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FACILE SYNTHESIS AND PHYSICAL AND SPECTRAL CHARACTERIZATION OF 2,6-DI-*tert*-BUTYL-4-NITROPHENOL (DBNP): A POTENTIALLY POWERFUL UNCOUPLER OF OXIDATIVE PHOSPHORYLATION

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Abstract—The compound 2,6-di-*tert*-butyl-4-nitrophenol (DBNP), a potentially powerful uncoupler of ATP-generating oxidative phosphorylation, has been physically and spectroscopically characterized using X-ray crystallography, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), GC-MS spectrometry, Fourier-transformed IR (FTIR) spectrophotometry, UV-Vis spectrophotometry, and FT ^{1}H- and ^{13}C-NMR spectroscopy. However, DBNP is not commercially available; therefore, it had to be synthesized in the laboratory prior to toxicity studies. The DBNP was prepared from 2,6-di-*tert*-butylphenol (DBP) precursor in hexane through an electrophilic aromatic substitution process using NO_2. A collective yield of 75% was obtained by using two empirically determined end points that prevented the coprecipitation of reaction by-products and resulted in the formation of DBNP in high purity. Excessive amounts of NO_2 in reaction mixtures resulted in the decomposition of preformed DBNP. With a pK_a value of 6.8 and a higher degree of lipophilicity, DBNP may prove to be a stronger uncoupler of oxidative phosphorylation than 2,4-dinitrophenol (pK_a = 4.09) due to the expected enhancement of passive-diffusion kinetics across biological membranes at the physiological pH of 7.4. The present study is intended to provide analytical toxicologists, industrial hygiene monitors, and other professionals involved in chemical health and safety with a comprehensive source of basic information on the synthesis and analytical chemistry of DBNP.

Keywords—Synthesis 2,6-Di-*tert*-butyl-4-nitrophenol Analysis ATP Uncoupler

INTRODUCTION

Quantum-mechanical calculations indicate that 2,6-di-*tert*-butyl-4-nitrophenol (DBNP; compound 1 in Fig. 1) should be second in potency only to 3,5-di-*tert*-butyl-4-hydroxybenzylidene malononitrile (SF 6847) (compound 2) [1], the most potent uncoupler of oxidative phosphorylation known [2]. The biological importance of DBNP has resulted primarily from its successful use as an agent against species and strains of mites resistant to commonly used insecticides [3]. In a separate study, however, DBNP was shown to be highly toxic to mammals [4].

Most recently, the inadvertent production of this butylated nitrophenol within U.S. Navy submarine environments has stimulated renewed interest in the characterization of its chronic and intrinsic toxicological properties (P.M. Huber, personal communication). The formation of DBNP occurs in aerosols of lubricants containing 2,6-di-*tert*-butylphenol (DBP; compound 3 in Fig. 1), which reacts with NO_2 formed from electrostatic precipitators used to remove particulate matter from the air. Formation of this toxicant was first recognized because of its propensity to yellow surfaces aboard the submarines. On March 20, 1992, the Navy Environmental Health Center (Norfolk, VA) was contacted by Submarine Squadron Two (Groton, CT) regarding a yellowing of surfaces aboard Navy submarines that occurred while the submarines were under way. Crew members have potentially been exposed to DBNP for extended periods in the closed atmosphere of submarines. Currently, there is little information concerning the toxicity or the specific mechanism of action of DBNP.

Because DBNP is an uncommon, commercially unavailable product, it must be prepared in the laboratory prior to toxicity studies. The present study was intended to provide analytical and descriptive toxicologists, industrial hygiene monitors, and other professionals involved in chemical health and safety issues with a heretofore unavailable, comprehensive source of basic analytical and synthetic information on DBNP.

