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Alcohols and ethanolamines as hydroxyl radical scavengers

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Abstract

Photogenerated hydroxyl radicals in a model system comprising aqueous solutions of dequalinium chloride and equimolar amounts of hydrogen peroxide were studied in the presence of mono-, di- and triethanolamine. These compounds acted as hydroxyl radical scavengers, the maximal potency was observed with diethanolamine. Protonation of the basic centre of these amines maintained the hydroxyl radical scavenging properties with triethanolamine having the greatest effect. The reactions and their pharmaceutical implications are discussed. Extensions of this work to encompass 1,2-, 1,3- and 1,4- diols are described and show these compounds to have very modest hydroxyl radical scavenging properties.

Keywords: Dequalinium chloride; Diol; Ethanolamine; Hydrogen peroxide; Hydroxyl radical; Photolysis

1. Introduction

The hydroxyl radical is regarded as a serious spoilage agent in aqueous formulations (Barnes and Sugden, 1986) and can be formed in aqueous systems by quite modest inputs of energy, particularly light energy from solar or artificial light sources such as fluorescent lighting. The formation of these radicals in aqueous solutions is facilitated by the presence of dyes and other aromatic compounds which act as sensitizers (Martin and Logsdon, 1987). The presence of trace transition metal impurities, e.g., copper from manufacturing equipment, which can act as mild oxidants and facilitate the decomposition of water into hydroxyl radicals. Sugars such as mannitol have been demonstrated to possess hydroxyl radical scavenging properties (Kochi, 1973), and mannitol being a sugar alcohol has six hydroxyl groups. The hydroxyl radical reacts with primary aliphatic alcohols by α-hydrogen abstraction due to the electrophilic nature of the hydroxyl radical (Anbar et al., 1966). The objective of the present work is to investigate the structural requirements for alcohols which will act as hydroxyl radical scavengers and therefore to suggest alternative scavengers for use in aqueous formulations. It was decided to study the hydroxyl radical scavenging effects of a number of diols and amino alcohols, the latter being used as formulation adjuncts, for example emulsifying agents in the form of soaps, in a model system of dequalinium chloride in aqueous solution with equimolar amounts of hydrogen peroxide incorporated and to generate the

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Table 1
Photodegradation results of of dequalinium chloride (DC) (30 μg/ml) with additives

System	Order of reaction	Rate constant × 10^{-2}
DC + hydrogen peroxide control 1	First	12.69
DC + monoethanolamine + hydrogen peroxide	First	10.64
DC + diethanolamine + hydrogen peroxide	First	4.40
DC + triethanolamine + hydrogen peroxide	First	8.11
DC + hydrogen peroxide control 2	First	18.49
DC + propane-1,3-diol + hydrogen peroxide	First	14.28
DC + propylene glycol + hydrogen peroxide	First	22.79
DC + butan-1,4-diol + hydrogen peroxide	First	19.11
DC + hydrogen peroxide control 3	First	21.23
DC + dipyridamole + hydrogen peroxide	First	14.30

hydroxy radicals by the action of simulated sunlight at 38 ± 1°C.

2. Materials and methods

2.1. Materials

Materials used were: butan-1,4-diol (BDH), dequalinium chloride (Aldrich Chemical Co.), diethanolamine (BDH), dipyridamole (Sigma Chemical Co.), ethanolamine (BDH), hydrochloric acid (Fisons), hydrogen peroxide (Sigma Chemical Co.), propane-1,3-diol (BDH), propylene glycol (BDH), triethanolamine (BDH).

2.2. Apparatus

A Cecil 272 spectrophotometer with matched 1-cm silica cells was used.

2.3. Methods

A calibration graph was constructed using a series of dilutions of dequalinium chloride in deionised water (4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 mg/100 ml) and the absorbance measured at 326 nm. The linear regression analysis based on the mean of three replicates gave a regression coefficient of 0.9998 ($p = 0.001$). A stock solution of dequalinium chloride in deionised water (30 mg/l) was prepared and wrapped in aluminium foil to exclude light. A 99-ml aliquot of this solution was taken and 1 ml of 30% v/v hydrogen peroxide solution was added. Similar solutions were prepared individually containing equimolar amounts of the following substances with respect to dequalinium chloride: butan-1,4-diol (5.9 mg/l), diethanolamine (6.0 mg/l), dipyridamole (28.69 mg/l), ethanolamine (3.47 mg/l), propane-1,3-diol (4.33 mg/l), propylene glycol (4.33 mg/l) and triethanolamine (8.48 mg/l) by adding appropriate volumes from a stock solution.

