N-CHLOROSUCCINIMIDE AS A POTENTIAL REAGENT IN THE CHLORINATION OF THE REGIOISOMERS OF DIHYDROXY BENZOIC ACID IN AQUEOUS SOLUTION: STRUCTURE - ACTIVITY ASSESSMENT

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ABSTRACT

N-Chlorosuccinimide (NCS) has been used to chlorinate the three regioisomers of dihydroxy benzoic acid in aqueous solution. All the three reactions were found to be fast and required the use of hydrodynamic voltammetry to estimate the relative reactivity of the isomers by kinetic verification. The specific reaction rates for the chlorination of 2,4-dihydroxy benzoic acid, 2,6-dihydroxy benzoic acid and 3,5-dihydroxy benzoic acid have been found to be 76, 14 and 31 $M^{-1} s^{-1}$ at 25s. $0^{o}C$, respectively, thereby providing a quantitative estimation of the relative reactivities of these isomers elucidating the steric compulsions in the mechanistic routes of these reactions. NMR investigations confirmed the product in all the three cases to be the monochloro derivative. Green chemistry principles have been followed in the study.
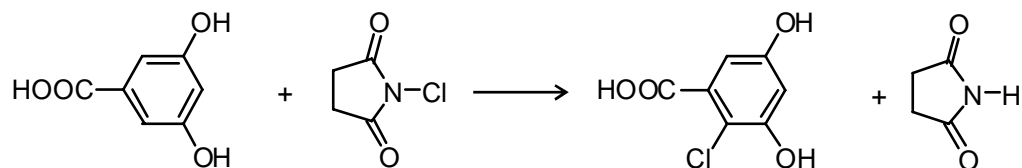
Key words: Chlorination, Dihydroxy benzoic acid, Hydrodynamic voltammetry.

INTRODUCTION

Chlorination of drinking water to control microbial contamination invariably yields carcinogenic and recalcitrant by-products from reactions of chlorine with organic impurities present in water[1]. These are trihalomethanes and dihalo derivatives of aromatic substrates. Hence, the study and analysis of chlorination reaction products has gained significance. Halogenated compounds are also precursors of several drug molecules[2]. They are of importance in organic synthesis in coupling reactions[3]. The reactivity of these substrates stems from their nature, the substituents present on them and their regiospecificity. Steric considerations of the reaction route, reagent and solvent used, also play a key role in the dynamics of these reactions[4]. The relative reactivity of the different regioisomers in these reactions has often been qualitatively speculated but a quantitative assessment has been found lacking in aqueous solutions due to the rapidity of these reactions. Special techniques for their kinetic study are needed. Presently, we have adopted the hydrodynamic voltammetry technique to quantitatively estimate the reactivity of the three regioisomers of dihydroxy benzoic acid in aqueous medium by using N-chlorosuccinimide as the reagent. The specific reaction rates of the three reactions studied are a quantitative justification of the speculated reactivity of the three regioisomers. Since the reactions are fast and are completed in a minute, microgram quantities of chemicals are utilized in the reactions and the reactant solutions are very dilute in the investigations hence green chemistry principles are inherently followed in the study.
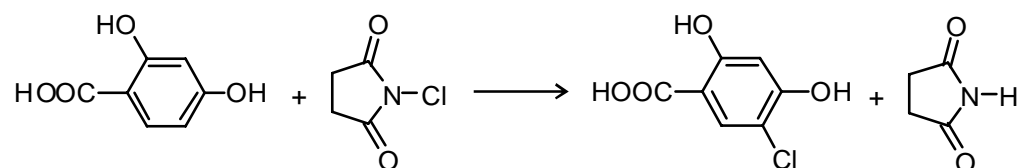
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The three reactions under study are as follows;

(a) Chlorination of 3,5-dihydroxy benzoic acid by NCS
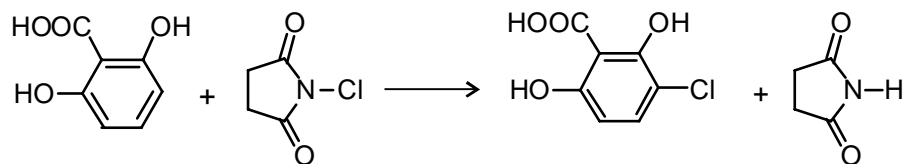

3, 5-Dihydroxy benzoic acid

(b) Chlorination of 2,4-dihydroxy benzoic acid by NCS

2, 4-Dihydroxy benzoic acid

(c) Chlorination of 2,6-dihydroxy benzoic acid by NCS

2, 6-Dihydroxy benzoic acid

In these reactions, only NCS is the electroreducible species among the reactants and products. Hence, the reactions can be followed by measuring the decrease in the diffusion limited current due to NCS in the reaction, at a rotating microelectrode.