Previous attempts to nitrate DBP (compound 3 in Fig. 1) in protic solvents resulted in the formation of compounds such as 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (compound 4) (red needles, m.p. 246–247°C) [5,6]; 2,4-dinitro-6-*tert*-butylphenol (compound 5) (bright yellow crystals, m.p. 126–127°C) [7]; 4,4′-dihydroxy-3,3′,5,5′-tetra-*tert*-butylbiphenyl (compound 6) (m.p. 185–185.5°C) [7]; and 2,6-di-*tert*-butyl-1,4-benzoquinone (compound 7) (deep-yellow needles, m.p. 65–66°C) [7]. The DBNP was success-

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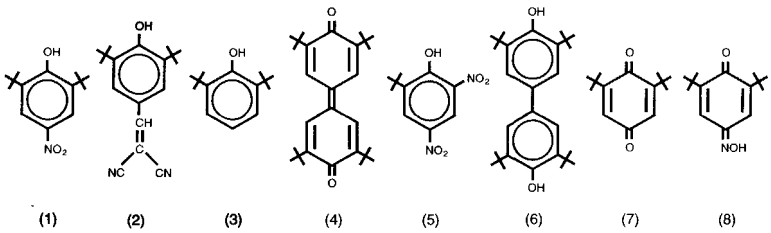

Fig. 1. Typical literature-reported by-products (compounds 4–8 only) formed during the intended *p*-nitration of 2,6-di-*tert*-butyl-4-nitrophenol (DBP) (compound 3) to produce 2,6-di-*tert*-butyl-4-nitrophenol (DBNP) (compound 1). Note the structural similarities between DBNP (compound 1) and 3,5-di-*tert*-butyl-4-hydroxybenzylidene malononitrile (SF 6847) (compound 2).

fully prepared by the slow addition of dilute nitric acid in acetic acid to a solution of DBP in acetic acid [7]. While the latter procedure accomplished *p*-nitration of DBP, the synthetic scheme used for the isolation of DBNP from the complex reaction mixture invariably required time-consuming alkalinization, acidification, and solvent extraction steps for percentage yields of only 36%. Many decomposition pathways are available to DBNP once it is formed in protic media. One of these leads to the formation of 2,6-di-*tert*-butyl-1,4-benzoquinone-4-oxime (compound 8) (pale-yellow plates, m.p. 225–226°C), which has been reported to form during the thermal decomposition and acid-catalyzed hydrolysis of DBNP [7].

The melting range of 156 to 158°C has been typically reported for DBNP whenever DBP was nitrated with nitric acid or nitric–acetic acid mixtures in *protic* solvents and initially suggested the presence of hard-to-remove impurities that were unique to these synthetic procedures [7,8]. Synthetic schemes in *aprotic* solvents were considered in an attempt to limit the formation of DBNP decomposition products (compounds 4–8 in Fig. 1) via these pathways and to simplify its isolation from reaction mixtures. A synthetic procedure previously described involved the nitration of DBP in light petroleum ether by the addition of 30% nitric acid and washing of the precipitated DBNP with water until neutral (m.p. 156°C, 83.7% yield) [9]. Other investigators have reported melting in the range of 152 to 153°C [10]. The present study reports a novel and simple procedure for the synthesis of high-purity DBNP from the readily available precursor 2,6-di-*tert*-butylphenol (DBP). Additionally, basic physical and spectral properties are reported for this nitrophenol.

