_o, E_s, Verloop values or HB_1) yielded worse regression coefficients.

Up to now, electrochemical QSAR studies of 1,4-benzo- and naphthoquinones have been relatively limited. Zuman [7] has presented relationships of a series of quinones with, in general, electrochemical data collected from the available literature. Variations in the experimental conditions used obscure these correlations. Because the reaction constant ρ_R (Eqn. 2) depends strongly on the composition of the electrolyte, only a few compounds could be compared at the same time. Other papers reporting on $E_{1/2}$–σ relationships of 1,4-quinones also present regression equations using a limited number of compounds [8–10,44]. The results of the present correlation studies, however, show that also for a large number of compounds $E_{1/2}$ may be linearly correlated with the sum of σ_p of all quinone substituents, provided that steric interactions do not interfere.

Unknown σ values of several substituents have been determined, analogously to the methods described in the literature (e.g., [7,9,10]). Some critical remarks must be made here. As $E_{1/2}$ and hence the calculated σ_p values may be influenced by other than electronic effects (steric effects, hydrogen bond formation), which may be typical for and restricted to 1,4-quinoid compounds, the calculated σ_p values should preferably only be applied in the polarography of compounds of the 1,4-quinoid type when such additional effects are expected, e.g., in the case of polysubstitution. Several effects are represented in such σ_p values. They no longer correspond to the original Hammett constants, because these reflect only electronic properties of the substituent, but may be regarded as σ_o values. In a similar way, calculation of $E_{1/2}$ values of 1,4-quinoid compounds from a regression equation and known σ_p values might lead to erroneous results, because these additional effects may not be included in σ. In conclusion, the non-critical use of $E_{1/2}$ values and/or σ_p values in a study of substituent effects on the ease of reduction of quinoid compounds, without investigating the reduction mechanism and pH dependence, the possibility of additional (i.e., steric effects and the validity of σ_p values reported in the literature, will easily lead to erroneous results.

Substituent effects on aziridine protonation of the hydroquinone

An additional complication in the electrochemical correlation studies of aziridinylquinones is that relationships of $pK_{red(2)}$ with physicochemical parameters may be questionable. This polarographically determined pK value reflects the ease of protonation of the aziridine(s) at the working electrode, after the quinone has been reduced to the hydroquinone. In this study, the mercury electrode was used as a working electrode. In a study dealing with the electrochemical properties of AZQ at a glassy carbon electrode, the aziridinyl reduction wave could not be observed at all, indicating that the type of electrode is very important [45]. Further, $pK_{red(2)}$ is influenced by adsorption [2] and consequently it does not correspond with the true pK_a value of an aziridinyl ring of the hydroquinone. With polyaziridinylquinones, the pK_{red2} value obtained from the i vs. pH plot gives a kind of overall pK, because under the conditions used in d.c. polarography, differential-pulse polarography and cyclic voltammetry at least two aziridines are virtually simultaneously protonated, even for asymmetric bis(1-aziridinyl)quinones. In summary, from a thermodynamic point of view the pK_{red2} values cannot be compared with a standard pK_a value, which is directly related with the changes in standard free energy during protonation, as required for a linear free energy approach. However, it is assumed that shifts in the average, true pK_a value of the aziridines of the hydroquinone

on substitution of the quinone moiety and/or the aziridinyl rings coincide linearly with shifts in pK_{red2}, thus allowing a Hammett-type approach.

For a small group of aziridinylbenzoquinones (**27**, **33**, **35**, **41**, **43**, **44**, **47–49**, **51**, **52** and **55–57**) a good linear relationship between $E_{1/2}$ of the quinone reduction process and pK_{red2} of subsequent protonation and reductive opening of the aziridines can be obtained (equation not given here; $r^2 = 0.88$). However, increasing the number of compounds deteriorates the linear regression fit, as can be concluded from Eqn. 19 and Fig. 4a. An analogous relationship is found, taking σ_p of the substituents at positions 3 and 6 as a variable (Eqn. 20, Fig. 4b). It could be concluded from the residual analysis of the regression fit (not given here) that the deviations between the measured and the calculated pK_{red2} become more positive with increasing pK_{red2}. Hence measured values are generally too high with large values and too low with small values of pK_{red2} and the introduction of a second parameter, which may correct for these phenomena, is required. Surprisingly, a linear relationship was found between pK_{red2} and $MR_{3,6}$ with a positive coefficient for the steric variable (Eqn. 21, Fig. 4c). This indicates that the larger the substituent, the easier the aziridines are protonated. An explanation for this phenomenon might be that the substituent forces the aziridine out of the plane of the quinone moiety, thus disturbing the vinylogous amide structure. This empirically determined relationship may be used to correct partly for the deviations obtained in the regression fit with σ_p. Indeed, a more random pattern in the residual plot is observed (not given here), the square of the correlation coefficient is enhanced from 0.35 to 0.56 and the standard deviation is smaller when pK_{red2} is correlated with $\sigma_{p3,6}$ and $MR_{3,6}$ (Eqn. 22).

