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DIRECT OBSERVATION OF ELECTRON TRANSFER BETWEEN PHENOTHIAZINES AND 1,2-DIOXETANES

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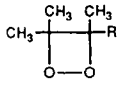
SUMMARY : Phenothiazine derivatives 4-7 efficiently reduce 3,3,4,4-tetramethyl-1,2-dioxetane (1a) to pinacol, whereby catalytic decomposition into acetone is a significant side reaction, while N-methylphenothiazine (9) is oxidized to its sulfoxide by malonyl (2) and dibenzoyl peroxide (3); a single-electron-transfer (SET) process is supported by UV-Vis spectroscopic detection of the phenothiazine radical cation.

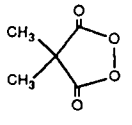
We recently reported [1] that the biologically active antioxidants glutathione, cysteine, NADH and ascorbic acid [2] efficiently reduce 1,2-dioxetanes **1a** and **1b** to their vic-diols. In the same way, we observed that sulfides efficiently reduce the peroxides **1** - **3** to their corresponding epoxides or anhydrides, the sulfide being oxidized to the corresponding sulfoxide. In view of the quite moderate photo-genotoxicity displayed by the dioxetanes [3], we suspected that these labile peroxides were efficiently detoxified in the cell through chemical action. A single-electron-transfer (SET) process was proposed for this novel redox reaction of dioxetanes. We now present experimental evidence supporting this supposition.

Cation radicals of phenothiazines are sufficiently stable to permit direct spectral (UV-Vis) detection [4]. In addition to serving as potential electron donors for mechanistic model studies of electron transfer reactions proposed in the reduction of 1,2-dioxetanes, the current interest in the phenothiazine concerns their wide use as antipsychotic drugs, whose therapeutic action and metabolism are believed to involve formation of the radical cation intermediates [5,6].



1a R = CH_3

1b R = CH_2OH



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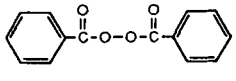

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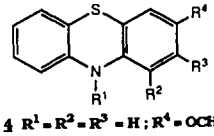


4 $R^1 = R^2 = R^3 = H$; $R^4 = OCH_3$

5 $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$

6 $R^1 = R^2 = R^3 = R^4 = H$

7 $R^1 = R^3 = R^4 = H$; $R^2 = OCH_3$

8 $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = CH_3$

9 $R^1 = CH_3$; $R^2 = R^3 = R^4 = H$

10 $R^1 = R^2 = R^3 = H$; $R^4 = NO_2$

The reduction of dioxetane **1a** [2,7] by the phenothiazines was performed as follows: A 5-ml, round-bottomed flask, provided with magnetic spinbar and nitrogen inlet and outlet tubes, was charged with 0.0500 mmol of the dioxetane **1a** in 1 ml acetonitrile and cooled to 15 °C by means of a MeOH bath, employing a cryostat. A solution of 0.100 mmol of the phenothiazine in 1 ml of the same solvent was added within 3 min. The reaction course was

monitored by UV-Vis spectrophotometry using a Replay and Time Scan Program, and TLC and ^{1}H NMR until the dioxetane was completely consumed. The product composition of the crude reaction mixture, i.e. acetone, pinacol and diphenothiazinyl derivatives [8], was determined by quantitative ^{1}H NMR using hexamethyldisiloxane as standard. The results are listed in Table 1. In this context it is important to state that a qualitative correlation was observed between the oxidation potentials of these reductants and their rate of reaction with dioxetane **1a**. Furthermore and mechanistically more significant, the more readily the phenothiazine is oxidized (low E_{ox}), the higher is the proportion of decomposition product (yield of ketone products), cf. Schema 1; however, for SET to take place at all, $E_{ox} < 0.8$ V. Thus, if

Table 1. Reaction of **1a** [2,7] with phenothiazine derivatives.