EXPERIMENTAL PROCEDURE

Chemicals

Reagent quality chemicals were used. The DBP (catalogue no. D-3292, 99% purity, CAS no. 128-39-2) was purchased from Sigma Chemical Company (St. Louis, MO). Gaseous NO_2 (4P cylinder, 99.5%, CAS no. 10102-44-0) was purchased from Matheson Gas Products Company (LaPorte, TX). [*Caution*: NO_2 is a potent oxidizer and corrosive agent. Because potential dermal and inhalation hazards are associated with its use, it is strongly recommended that this material be handled within a fume hood while wearing proper safety gear]. The HPLC-grade quality solvents were bubbled with nitrogen before use to remove dissolved oxygen. The microanalysis of recrystallized DBNP was performed by Galbraith Laboratories (Knoxville, TN). The single-crystal data were obtained using an Enraf Nonius computer-assisted diffractometer model 4 (CAD4) with graphite-monochromated Mo-Kα radiation. The structural resolution was obtained using direct methods with SHELXS86® [11], and the data-reduction/least-squares refinement was performed using the MoLEN® package [12]. The thermal decomposition data were obtained using a 2200 Dupont thermal gravimetric analyzer (TGA). The differential scanning calorimetry (DSC) data were obtained using a Perkin-Elmer 7 series and DuPont 2200 thermal analysis systems. Electron-impact (EI) mass spectral data were obtained using a Hewlett-Packard 5890 GC in series with a Hewlett-Packard 5971 MS detector. The IR spectral data were obtained using a Biorad model FTS-7 FTIR spectrophotometer with a resolution of 4 cm^{-1}. The UV-Vis spectral data were obtained using a Hewlett-Packard 8457A diode-array spectrophotometer. The ^1H- and ^{13}C-NMR spectral data were obtained using a Bruker model AC 200 NMR spectrometer.

*2,6-Di-*tert*-butyl-4-nitrophenol (DBNP) synthesis*

A clear, pale-yellow solution of DBP (106 g, 0.5 mol) was prepared in hexane (400 ml) with gentle stirring. A fritted glass tube was connected to an NO_2 gas cylinder using polypropylene tubing and the gaseous reagent bubbled through the stirred solution at about 500 ml/min under ambient conditions, as indicated in Figure 2. [*Caution*: To prevent dissolution of the fritted portion of the tube, NO_2 bubbling should be performed while the tube is submerged in hexane]. Beige crystals began to precipitate after approximately

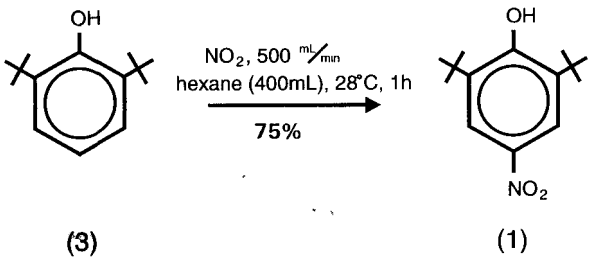

Fig. 2. Reaction conditions used for the synthesis of highly pure crystals of 2,6-di-*tert*-butyl-4-nitrophenol (DBNP) (compound 1).

20 min. The addition of NO_2 was ended after 1 h of reaction, at which time precipitate formation had stopped. The temperature of the reaction mixture at this time was 47°C. The solid was filtered and rinsed with three 50-ml volumes of hexane. The beige crystals were placed in boiling hexane (400 ml, 69°C) and the mixture sonicated to enhance dissolution. Fine needles recrystallized after cooling the solution to room temperature. Elemental analysis (Galbraith Laboratories, Knoxville, TX) of the purified product showed the chemical composition to be 67.09% C, 8.16% H, and 5.49% N. The theoretical values for DBNP are 66.95% C, 8.36% H, and 5.58% N. The HPLC analysis of the recrystallized product was performed by Sigma Chemical Company (St. Louis, MO) (ODS-2, 10 μm, 250 × 4.6 mm; 1 ml/min, 30% water and 70% acetonitrile; 210 nm) and indicated a purity of 99.5%. Filtrates were clear, orange solutions that contained dissolved NO_2, three other minor reaction products that were not identified, and high levels of DBP as evidenced by the use of GC-FID retention-time data to follow reaction progress.

RESULTS

DBNP physical and spectral characterization

X-ray crystallography. The single-crystal structure of DBNP grown from hexane is shown in Figure 3a. DBNP crystallizes in the acentric orthorhombic space group $Pna2_1$. Unit cell constants were determined from a least-squares fit of the angular settings of 25 reflections in the range of $7° < \Theta < 12°$. A total of 2,187 reflections were collected at room temperature with 838 over $3\sigma(I)$. Heavy atoms were refined anisotropically and hydrogen atoms isotropically. The final R was 0.042 with a weighted R of 0.045 [$w = 4 \cdot F_{obs}^2/(\sigma^2 \cdot F_{obs}^2 + 0.0016F_{obs}^4)$].