EXPERIMENTAL

Preparation of solutions

Stock solutions of the supporting electrolyte potassium nitrate, NCS and the three regioisomers of dihydroxy benzoic acid were prepared in conductivity water using AR grade chemicals.

Electrodes

The positive electrode was a platinum microcathode (RPE) rotating at 600 rpm.

The negative electrode was a saturated calomel electrode (SCE).

Calibration of the diffusion limited current

Diffusion currents at the RPE for different concentrations of chlorine solutions containing a large concentration of the supporting electrolyte are determined (Table 1). The plots of diffusion current Vs concentration are found to be linear at all temperatures.

Table 1: Calibration of diffusion current for NCS at various temperatures

Potential applied at the RPE Vs SCE: 0.1 V

[NCS]/10^{-4} (M)	Mean diffusion current (nA)						
	$10^{o}C$	$15^{o}C$	$20^{o}C$	$25^{o}C$	$30^{o}C$	$36^{o}C$	$40^{o}C$
0.5	3.8	4.2	4.6	5.0	5.5	5.7	6.3
1.0	7.8	8.6	9.3	10.1	10.8	11.6	12.2
2.0	15.7	17.0	18.5	20.0	21.5	23.0	24.2
3.0	23.4	25.8	27.9	30.1	32.4	33.8	36.0
4.0	31.4	34.2	37.1	40.1	43.0	46.0	48.5

Kinetic measurements

25 cm^3 each of equal concentrations of the dihydroxy benzoic acid isomer and NCS [1.0 x 10^{-3} M] containing the supporting electrolyte and the buffer solutions for 7 pH, are mixed in a reaction vessel kept in a thermostat. The two electrodes are contained in this reaction vessel and the time of mixing is noted. At every 10 seconds, the decreasing diffusion current values are recorded for at least one half-life of the reaction. Double dilution occurs upon mixing.

The plots of [NCS]$^{-1}$ Vs time are found to be linear at all temperatures. The slopes of these plots are the specific reaction rates of the reactions under investigation[5]. Table 2 shows a typical set of data for the chlorination of 3, 5-dihydroxy benzoic acid by NCS in aqueous solution at 25.0^{o}C and 7 pH.

Table 2: Kinetics of chlorination of 3, 5-dihydroxy benzoic acid at 25.0^{o}C by NCS. Initial NCS concentration in the reaction mixture after dilution: 5.0 x 10^{-4} M

Time (s)	Diffusion current (nA)				[NCS]/10^{-4} (M)	[NCS]$^{-1}$/10^3 (M^{-1})
	1	2	3	Mean		
20	37.4	38.5	38.0	38.0	3.85	2.60
30	33.2	33.5	33.4	33.4	3.33	3.00
40	30.4	30.4	30.6	30.5	3.13	3.20
50	28.8	28.6	28.8	28.7	2.85	3.50
60	26.5	26.7	26.4	26.5	2.63	3.80

The plot of [NCS]$^{-1}$ versus time is the specific reaction rate k for the chlorination of 3,5-dihydroxy benzoic acid in aqueous solution at 25.0^{o}C and 7 pH = 31 M^{-1}s^{-1}

RESULTS AND DISCUSSION

The chlorination reactions of all the three regioisomers are found to be rapid and follow second order kinetics as the plots of [NCS]$^{-1}$ Vs time are linear. The formation of the monochloro derivatives in all the three cases is ascertained by stoichiometry and by NMR investigations. The results are presented in Table 3.

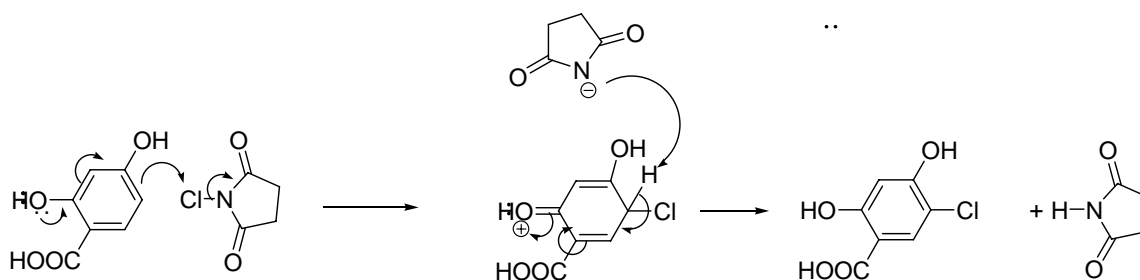**Table 3: Specific reaction rates (k) for the chlorination of dihydroxy benzoic acid isomers at 25.0°C**