The above-described combination was further extended by the parameter HB_1, which describes the ability of the substituent to form hydrogen bonds. This process was hypothesized to be of importance, as a hydrogen bond between the aziridine nitrogen (as acceptor) and a donor part of the substituent will stabilize the unprotonated form of the aziridinyl ring and thus a decrease in its pK_{red2} value is expected. The introduction of this parameter significantly improves the regression equation (equation not given here; $r^2 = 0.77$). The negative sign of its coefficient indicates a decrease in pK_{red2} with an increase in HB_1, which is in accordance with the hypothesis.

The fourth parameter used in the regression analysis of pK_{red2} is an indicator variable I, which distinguishes the compounds with methyl-substituted aziridinyl rings ($I = 1$) from those with non-methylated aziridines ($I = 0$). It was decided to use this variable as it includes all effects (electronic and steric) of the methyl group on protonation of the aziridines. These effects can also be described by a Taft σ^* value and an additional steric parameter, which extends, however, the number of variables. Further, there is no variation in the contribution of this group. Hence, a combination of all effects into one indicator variable seemed better. Comparison of Eqns. 22 and 23 exhibits a significant improvement of the regression fit ($r^2 = 0.86$), which is further improved by exclusion of compounds **51**, **60** and **61** (Eqn. 24; $r^2 = 0.94$). Why these compounds deviate from this relationship is not clear. Using Eqn. 24 the pK_{red2} values of the reference compounds **27** and **28** ($\sigma_{p3,6} = 0.00$) can be calculated and are found to be 7.59 and 8.16, respectively, which corresponds very well with the measured values of 7.5 and 8.1, respectively.

Summarizing these results, it may be concluded that electrochemical properties of quinoid compounds, i.e., reduction of the quinone moiety in aqueous media, may be well described by σ_p. Regression equations have been developed that can be used to calculate $E_{1/2}$ values of a new quinone when all σ_p values are known (Eqns. 16 and 17). Deviations may be a result of steric interactions or of a different reduction mechanism. Unknown σ_p values may be determined from Eqn. 5. As several effects (steric effects, hydrogen bond formation) may be represented in such "new" σ_p values, they no longer correspond to the original Hammett constants. Application of these "new" values (which may be regarded as σ_o values) should therefore preferably be restricted to the polarography of 1,4-quinoid compounds.

Equation 24 offers the possibility of predicting the pK_{red2} value of a new bis(1-aziridinyl)-1,4-

benzoquinone which may be of importance for the cytostatic activity of the compound.