Each test solution was irradiated with simulated sunlight by the method of Evans et al. (1975) for 5 h with absorbance readings taken at 326 nm at time zero and every half hour thereafter.

2.4. Treatment of results

The reaction order and rate constant were measured by taking linear regression analyses of the percentage residual dequalinium chloride, the log of the percentage dequalinium chloride remaining, and the reciprocal of the percentage dequalinium chloride remaining versus time. The plot representing the best straight line as determined by the method of Patel and Sugden (1992) was deemed to represent the order of reaction and the rate constant was calculated from the slopes of the graphs.

Table 2
Photodegradation of dequalinium chloride (DC) (25 μg/ml) with alkanolamines and hydrochloric acid

System	Order of Reaction	Rate Constant × 10^{-2}
DC + hydrogen peroxide (control with acid)[a]	First	35.14
DC + hydrogen peroxide + monoethanolamine + HCl[a]	First	11.21
DC + hydrogen peroxide + diethanolamine + HCl[a]	First	16.56
DC + hydrogen peroxide + triethanolamine + HCl[a]	First	6.29

[a] Equimolar amounts of hydrochloric acid were added with respect to the alkanolamine.

3. Results and discussion

The results of the experiments are shown in Tables 1 and 2.

Examination of Table 1 shows that in the first set of experiments in which the hydroxyl radical scavenging action of the alkanolamines is tested all the reactions assessed followed first order kinetics. The incorporation of ethanolamines results in a reduction in the rate constant from 12.69 × 10^{-2} to 10.64 × 10^{-2} with monoethanolamine, to 4.40 × 10^{-2} with diethanolamine and to 8.11 × 10^{-2} with triethanolamine. Anbar et al. (1966) have shown that hydroxyl radicals abstract a hydrogen atom from the α carbon atom of primary alcohols. Amines also react with hydroxyl radicals at the N–H bond (Simic et al., 1971). In the case of the alkanolamines tested there are up to four potential sites for hydrogen abstraction and it would be reasonable to expect that triethanolamine, having three CH_2CH_2OH groups would be the most active of the three alkanolamines tested. However, it is diethanolamine which has the smallest rate constant and thus this alkanolamine is the most active, of those tested, as a hydroxyl radical scavenger. These experimental results cannot be explained in terms of the base strength since the pK_a values of the compounds tested are: monoethanolamine, 9.5; diethanolamine, 8.88 and triethanolamine, 7.76 (Dean, 1992). Therefore, it is most likely that mono- and dialkanolamines react primarily with hydroxyl radicals at the N–H bond. Triethanolamine not having an N–H bond can only react with hydroxyl radicals at the CH_2CH_2OH groups. Examination of molecular models shows that the extent of hydrogen bonding in triethanolamine is not such as to make this molecule sterically hindered to the approach of the hydroxyl radical. Consequently, the reduced scavenging action of this triethanolamine may be regarded as being due to the absence of the N–H bond. The experiment with dipyridamole, a known hydroxyl radical scavenger (Suzuki et al., 1992) was carried out to study the effect of having four CH_2CH_2OH groups with a number of basic centres all of which were tertiary amines. The rate constants were 14.30 × 10^{-2} with the control at 21.23 × 10^{-2}.

These results indicated that the hydroxyl radical scavenging effect noted in the present work was due in part to the number of CH_2CH_2OH groups and the presence of a secondary amine group in the structure of the scavenging alkanolamine was necessary for good activity.