The nitro group is virtually coplanar with the aromatic ring and exhibits an O2—N—C4—C3 torsional angle of 0.4(6)° (see Fig. 3a for atom numbering). The hydroxy-group hydrogen H1 is rotated from the plane of the aromatic ring to exhibit the C6—C1—O1—H1 torsional angle of −17(4)°. Intermolecular atomic distances found were: O1 . . . O2, 2.841(4) Å; H1 . . . O3, 2.94(5) Å; and O1 . . . O3, 3.439(5) Å. An intermolecular hydrogen-bonding interaction was found between the hydroxy-group hydrogen H1 of one DBNP molecule and the nitro-group oxygen O2 of an adjacent one in a head-to-tail arrangement. The resultant hydrogen-bonding interaction H1 . . . O2 distance is 2.17(5) Å and the angle subtended by the intervening atoms O1 . . . H1 . . . O2 is 137(4)°. This configuration serves to maximize the intermolecular hydrogen-bonding interaction and relieves steric repulsion among intramolecular hydroxy and vicinal *tert*-butyl groups. Figure 3b shows a single-crystal stereoscopic pair for DBNP [unit-cell dimensions: a = 9.590(1), b = 13.111(3), c = 11.434(2) Å; unit-cell volume V = 1,437.6(7) Å^3; and the number of DBNP molecules per unit cell of Z = 4)].

TGA studies. The thermal stability of DBNP was tested by exposing the nitrophenol sample boat to a heated zone (10°C/min) containing helium flowing at a rate of 40 ml/min. The DBNP sample began to lose mass at about 125°C, achieved its fastest rate of mass loss at the extrapolated on-