No.	Phenothiazine [a]	E_{ox} [4] (V)	Radical cation λ_{max} (nm)	Reaction time [b] t (h)	Product balance (%)	Product yields (mol) [c,d] Diphenothiazinyl deriv. [8] (λ_{max}, nm)	Pinacol	Acetone
1.	**4** [9]	0.590	550	10	99	0.087 (596, 848)	0.087	0.91
2.	**5** [9]	0.651	529	28	99	0.50 (756, 773)	0.50	0.50
3.	**6**	0.696	521	36	96	0.79 (660)	0.79	0.21
4.	**7** [10]	0.698	478, 517	38	91	0.89 (648)	0.89	0.11

[a] Stoichiometry 2:1. [b] Time required for 100% conversion in acetonitrile, 15 °C.
[c] Determined ^{1}H-NMR spectroscopically. [d] 100% conversion; normalized to 1.00 mol; ±2% error limits.

the phenothiazine (PTZ) is easily oxidized via SET, e.g. **4** (E_{ox} = 0.590 V) the phenothiazinyl radical cation ($PTZ^{+\cdot}$) is sufficiently stable and reluctant to transfer a hydrogen atom (H·) to the dioxetane radical anion; the latter preferentially fragments, i.e. $k_{frag} > k_H$ and [Acetone]/[Pinacol] is large (cf. Entry 1 in Table 1). If PTZ is, however, harder to oxidize, e.g. **7** (E_{ox} = 0.698 V), the $PTZ^{+\cdot}$ is less stable and more prone to transfer a hydrogen atom (H·) to the dioxetane radical anion; more reduction to pinacol takes place, i.e. $k_{frag} < k_H$ and [Acetone]/[Pinacol] is small (cf. Entry 4 in Table 1). Moreover, according to Bordwell [11], the acidity (pK [$HA^{\oplus\cdot}$]) of a radical cation $HA^{\oplus\cdot}$ derived from the corresponding acid depends on the oxidation potential (E_{ox} [HA]) of the acid HA, i.e. the more readily the acid HA is oxidized (low E_{ox} [HA]), the less acidic is the radical cation $HA^{\oplus\cdot}$ (high pK [$HA^{\oplus\cdot}$]). Thus, a plot of ln [Acetone]/[Pinacol] vs. E_{ox} (PTZ) displays a negative slope (Figure 1). The strongly electron-donating substituents favor the electron transfer process but disfavor the proton transfer process, since it is known [14] that an increase in the electron donor ability of substituents leads to a decrease in the proton donor ability of the oxidized species.

