J. Phys. Chem. A **2007,** *111,* 2587−2601

Elusive Forms and Structures of *N*-Hydroxyphthalimide: The Colorless and Yellow Crystal Forms of *N*-Hydroxyphthalimide

Hendrik Reichelt, Chester A. Faunce, and Henrich H. Paradies*

Joule Physics Laboratory, Materials Research Institute, The University of Salford,
Greater Manchester M5 4WT, United Kingdom

Received: December 14, 2006; In Final Form: February 2, 2007

A comprehensive structural characterization of the colorless and yellow forms of *N*-hydroxyphthalimide (NHP), the deuterated form (NDP), and the ethoxylated form (ethoxy-NHP) has been carried out using single-crystal X-ray diffraction, FTIR and Raman spectroscopies, and scanning electron microscopy. Both NHP and NDP forms crystallize in the monoclinic space group ($P2_1/c$, No. 14). The various forms of NHP differ in the way in which the molecules adjoin one another through their *N*-hydroxyl groups and how the carbonyls of the isoindole-1,3-dione ring differ through intermolecular hydrogen bonding. Although the hydrogen bonding about the *b* axis is virtually the same, the isoindole-1,3-dione ring experiences different twists for the two NHP forms. Both the colorless and yellow forms of NHP exhibit strong intermolecular hydrogen bonding between O(3) and H(1). In the yellow form, the *N*-hydroxyl group is significantly out of the plane (∼1.19°), but the *N*-hydroxyl group in the colorless form is only ∼0.06° out of the plane. Both forms of NHP reveal an infinite chain of intermolecular hydrogen-bonded molecules in the direction of the *b* axis; however, the molecules are ordered differently within the unit cells. The hydrogen-bond geometry for the yellow form of NHP is O(2)−H(1)···O(3), with an angle of 185°, intermolecular distances of O(2)···O(3) = 2.68 Å and H(1)···O(3) = 1.70 Å, and an intramolecular hydrogen bond of O(1)···H(1) = 1.17 Å. The colorless form of NHP shows an intermolecular hydrogen-bond geometry between O(3) and H(1) with a distance of 1.78 Å; the O(2)−O(3) distance is 2.71 Å. The O(2)−H(1)···O(3) angle is 159°, and the intramolecular distance is O(1)···H(1) = 0.97 Å. The *N*-ethoxy derivative of NHP crystallizes in an orthorhombic space group (*Pnma*, No. 62) and exhibits no hydrogen bonding, displaying a strong head-to-tail stacking of the planar rings along the needle axis direction.

Introduction

Polymorphism, the existence of more than one crystalline form of a material, is a frequently observed phenomenon in molecular crystals; however, the control and understanding of this phenomenon remain limited.[1] Polymorphism also plays a significant role in active pharmaceutical ingredients and might be critical from both regulatory and intellectual-property perspectives.[2] Polymorphs exhibit different physical and/or chemical properties depending on the flexibility of the material, the nature of the solvent, the temperature, and other conditions related to crystal growth.[3] Active pharmaceutical polymorphs have also been modified using templates such as amino acids and amino sugars[4] and have been employed as solvates and salts. Pharmaceutical cocrystallization of biologically active compounds has also been successfully applied recently and described in a report on the cocrystallization of aspirin with levitiracetam.[5] When different possible structures of a compound have similar energies, the relative stabilities of the alternative structures can be influenced by changes in solvent, concentration, temperature, and cooling rate. Structural stability can also be altered by other experimental variables, such as whether crystallization is from solution, sublimation, or a melt. All of these parameters can result in a profusion of polymorphs, many of which have not been studied or found systematically.[6]

N-Hydroxyphthalimide (2-hydroxyisoindole-1,3-dione, NHP; Figure 1A) was first reported in 1880;[7] however, renewed interest has grown in this material as a useful catalyst on an industrial scale in the production of cyclohexyl nitrate from cyclohexane and of 2-methyl-2-nitropropane from isobutene.[8] The molecule has also proved to be extremely useful in the oxidation of organic substrates by molecular oxygen, where NHP and acetaldehyde have been used as oxidation mediators.[9] NHP has also been employed in selective catalytic oxidation, using dioxygen as the primary oxidant. This represents a critical technology in an area of continuing research and development.[10] The molecule has been found to be an efficient electron carrier in electrochemical oxidation, converting secondary alcohols to ketones.[11] Daicel of Tokyo has used NHP in the development of custom production in proprietary air-oxidation technology,[12] and it can also be used to oxidize cyclohexane to adipic acid and *p*-xylene to *p*-toluic acid in the presence of Mn^{2+} or Co^{2+} salts. A further use of the system is to mediate the reaction of adamantane with carbon monoxide and oxygen to form 1-adamantanecarboxylic acid.[13] When long-wavelength light (>300 nm) is used, hydroperoxides efficiently generate hydroxyl radicals without the use of metal ions and would be an extremely useful source of hydroxyl radicals, particularly in the design of DNA-cleaving molecules.[14] It is also apparent that the anion of NHP in solution is highly chromophoric in nature and that the corresponding "salts", e.g., Me^+ (Na^+, K^+, NH_4^+, Li^+, Cs^+, and Ag^+) and Me^{2+} (Co^{2+}, Cu^{2+}, Mn^{2+}), have a complex

---

* Corresponding author. Phone: +44-161-295-4286 or +49-2371-12305. Fax: + 44-161-295-5575 or +49-2371-149705. E-mail: HParadies@aol.com.