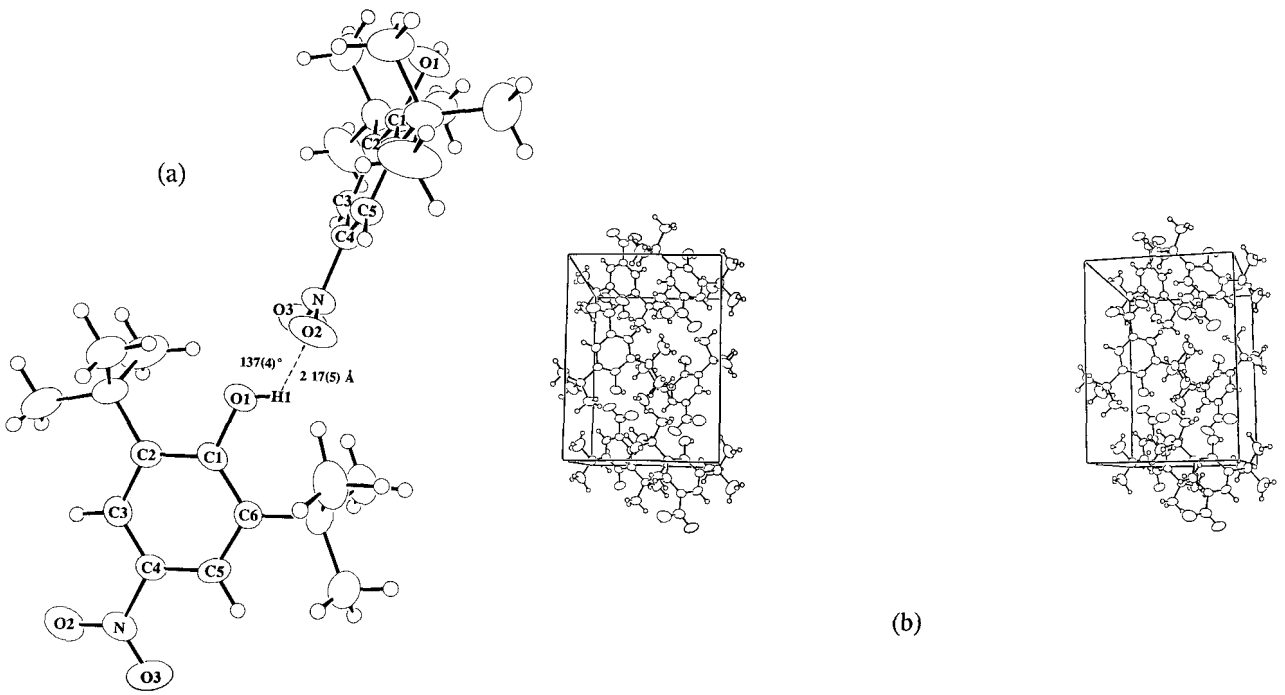

Fig. 3. **(a)** Single-crystal structure of 2,6-di-*tert*-butyl-4-nitrophenol (DBNP) produced by a FORTRAN thermal ellipsoid plot program [13] [compound (1) in Figs. 1 and 2] grown from hexane showing bond length and angle subtended by the intervening atoms involved in the hydrogen-bonding interaction. **(b)** Stereoscopic pair showing the presence of four DBNP molecules per unit cell.

set of 177.83°C, and lost 100% of its original mass at about 212°C. Note that an independent study showed that after 3 h of heating in dodecane at a temperature of 215°C, DBNP decomposed to form the compound 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (compound 4 in Fig. 1) [7]. Indeed, during the present study, it was evident that DBNP thermally decomposed (rearranged) to form a bright yellow compound that was not identified.

DSC studies. The DSC thermogram of the recrystallized DBNP (20°C/min) was obtained in an inert helium atmosphere at constant atmospheric pressure. The first thermogram consisted of one endotherm, which occurred at the extrapolated onset of 157.8°C (ΔH_1 = 123.5 J/g); whereas after cooling to room temperature and reheating, the same sample exhibited a new endotherm at the extrapolated onset of 152.49°C (ΔH_2 = 85 J/g). The DSC thermogram of some DBNP samples exhibited both endotherms concurrently. Thus, the data suggest that two well defined crystalline domains exist for DBNP. The proposed existence of two stable packing configurations is further supported by the typically encountered discrepancy in literature-reported melting point data for this nitrophenol (i.e., 152 to 153°C vs. 156 to 158°C).

GC-MS spectrometry. The GC-MS fragmentation pattern and relative intensities for DBNP obtained in the electron-impact (EI) mode at 70 eV were as follows: *m/z* cations = 175 (3.7%); 220 (4%); 192 (7%); 237 (14%); 251 (M^+, 17%); 208 (30%); and 236 (100%).

UV-Vis spectrophotometry. The UV-Vis spectral profile for DBNP in solvents of different polarity is shown in Figure 4. The data for each solvent tested are reported as λ_{nm} (ϵ_{nm},$cm^{-1} \cdot M^{-1}$): hexane, 230 (10,065), 300 (9,435); methylene chloride, 232 (7,906), 320 (10,092); methanol, 212 (10,997), 234 (7,818), 320 (9,291); and water [(pH 3: 194, 234, 334); (0.1 N NaOH, pH 12: 452 (30,507))]. The spectral parameter ϵ_{nm} was calculated using a five-point linear regression of dilute samples with absorbances of less than ca. 1 to ascertain linear Lambert-Beer's law behavior. The DBNP is practically insoluble at pH values below its pK_a (6.8); therefore, ϵ_{nm} values for absorption maxima at this pH were not calculated.

Fourier-transformed ^{1}H-NMR. ($CDCl_3$, Trimethylsilane [TMS], 200 MHz). The δ_{ppm} = singlet at 1.4795 for 2,6-$C(CH_3)_3$ protons; singlet at 5.9432 for −OH proton; and a singlet at 8.1270 for magnetically equivalent *H3* and *H5* (see structure in Fig. 3a).

