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Oxidation resilient dithizones – Synthesis, cyclic voltammetry and DFT perspectives

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ABSTRACT

Towards improving the resistance of dithizone against oxidation, a series of halogenated derivatives were synthesized. The synthetic limit at which fluorination permanently alters the properties of dithizone was found in the transition from mono- to difluorophenyl substituted dithizones. Relative to unsubstituted dithizone, the *ortho*-fluoro- and difluorophenyl derivatives exhibit a decline in molar absorptivity, which increasingly renders it less effective in its traditional application as trace metal analysis reagent. By the use of cyclic voltammetry, oxidation resilience was quantified, with largest positive shift in first oxidation peak potential found for 3-fluorodithizone (279 mV). DFT calculated HOMO and LUMO energies of the dithizone derivatives were related to corresponding oxidation ($E_{pa,1}$) and reduction potentials ($E_{pc,C}$). Correlations between E_{HOMO} and $E_{pa,1}$, and E_{LUMO} and $E_{pc,C}$ yielded R^2 values of 0.98 and 0.95, respectively. Computed molecular orbital and time dependent DFT oscillator renderings agree closely with experimental observations.

1. Introduction

During extensive research on phenylhydrazines in 1878, Emil Fischer discovered the dithizone compound [1]. The potential of this ligand in trace metal analyses was illustrated only in 1925 [2], after which its use for this purpose increased greatly. In the application of dithizone as complexing agent, spectrophotometric limits down to 12 ppb for lead detection in plants were achieved recently [3].

Through the years several articles appeared reporting on the synthesis of dithizone [4]. All these methods are essentially related, entailing the diazotization of aniline, followed by reaction with nitromethane to form nitroformazan, and exposure to NH_3/H_2S gas to form the thiocarbazide, H_4Dz, which then is oxidized to dithizone, H_2Dz. The initial method of Fischer utilized carbon disulfide to directly convert phenylhydrazine to thiocarbazide, while Mirkhalaf more conveniently employed aqueous ammonium sulfide in synthesizing dithizone [4]. Only a few old reports dealt with phenyl substituted derivatives, mainly with regard to the syntheses and spectroscopy there-of [5].

During interaction with iodine or a variety of metal containing oxidizing agents, H_2Dz easily oxidizes to the disulfide, $(HDz)_2$, and further to dehydrodithizone, Dz. The structures of H_4Dz, H_2Dz, KHDz and Dz have been solved [6]. Ogilvie and Corwin showed that Dz may be chemically reduced back to H_2Dz [7]. The ability of dithizone to act as weak reducing agent has been reported by several authors [8].

Recently, the chemical and electrochemical oxidation and reduction of dithizone in organic media was described [9]. Comparative electrochemistry studies were done in two solvents, dimethylsulfoxide and dichloromethane, as well as for two supporting electrolytes, $[N(^nBu)_4][PF_6]$ and the extremely non-interacting $[N(^nBu)_4][B(C_6F_5)_4]$ salt. Only by using the latter electrolyte, in CH_2Cl_2, it was possible to observe and assign the smallest reduction waves.

In view of the relative ease with which dithizone may be oxidized by a variety of oxidants and thus also acts as mild reducing agent, it was decided to investigate ways to stabilize this important analytical ligand against oxidation while not destroying its property as metal scavenger of high molar absorptivity. By systematic synthetic change of the electronic properties of dithizone, **1**, the aim therefore was to determine the cut-off point at which dithizone would bleach, and thus no longer be of use in the spectroscopic detection of trace metals. Towards this end a series of phenyl-halogenated derivatives were synthesized, including the 4-chloro, **2**, 4-fluoro, **3**, 3-fluoro, **4**, 2-fluoro, **5**, 3,4-difluoro, **6**, 3,5-difluoro, **7**, and a 2,3,4,5,6-pentafluoro species, see Scheme 1.

The influence of electron-withdrawing halogen substituents on oxidation and reduction potentials of **2**–**5** was quantified by cyclic voltammetry. Lastly, the correlation of computed orbital energies with experimental redox potentials were investigated as alternative more convenient theoretical approach for quantifying substituent electronic effects on dithizone. Theoretically calculated HOMO and LUMO energies are closely associated to oxidation and reduction potentials of molecules. As stated by Koopman's theorem [10], ionization energy is equal to the HOMO energy of a molecule, but of opposite sign, with the consequence that oxidation