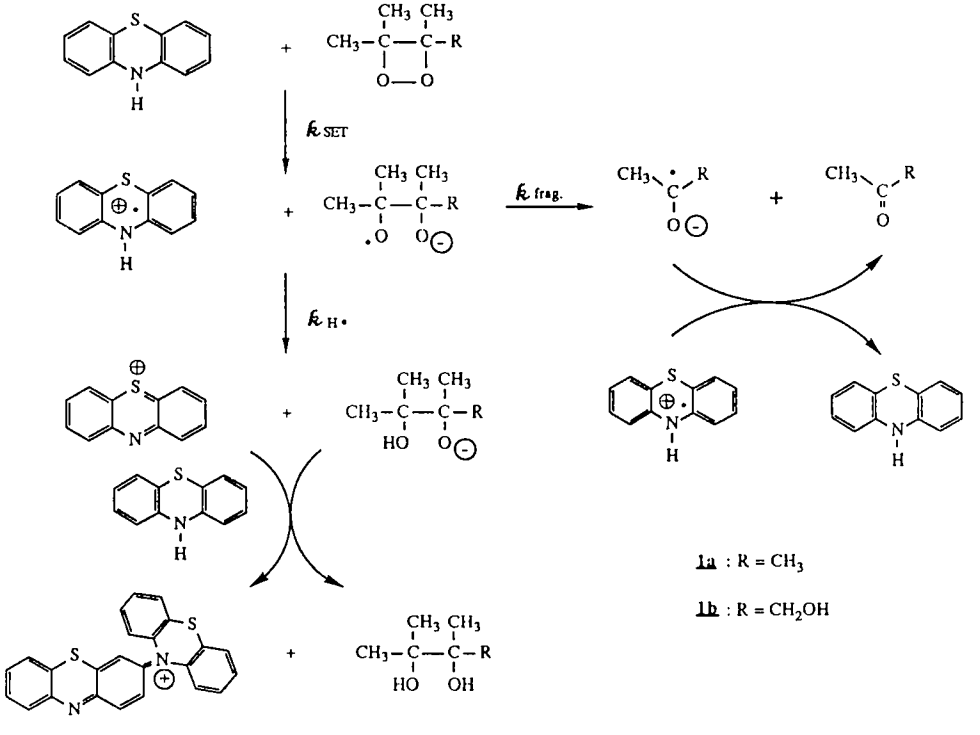
3,10-Dimethylphenothiazine (**8**) [12] with E_{ox} = 0.750 V reacted with dioxetane **1a** under the same conditions to produce after 60 h 17% of 2,3-epoxide-2,3-dimethyl-butane as well as of 3,10-dimethylphenothiazine sulfoxide and as main product 83% acetone. Phenothiazines **9** [14] and **10** [15] with E_{ox} = 0.846 V and 0.900 V respectively, did not react with dioxetane **1a** at all, but with malonyl peroxide (**2**) and dibenzoyl peroxide (**3**) (which presumably have higher reduction potentials than dioxetane **1a**). In view of the increased oxidation potentials of these

phenothiazines [4], the reduced reactivity towards electron transfer with dioxetanes is not surprising.

The oxidation of N-methylphenothiazine (9) [14] by dimethyl malonyl peroxide (2) [16] and benzoyl peroxide (3) was run as follows: A 25-ml, round-bottomed flask, provided with magnetic spinbar and nitrogen inlet and outlet tubes, was charged with 1.50 mmol of the particular peroxide 2 or 3 in 10 ml acetonitrile and cooled to 15 °C by means of a MeOH bath, employing a cryostat. A solution of 1.50 mmol of the N-methylphenothiazine (9) in 10 ml of the same solvent was added within 5 min. The reaction course was monitored by UV-Vis spectrophotometry and TLC and ^{1}H NMR until the peroxide was completely consumed. The product composition [17] of the crude reaction mixture derived from 2 was determined by quantitative ^{1}H NMR (hexamethyldisiloxane was used as internal standard), affording 0.140 g (1.23 mmol, 82%) of the polymeric dimethylmalonic anhydride [18] and 0.282 g (1.23 mmol, 82%) of N-methyl-phenothiazine sulfoxide [19]. The product composition derived from 3 was determined after isolation by means of columm chromatography on silical gel, eluting with 5:1 methylene chloride/methanol. Two fractions were collected, namely 0.212 g (0.937 mmol, 62%) benzoic anhydride and 0.213 g (0.930 mmol, 62%) N-methyl-phenothiazine sulfoxide. In both cases the transient N-methylphenothiazine radical cation was observed at 441, 512, 760, 848 nm, identical to the literature [20].

In conclusion, the present study confirms the involvement of SET in the reaction of peroxides 1 - 3 with phenothiazines (PTZ) 4 - 9 through the direct observation by UV-Vis spectrophotometry of their corresponding radical cations. For the dioxetanes, in addition to hydrogen and/or proton transfer by the phenothiazine derivative, also catalytic decomposition of the dioxetane into ketone products (presumably via electron back transfer) is observed.