10.1021/jp068599y CCC: $37.00 © 2007 American Chemical Society
Published on Web 03/14/2007

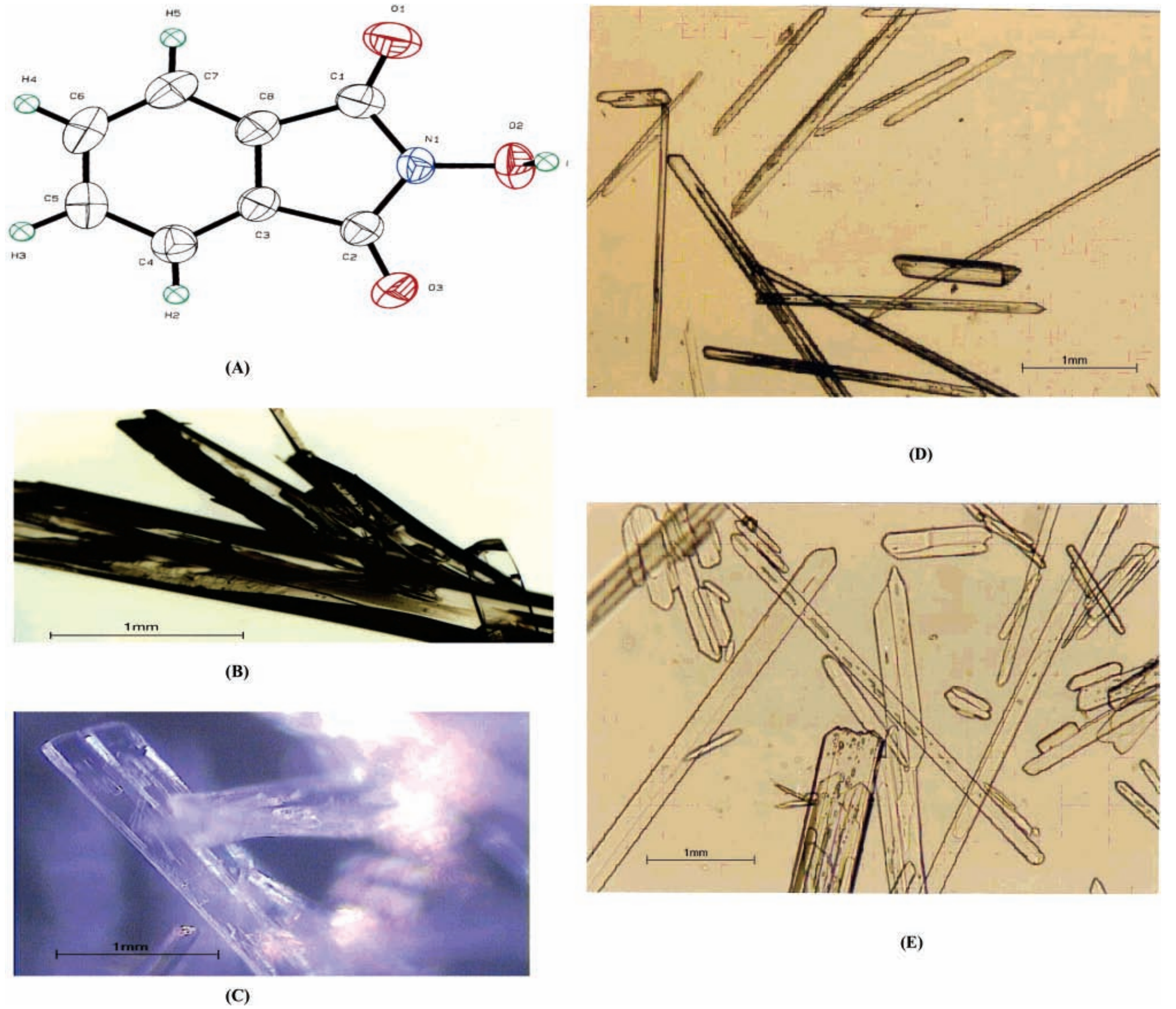

Figure 1. (A) Molecular structure of *N*-hydroxyphthalimide (NHP) drawn at the 50% probability level. Morphologies of (B) the colorless form of NHP I, (C) the yellow form of NHP, (D) the light-yellow form of NDP, and (E) the light-brown form of NDP. All forms were grown from the appropriate solvents at 20 °C, e.g., *n*-hexane for the colorless form and ethanol for the yellow form of NHP (see text).