Fourier-transformed ^{13}C-NMR. ($CDCl_3$, TMS, 200 MHz, broad-band ^{1}H-decoupled). The δ_{ppm} = singlet at 29.911 for 2,6-$C(CH_3)_3$; singlet at 34.550 for 2,6-$C(CH_3)_3$; a singlet at 121.343 for magnetically equivalent *C3*, *C5*; a singlet at 136.648 for magnetically equivalent *C2*, *C6*; a singlet at 140.741 for *C1*; and a singlet at 159.505 for *C4*. A triplet centered on 76.363, 76.999, and 77.636 results from the $CDCl_3$ solvent spin–spin interactions.

Fourier-transformed IR spectrophotometry. The KBr-pellet FTIR spectrum of hexane-recrystallized DBNP exhibited the following absorption ν_{max} values: 3,542 (sharp, not hydrogen-bonded (free) O−H symmetric stretch); 2,953 (C−H aliphatic symmetric stretch); 3,000, 3,100 (C−H aromatic symmetric stretch); 1,507 (NO_2 asymmetric stretch); 1,338, 1,305, 1,399 (NO_2 symmetric stretch and/or O−H in-plane bending); 1,240 (phenolic O−H bend), 1,103 (C−N stretching); and 684, 627, 546 cm^{-1} (−NO_2 rocking and wagging).

DISCUSSION

DBNP synthesis

Although the successful *p*-nitration of DBP to form DBNP is favored on the basis of thermodynamic and kinetic arguments, the exclusive precipitation of DBNP was strongly favored only under specific conditions in the present study. The following two empirical end points were found to be useful visual indicators that ascertained proper NO_2 delivery rates conducive to the formation of highly pure DBNP: (a) prevent effervescence of the reaction mixture early in the nitration by delivering NO_2 at an empirically determined flow rate for a particular volume of DBP–hexane solution [(e.g., in the present study, 500 ml/min of NO_2 for 400 ml hexane (0.5 mol DBP)]; and (b) discontinue NO_2 delivery when the reaction mixture begins to acquire an orange or brownish hue because the formation and the eventual coprecipitation of reaction by-products begin at this point.

When an attempt was made to increase the actual yield, the saturation of reaction mixtures with excessive amounts of dissolved NO_2 caused the decomposition of preformed DBNP and evolution of an unidentified gas. Indeed, a previous study has reported a similar occurrence in which a nitrogen-deoxygenated DBNP solution in benzene bubbled with NO_2 gas at an unspecified rate (10°C) resulted in the quantitative conversion of DBNP into 2,4-dinitro-6-*tert*-butylphenol (compound 5 in Fig. 1) [8]. Although a yield of 54% was obtained after the first reaction/filtration sequence, the average collective actual yield of 75% was obtained by nitrating unreacted DBP in the mother liquor (second reaction/filtration sequence) to the extent indicated by the empirically determined end points (a) and (b) defined above. When performing the second nitration, adding enough hexane to the mother liquor yielded a clear solution. This practice prevented coprecipitation of reaction by-products when the nitration step was repeated and thereby enhanced the purity of the final DBNP product.

DBNP physical and spectral characterization

The heretofore unreported scientific contention that DBNP crystallizes in two different configurations is supported by the presence of two DSC endotherms at 152.49 and 155.75°C. Although the stereochemistry of the two crystalline domains remains to be elucidated, their existence is further supported by the discrepancy in literature-reported melting point values typically encountered for this nitrophenol (152–153°C vs. 156–158°C). The X-ray single-crystal data for DBNP suggest the presence of one hydrogen-bonding interaction between the hydroxy-group hydrogen H1 of one DBNP molecule and the nitro-group oxygen O2 of an adjacent molecule in a head-to-tail arrangement (Fig. 3a). The H1 . . . O2 hydrogen-bonding interaction distance is 2.17(5) Å, and the angle subtended by the intervening O1 . . . H1 . . . O2 atoms is 137°. Indeed, this interaction is so weak to a degree that its presence escaped IR detection. The