SCHEME 1



Acknowledgements

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References

1) W. Adam, B. Epe, D. Schiffmann, F. Vargas, D. Wild, Angew. Chem. Int. Ed. Engl. **27** (1988) 429.
2) W. Adam, F. Vargas, B. Epe, D. Schiffmann, D. Wild, Free Rad. Res. Commun. **5** (1989) 253.
3) W. Adam, A. Beinhauer, B. Epe, R. Fuchs, A. Griesbeck, H. Hauer, P. Mützel, L. Nassi, D. Schiffmann, D. Wild, T. Friedberg, F. Oesch (Eds.), "Primary Changes and Control Factors in Carcinogenesis", Deutscher Fachschriften-Verlag: Wiesbaden (1986), pp. 64 - 67.
4) C. Bodea, I. Silberg, Adv. Heterocycl. Chem. **9** (1968) 321; J. Cymerman-Craig, M. E. Tate, Progr. Drug. Res. **3** (1961) 84.
5) I.S. Forrest, C.S. Carr, E. Usdin, Adv. Biochem. Psychopharmacol. **9** (1967) 1974.
6) L.N. Domelsmith, L.L. Munchausen, K.N. Houk, J. Am. Chem. Soc. **99** (1977) 6506.
7) K. R. Kopecky, J. E. Filby, C. Mumford, P. Lockwood, J. Y. Ding, Can. J. Chem. **53** (1975) 1103.
8) Identified through their UV-Vis spectra; C. Jackson, N. K. D. Patel, Tetrahedron Lett. **1967**, 2255; Y. Tsujino, ibid. **1968**, 2545.
9) H. Gilman, D. Shirley, J. Am. Chem. Soc. **66** (1944) 888.
10) S. Massie, P. Kadaba, J. Org. Chem. **21** (1956) 347.
11) F. G. Bordwell, J.-P. Cheng, J. Am. Chem. Soc. **111** (1989) 1792.
12) C. J. Schlesemer, C. Amatore, J. K. Kochi, J. Chem. Soc. Chem. Commun. **1987**, 120.
13) J. M. Bisson, P. Hanson, D. Slocum, J. Chem. Soc. Perkin II, **1978**, 1331.
14) International Business Machines Corp. (R. R. Schumaker, Inv.) French Pat. 1,527,778 (Juni 07, 1968) [Chem. Abstr. **71** (1969) P 81175d].
15) F. Kehrmann, O. Nossenko, Ber. Dtsch. Chem. Ges. **46** (1913) 2809.
16) W. Adam, R. Rucktäschel, J. Am. Chem. Soc. **93** (1971) 557.
17) The products were identified by comparison of their m.p., IR, ^{1}H and ^{13}C NMR spectra with those of the authentic compounds.
18) C. L. Perrin, T. Arrhenius, J. Am. Chem. Soc. **100** (1978) 5249.
19) M. C. Hovey, J. Am. Chem. Soc. **104** (1982) 4196; F. Pautet, R. Barret, M. Daudon, Pharmazie, **40** (1985) 202.
20) G. Cauquis, A. Deronzier, J.-L. Leage, D. Serve, Bull. Chem. Soc. Fr. **1977**, 295.

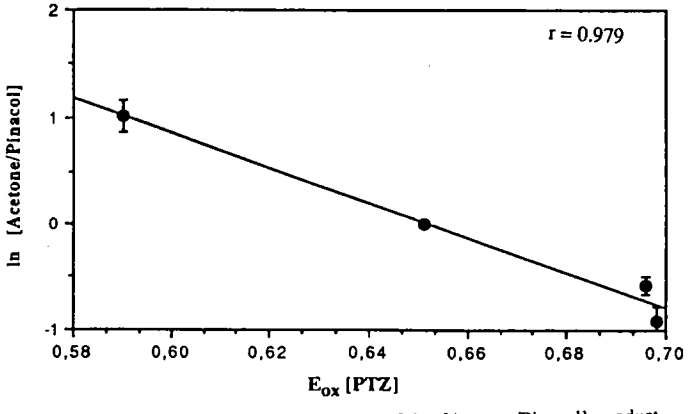

Figure 1. Logarithmic dependence of the [Acetone/Pinacol] product ratios *vs.* oxidation potentials (E_{ox}) of the phenothiazines.

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