Propylene glycol (propane-1,2-diol) causes a slight rise in rate constant from 18.49 × 10^{-2} to 22.79 × 10^{-2}. This suggests that the radicals formed from the reaction of this diol and hy-

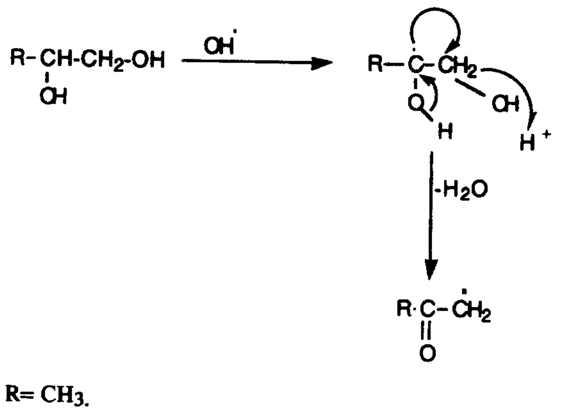


Fig. 1. Reaction of 1,2-diols with hydroxyl radicals.

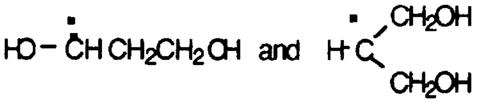


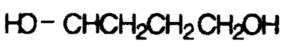
Fig. 2. Propane-1,3-diol forms two radicals on reaction with hydroxyl radicals.

droxyl radicals may be reactive with respect to dequalinium chloride. Fig. 1 shows how propylene glycol and other 1,2-diols react with hydroxyl radicals under acid conditions (the deionised water used in this work has a pH of 6.1) to give a carbonyl radical (Buley et al., 1966; Gilbert et al., 1972; Barnes et al., 1993) (Fig. 1).

The carbonyl radical thus formed may then degrade dequalinium chloride. This sequence of reactions could explain why propylene glycol does not act as a hydroxyl radical scavenger. The implications of these reactions could be significant in formulations where propylene glycol is used as an additive, for example as a co-solvent or humectant.

Propane-1,3-diol shows a modest hydroxyl radical scavenging property with a fall in rate constant from 18.49 × 10^{-2} for the control to 14.28 × 10^{-2} with propane-1,3-diol. This diol would not be expected to undergo similar reactions to those shown above. Buley et al. (1966) have shown that propane-1,3-diol forms two radicals on reaction with hydroxyl radicals (Fig. 2).

It is possible that these radicals facilitate the decomposition of the dequalinium chloride to a similar extent to hydroxyl radicals and this could explain why propane-1,3-diol has little effect as a hydroxyl radical scavenger in the system tested. Similarly in the case of butane-1,4-diol the rate constant is 19.11 × 10^{-2}. which is close to that of the control at 18.49 × 10^{-2}. This result indicates that this diol has no real hydroxyl scavenging effect. Buley et al. (1966) have shown that this diol reacts with the hydroxyl radical to yield a radical by hydrogen abstraction from one of the α-hydrogen atoms (Fig. 3). Which may facilitate the decomposition of dequalinium chloride and thus explain the poor scavenging performance of this diol in the system tested.



$HO-\overset{\bullet}{C}HCH_2CH_2CH_2OH$

Fig. 3. Radical given by diol reaction with hydroxy radical.

Examination of Table 2 shows that, in acid conditions, triethanolamine hydrochloride has the greatest hydroxyl radical scavenging effect. Simic et al. (1971) have reported that protonation of a basic centre of an amine has a deactivating effect on the compounds with respect to hydroxyl radicals and thus the reactions which occur must take place at the carbon atoms furthest away from the protonated nitrogen atom. In this case the compound with three possible reaction sites would be most likely to react with these radicals and be the best scavenger of the compounds tested. The fact that diethanolamine hydrochloride was an inferior scavenger to monoethanolamine hydrochloride was unexpected and may possibly be due to some degree of steric hindrance or to experimental error. Triethanolamine soaps in which the base is converted into a fatty acid salt, with a positive charge on the nitrogen atom, are used in formulation science as emulsifying agents and the hydroxyl radical scavenging properties of such salts of triethanolamine may be of interest where formulations contain materials which actively promote hydroxyl radical formation such as dyes or titanium dioxide, of which the latter is used in sun blocking preparations. Titanium dioxide in aqueous suspensions readily facilitates the formation of hydroxyl radicals on irradiation with light (Bresova et al., 1991; Chen and Chou, 1993; Mills and Hoffmann, 1993).

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