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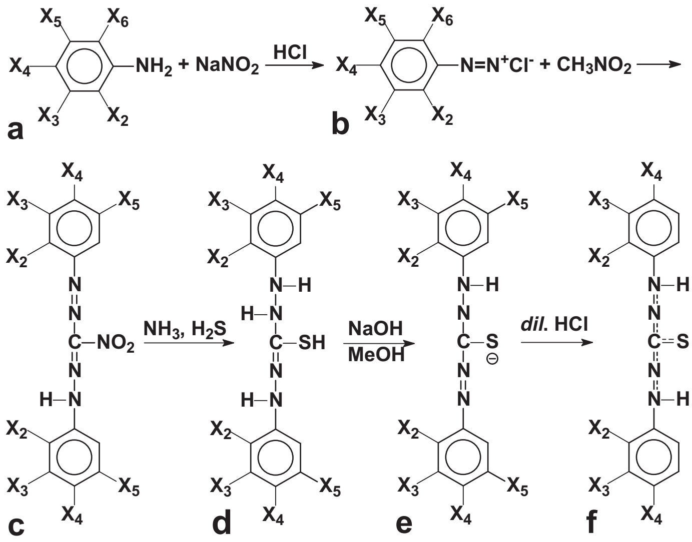

2(a-f) X_4 = Cl; X_2, X_3, X_5 & X_6 = H

3(a-f) X_4 = F; X_2, X_3, X_5 & X_6 = H

4(a-f) X_3 = F; X_2, X_4, X_5 & X_6 = H

5(a-f) X_2 = F; X_3, X_4, X_5 & X_6 = H

6(a-f) X_3, X_4 = F; X_2, X_5 & X_6 = H

7(a-e) X_3, X_5 = F; X_2, X_4 & X_6 = H

8(a-b) X_2, X_3, X_4, X_5 & X_6 = F

Scheme 1. The synthesis of halogenated dithizones, **f** (**2**–**6**), and the thiocarbazone, **e** (**7**). The pentafluoro derivative (**8**) reacts differently by forming a triazene (see Fig. 1), after the first step. Substitution (X) patterns are indicated.

potentials may be related to HOMO energies. The electron located in the HOMO orbital is removed during oxidation. In a similar way LUMO energy is related to reduction potentials. During reduction an electron is acquired by the LUMO orbital. Both HOMO and LUMO energies may readily be calculated, i.e. by means of DFT and other computational methods, as extensively discussed elsewhere [11].

2. Experimental

2.1. Materials and apparatus

Unless otherwise stated, dithizone, **1**, all synthesis reagents, and solvents (Sigma–Aldrich, Merck) were used without further purification. Hydrogen sulfide gas was prepared by the reaction between iron sulfide and hydrochloric acid, while ammonia gas was supplied by Afrox Gas company. CH_2Cl_2 was dried by refluxing under nitrogen over calcium hydride, and redistilled immediately prior to use. Water was doubly distilled. ^1H NMR spectra at 20 °C were recorded on a Bruker Avance DPX 300 NMR spectrometer at 300 MHz with chemical shifts presented as δ values referenced to $SiMe_4$ at 0.00 ppm utilizing acid free $CDCl_3$ as solvent. $CDCl_3$ was rid of acid by passing through basic alumina immediately before use. $[N(^nBu)_4][B(C_6F_5)_4]$ was synthesized according to published procedures [12]. Melting points were determined on a Reichert Thermopan microscope with a Koffler hot-stage and are uncorrected.

2.2. Quantum computational methods

Density functional theory (DFT) calculations were performed using the B3LYP/6-311G(d,p) [13] functional and basis sets as implemented in the GAUSSIAN (G09) package [14]. Optimized geometries were calculated for the neutral species. Molecular orbital representations and energies were processed and visualized with the Chemcraft software package, applied to the former output files [15]. Simulated UV–Vis spectra were calculated using the time dependent (TD) DFT method [16] implemented in the G09 program. During TDDFT calculations both the B3LYP and the long range corrected functional CAM-B3LYP were employed [17].

2.3. Syntheses

Syntheses of dithizone derivatives **2**–**6**, as well as attempted syntheses of dithizones **7** and **8** were performed by adapting the method reported by Pelkis et al. [4]. The general recipe is given, using **2** as representative example. Characterization data of all the compounds is given after the synthetic procedure to obtain **2**.

2.3.1. 4-Chlorophenyldithizone, $(4\text{-}ClPhNHN)_2CS$, 2

2.3.1.1. Nitroformazan. In a 100 ml beaker, 4-chloroaniline (5 g, 39 mmol) was added to a mixture of concentrated hydrochloric acid (20 ml) and water (35 ml) at 0 °C. Diazotization was done by the slow addition of sodium nitrite (3.5 g, 50 mmol) and stirring (*ca* 1 h) until all the aniline was dissolved. In a 500 ml beaker the diazo solution was added, with stirring, to a cold mixture of sodium acetate (80 g, *ca* 1 mol), glacial acetic acid (45 ml, 0.75 mol) and water (25 ml). Nitromethane (6.8 g, 111 mmol) was added after 10 min. After stirring for 2 h at room temperature the solution volume was increased with water to 400 ml. After stirring for another 1 h, the red formazyl derivative was filtered in a large Büchner funnel, washed with copious amounts of water and then with a small amount of ethanol and ether. The nitroformazan product was