S. No.	Regioisomer	k (M⁻¹s⁻¹)
1	2,4-Dihydroxy benzoic acid	14
2	2,6-Dihydroxy benzoic acid	76
3	3,5-Dihydroxy benzoic acid	31

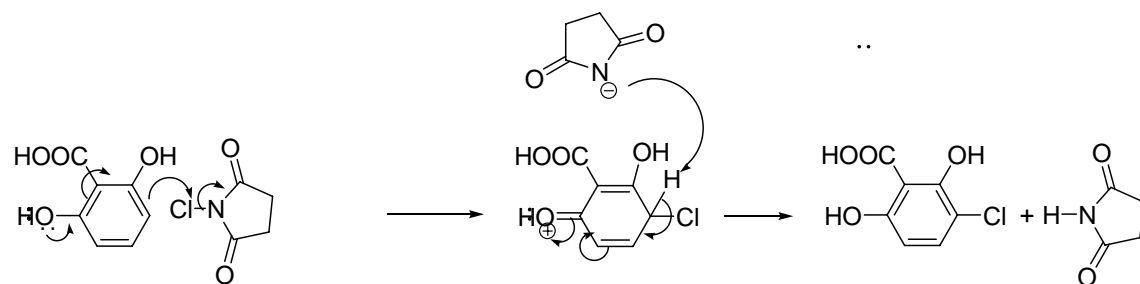The probable mechanisms for the chlorination of the three isomers may be suggested as follows;

(a) Chlorination of 3,5-dihydroxy benzoic acid by NCS
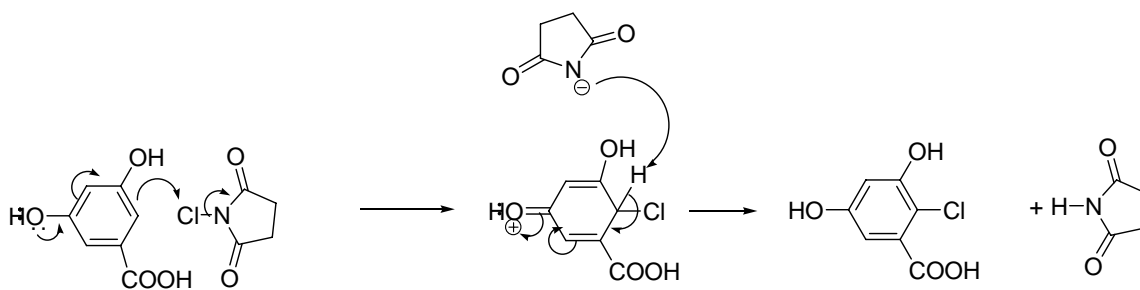
(b) Chlorination of 2,4-dihydroxy benzoic acid by NCS

(c) Chlorination of 2,6-dihydroxy benzoic acid by NCS

CONCLUSION

The values of the specific reaction rates for the chlorination of the dihydroxy benzoic acid regioisomers in aqueous medium at 25.0°C presented in Table 1. These, may be interpreted as follows. The –COOH group being electron withdrawing, is meta directing while the –OH group is electron donating, hence is ortho and para directing. In 2,4-dihydroxylic acid, the two –OH groups and the –COOH group activate position 5 in unison, relative to position 3 due to steric congestion at the latter. Hence, 5-chloro-1,3-

dihydroxy benzoic acid is formed at the fastest rate among the three regisomers studied. 2,6-dihydroxy benzoic acid shows the slowest relative rate as there is crowding of the bulky –COOH group with the two –OH groups. The closeness of these substituents favours intramolecular hydrogen bonding among them resulting in reduced nucleophilicity of the benzene ring. This is reflected in the slowest rate observed. In 3,5-dihydroxy benzoic acid, the two –OH groups block the positions meta to the –COOH group resulting in the formation of the 2-chloro-3,5-dihydroxy benzoic acid. The position between the two –H groups is less activated due to steric hindrance.

These steric compulsions are reflected in the relative reactivity of the regioisomers under study in a quantitative manner in these investigations.

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