Tetrahedron Letters No.9, pp. 885-889, 1966. Pergamon Press Ltd.
Printed in Great Britain.

DISPLACEMENT REACTIONS. X. OXIBASE SCALE PARAMETERS OF AN ANTI-RADIATION DRUG-MEA[1]

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(Received 24 November 1965)

Mercaptoethylamine, MEA, is one of the anti-radiation drugs.

$$H_2NCH_2CH_2SH$$

MEA

The theories of drug protection can all be generalizied as simple S_N2 displacement reactions with MEA serving as a nucleophile with (a) disulfides,[4,5] (b) peroxides[6], (c) free radicals,[7] and (d) metal ions.[8] In the present note, the oxibase parameters[1] of MEA at 25° have been determined by reacting MEA with methyl iodide, ethyl tosylate, and β-propiolactone in water as a function of pH.

MEA exists in solution in four forms: $H_3\overset{+}{N}CH_2CH_2SH$, $H_2NCH_2CH_2SH$, $H_3\overset{+}{N}CH_2CH_2S^-$ and $H_2NCH_2CH_2S^-$ (called $H_2N\text{-}S^-$). Using data [9,10] on the electrometric and spectrophotomeric titration, the fraction of each species has been computed as a function of pH. The kinetics were determined in deoxygenated inert buffer solutions of pH 2 to 13(μ 0.05 to 0.18) using the change in the ultraviolet spectra with time. Concentrations of the reactants were varied by at least eight fold to determine the reaction order. All calculations[11] of rate constants were handled using a program for the IBM 7094.

In all about 300 separate kinetic experiments were performed at temperatures from 0 to 53°C. All the reaction products, with MEA the limiting reagent, were the S-alkylated derivations: S-methyl, S-ethyl and the β-S—propionate as determined by elemental analysis, infrared spectra, ultraviolet spectra, n.m.r. and the formation of derivatives.

The rate law for each substrate, M, was

$$v = k_1 (H_3\overset{+}{N} - SH)\,M + k_2 (H_2N - SH)\,M + k_3 (H_3\overset{+}{N} - S^-)\,M + k_4 (H_2N - S^-)\,M \qquad (1)$$

All reactions of M with the medium (water, buffer salts or OH^-) were accounted for in deriving the values of k_i for each substrate. The kinetic rate constants are presented in Table I only at 25°.

In Table II the E and H values of the nucleophiles have been computed[12] using the oxibase scale:

$$\frac{\log k/k_0}{E} = \alpha + \beta\,\frac{H}{E} \qquad (2)$$

and a multiple linear regression computer program using the experimental data.[13] The H values[14] ($= pK_a + 1.74$) have been computed from the ionisation constants[3,9,10]

The agreement between the kinetically determined E values is quite good. The magnitude of the E values for the thiolate forms indicate that these are some of the best nucleophiles (most easily oxidized) for S_n2 reactions.[13,14] See Table II.

Table II

Oxibase Parameters at 25° in Water

	E volts	H
$H_3\overset{+}{N}CH_2CH_2SH$	1.65[b], 1.68[c]	-8
$H_3\overset{+}{N}CH_2CH_2S^-$	2.84[a], 2.90[b], 2.90[c]	10.3
$H_2NCH_2CH_2S^-$	3.06[a], 3.11[b]	12.5

a. Determined using methyl iodide.

b. Determined using ethyl tosylate.

c. Determined using β-propiolactone.

Table I

Second Order Rate Constants in Water at 25.00° M^{-1} sec $^{-1}$

Substrate	k_1	k_2	k_3	k_4	pH range
CH_3I	-	-	0.468^{a}	2.16^{b}	5.67-12.3
C_2H_5OTs	1.85×10^{-6} [c]	-	5.31×10^{-3} [d]	1.28×10^{-2} [e]	4.97-12.1
β-propiolactone	6.45×10^{-4} [f]	10×10^{-4} [g]	0.25^{h}	12^{i}	$2.24\text{-}4.11^{f\text{-}h}$

a. ± 0.074, estimated σ. $\Delta H^{\ddagger}$ = 19.3 kcal/mole; $\Delta S^{\ddagger}$ = 4.4 gibbs; from data at 0°, 13.5,25 and 30°±0.01.

b. ± 0.06.

c. $\Delta H^{\ddagger}$ = 22.3; $\Delta S^{\ddagger}$ = +1.1; data at 25, 31, 35, 41, 46, 50, and 53° ± 0.01.

d. $\Delta H^{\ddagger}$ = 16.6; $\Delta S^{\ddagger}$ = 14.4; same as c.

e. $\Delta H^{\ddagger}$ = 14.7; $\Delta S^{\ddagger}$ = -20; same as c.

f. ± 0.17

g. Estimate.

h. ± 0.05

i. Estimated using a stopped-flow mixer and spectrometer with a Tek-scope.

In conclusion MEA has large enough E and H values thermodynamically to displace rapidly other thiolate anions.[15]

$$H_2NCH_2CH_2S^- + RSSR \rightleftharpoons H_2NCH_2CH_2SSR + RS^- \qquad (2)$$

$$E_{MEA} > E_{RS^-}$$

MEA has large E and H values so that it would firmly bind metals (as Cu(I) which has an $\alpha=4.95$ and $\beta=0.16$).[14]

Since the removal of free radicals occurs by oxidation-reduction processes the ease

$$H_2NCH_2CH_2S^- + \cdot OH \longrightarrow H_2NCH_2CH_2S\cdot + {}^-OH \qquad (3)$$

of oxidation of the thiolate would facilitate reaction with free radicals. Reaction (3) is an S_n2-type reaction.

The $\underline{\alpha}$ and $\underline{\beta}$ values[14] of H_2O_2 allow the calculation of the rate of reaction of $H_2NCH_2CH_2S^-$ to be $3 \times 10^{-2}\ M^{-1}\ sec^{-1}$ and with $H_3\overset{+}{N}CH_2CH_2S^-$ to be $5.8 \times 10^{-3}\ M^{-1}\ sec^{-1}$ in water at 25°. These rates (even estimated at 37.5°) are too slow to serve as an effective means of radiation protection by reduction of dilute inter and intracellular hydrogen peroxide in vivo. Thus we feel that reduction of hydrogen peroxide in vivo is not one of the radiation protection mechanisms of MEA.

Design of new anti-radiation drugs should take into account the extreme sensitivity of drug properties with the ease of oxidation (high E values).

Acknowledgment- The studies have been supported by the Walter Reed Army Institute of Research (WRAMC-MD-2107), the NSF (NSF-G15750) and the National Institutes of Health (RH-00279).

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