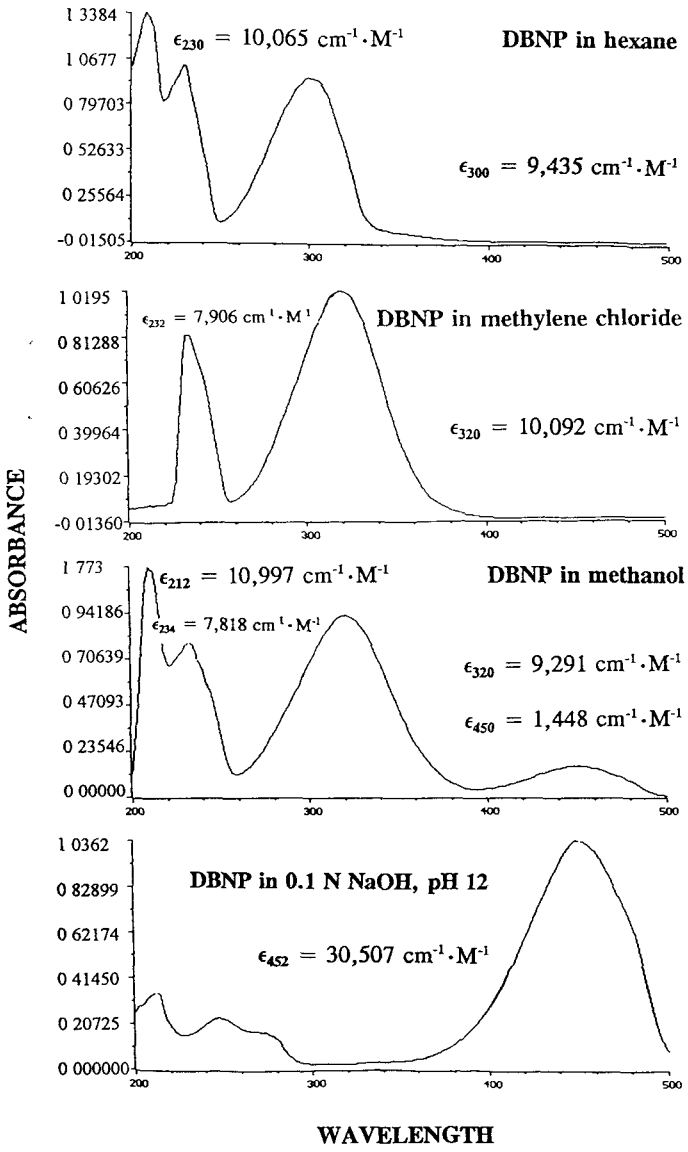

Fig. 4. UV-Vis spectra for DBNP [(compound 1) in Figs. 1 and 2] showing λ_{nm} maxima and corresponding absorption coefficient ϵ_{nm} values in solvents of different polarity.

role the hydrogen-bonding interaction plays in the stability and stereochemistry of the two putative crystalline domains remains to be elucidated by further crystallographic studies. On the basis of the UV-Vis data, suitable solvents for DBNP quantitative trace analysis are methanol (DBNP ϵ_{212} = 10,997 cm^{-1}·M^{-1}) and water buffered at pH 12 (DBNP ϵ_{452} = 30,507 cm^{-1}·M^{-1}).

DBNP toxicological relevance

The hypothesis that DBNP might express its intrinsic toxicity by uncoupling oxidative phosphorylation is supported by preliminary toxicity studies in this laboratory, which indicate that administration of DBNP (i.v. 3.3 mg DBNP/kg in DMSO as vehicle) to rodents causes a marked elevation in body temperature (hyperthermia) and death within 1 h, followed by the quick onset of rigor mortis. Both of these observations are consistent with depletion of ATP stores, that is, disruption of mitochondrial respiration, possibly caused by the obliteration of electrochemical proton gradients across the inner mitochondrial membrane. With a pK_a value of 6.8 and a higher degree of lipophilicity, DBNP may prove to be a stronger uncoupler of oxidative phosphorylation than 2,4-dinitrophenol (pK_a = 4.09) due to the expected enhancement of its passive diffusion kinetics across biological membranes.

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