REFERENCES

1 R.J. Driebergen, J. den Hartigh, J.J.M. Holthuis, A. Hulshoff, W.J. van Oort, S.J. Postma Kelder, W. Verboom, D.N. Reinhoudt, M. Bos and W.E. van der Linden, Anal. Chim. Acta, 233 (1990) 251.
2 R.J. Driebergen, J.J.M. Holthuis, J.S. Blauw, S.J. Postma Kelder, W. Verboom, D.N. Reinhoudt and W.E. van der Linden, Anal. Chim. Acta, 234 (1990) 285.
3 J. Shorter, in N.B. Chapman and J. Shorter (Eds.), Advances in Linear Free Energy Relationships, Plenum, New York, 1972, Ch. 2.
4 N.B. Chapman, in N.B. Chapman and J. Shorter (Eds.), Correlation Analysis in Chemistry—Recent Advances, Plenum, New York, 1978, Ch. 10.
5 C. Hansch, in C. Hansch and A. Leo (Eds.), Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley, New York, 1979, Chs. 1, 2, 3, 5 and 6.
6 Y.C. Martin, in G.L. Grunewald (Ed.), Quantitative Drug Design, Dekker, New York, 1978.
7 P. Zuman, in P. Zuman (Ed.), Substituent Effects in Organic Polarography, Plenum, New York, 1967, Chs. 1, 2 and 8.
8 Y.C. Martin, T.M. Bustard and K.R. Lynn, J. Med. Chem., 16 (1973) 1089.
9 E.R. Brown, K.T. Finley and R.L. Reeves, J. Org. Chem., 36 (1971) 2849.
10 W.F. Gum Jr. and M.M. Joullié, J. Org. Chem., 32 (1967) 53.
11 W. Ried and H. Schaefer, Justus Liebigs Ann. Chem., 752 (1971) 102.
12 H. Teuber and W. Rau, Chem. Ber., 86 (1953) 1036.
13 H. Nakao, M. Arakawa, T. Nakamura and M. Fukushima, Chem. Pharm. Bull., 20 (1972) 1968.
14 K.J.M. Andrews, D.H. Marrian and D.R. Maxwell, J. Chem. Soc., (1956) 1844.
15 H.W. Moore, H.R. Shelden and D.F. Shellhamer, J. Org. Chem., 34 (1969) 1999.
16 Y. Garreau, Bull. Soc. Chim. Fr., (1950) 501.
17 R. Baltzly and E. Lorz, J. Am. Chem. Soc., 70 (1948) 861.
18 L.F. Fieser and J.L. Hartwell, J. Am. Chem. Soc., 57 (1935) 1482.
19 US Rubber, Belg. Pat., 614 136 (1962); Chem. Abstr., 57 (1962) 15031.
20 H.J. Teuber and O. Gosauer, Chem. Ber., 98 (1965) 2939.
21 Geigy, Fr. Pat., 1 345 524 (1963); Chem. Abstr., 60 (1964) 11951.
22 R.J. Driebergen, Dissertation, University of Utrecht, 1987.
23 K. Konig, Chem. Ber., 92 (1959) 257.
24 J.R. Luly and H. Rapoport, J. Org. Chem., 46 (1981) 2745.
25 A. Marxer, Helv. Chim. Acta, 38 (1955) 1473.
26 Farbenfabrieken Bayer, Br. Pat., 762 723 (1956); Chem. Abstr., 51 (1957) 12153h.
27 F. Chou, A.H. Khan and J.S. Driscoll, J. Med. Chem., 19 (1976) 1302.
28 W. Gauss and S. Petersen, Angew. Chem., 69 (1957) 252.
29 U. von Gizycki, Angew. Chem., 83 (1971) 408; A.H. Khan and J.S. Driscoll, J. Med. Chem., 19 (1976) 313.
30 H. Nakao, M. Arakawa, T. Nakamura and M. Fukushima, Chem. Pharm. Bull., 20 (1972) 1968.
31 K. Wallenfels and W. Draber, Justus Liebigs Ann. Chem., 667 (1963) 55.
32 L.F. Fieser, W.P. Campbell, E.M. Fry and M.D. Gates, Jr., J. Am. Chem. Soc., 61 (1939) 3216.
33 E.F. Pratt, R.W. Luckenbaugh and R.L. Erickson, J. Org. Chem., 19 (1954) 176.
34 A. Inoue, N. Kuroki and K. Konishi, Bull. Univ. Osaka Pref., Ser. A, 8 (1959) 31.
35 T. Sasaki, K. Kanematsu and A. Kakehi, Tetrahedron, 28 (1972) 1469.
36 S.N. Falling and H. Rapoport, J. Org. Chem., 45 (1980) 1260.
37 J.R.E. Hoover and A.R. Day, J. Am. Chem. Soc., 76 (1954) 4148.
38 Schenley Industries, US Pat., 2 913 453 (1959); Chem. Abstr., 54 (1960) 8097c.
39 G. Casini, F. Claudi, M. Grifantini and S. Martelli, J. Heterocycl. Chem., 11 (1974) 377.
40 Farbenfabrieken Bayer, Br. Pat., 796 218 (1958); Chem. Abstr., 53 (1959) 406e.
41 G. Yang, E.J. Lien and Z. Guo, Quant. Struct.–Act. Relat., 5 (1986) 12.
42 G. Kortüm, in G. Kortüm, W. Vogel and K. Andrussow (Eds.), Dissociation Constants of Organic Acids in Aqueous Solution, Butterworths, London, 1961, Ch. 4.
43 M.K. Kalinowski and T.M. Krygowski, Croat. Chem. Acta, 58 (1985) 107.
44 B.S. Iyengar, S.M. Sami, S.E. Tarnow, W.A. Remers, W.T. Bradner and J.E. Schurig, J. Med. Chem., 26 (1983) 1453.
45 M.M. Mossoba, M. Alizadeh and P.L. Gutierrez, J. Pharm. Sci., 74 (1985) 1249.