structure.[15] However, these are very different forms of the known oxime−metal complexes.[15] The two crystalline forms of NHP reportedly display different colors, colorless (white) and yellow, with the colors depending on the solvent in which the NHP is synthesized.[16] The cause of the different colors, i.e., whether the forms are different structures, polymorphs, or metastable compounds, has never been explained. Studies of the material undertaken since the late 1950s have been inconclusive, and the differences in physical properties such as the results of UV−absorption spectra from various solvents have all proved to be very similar. The variations in physical properties, including color, have been attributed to synthesis problems,[17] such as oximes, impurities, and contamination from a fluorescent compound that could not be isolated or characterized. Thus, it would seem that *N*-hydroxyphthalimide (2-hydroxyisoindole-1,3-dione) is somewhat of an enigma.

The anomalies mentioned above provided the impetus in initiating this investigation. In this article, the conformational characteristics of the various crystalline forms of NHP with respect to packing, hydrogen bonding, and vibrational properties are elucidated. The hydroxyl group at the nitrogen is the only functional chemical group in the NHP molecule. This hydroxyl group appears to have a marked influence on the elusive forms of NHP (colorless and yellow), as well as on the deuterated form. Deuteration takes place only at the hydrogen of the N−O−H moiety. Another promising chemical modification was found from ethoxylation and by analyzing the *N*-ethoxy compound of NHP. It was, therefore, necessary to carefully prepare and analyze the various forms of the molecule, with respect to the impurities that can be acquired in the crystallization processes. The deuterated and ethoxylated forms of NHP enabled us to monitor the influence of the N−O−H conformational moiety and possible changes in the hydrogen-bonding pattern. More specifically, these patterns include intermolecular vs intramolecular hydrogen bonding within the various NHP crystal lattices. Information as to the structures of the NHP material under investigation was ascertained from the history of the molecule, i.e., how it was obtained and from which solvent the crystalline material was grown. In this investigation, different NHP structures were studied using FTIR and Raman spectroscopy and X-ray diffraction. One can infer from the combined experiments that there are at least two different packing motifs of NHP and that the presence of these motifs depends mainly on the solvent conditions, composition, and chemical purity (e.g., absence of alkali) at ambient temperature. It is, therefore, anticipated that this work will pave the way toward a more comprehensive understanding of the physical formation of the various crystal forms and provide a greater basic insight into the reactivity of NHP as a catalyst.

Experimental Section

A. Materials. Ethanol, methanol, acetone, ethyl acetate, toluene, benzene, xylene, *n*-hexane, cyclohexane, and acetic acid were of HPLC grade and were checked by measurements of the refractive index increment $(dn/dc)_{\mu,T}$ (20 °C); all were purchased from Merck AG, Darmstadt, Germany. Water was triply distilled (Quartz Apparatus from Heraeus, Heilbronn, Germany). Hydroxylamine hydrochloride was purchased from Aldrich and was of ACS grade, and sodium carbonate obtained from Merck AG, Darmstadt, Germany. D_2O and methyl iodide (ACS grade) were purchased from Aldrich (Milwaukee, WI).

B. Synthesis of the White Form of *N*-Hydroxyphthalimide. Hydroxylamine hydrochloride (13.01 g, 187.2 mmol) was added to 50 mL of toluene or benzene that had been preheated to 55 °C under continuous stirring. Sodium carbonate (22.02 g, 148.7 mmol) was then slowly added until all of the inorganic salt had dissolved. When the hydroxylamine hydrochloride and sodium carbonate had completely dissolved, phthalic anhydride was slowly added under constant stirring with the temperature maintained at100 °C. After a short period of time, the solution became turbid and viscous; heating was continued for 30 min, and then the solution was cooled to 5 °C. Fine, needlelike colorless crystals of NHP then appeared that could be collected from nonpolar solvents, e.g., toluene, benzene, *n*-hexane, *n*-pentane, and cyclohexane with a Buchner funnel. The melting point of the crystals was 238.4 °C (corrected), and a yield of 33% of theoretical was obtained.

C. Synthesis of the Yellow Form of *N*-Hydroxyphthalimide. Hydroxylamine hydrochloride (13.01 g, 187.2 mmol) was added to 50 mL of water (ethanol, methanol, acetone, or ethyl acetate), under stirring, after the solvent had been preheated to 55 °C. Sodium carbonate (22.02 g, 148.7 mmol) was then added as described for the colorless form of NHP. After the hydroxylamine hydrochloride and sodium carbonate had completely dissolved, phthalic anhydride was slowly added with continuous stirring. After several minutes, the solution became orange, and after 10 min, a thick pale yellow slurry formed. Another 50 mL of water (ethanol, methanol, acetone, or ethyl acetate) was then added, and heating at between 50 and 60 °C was continued for 1 h. The solution was chilled and acidified with hydrochloric acid (acetic acid) until the strong yellow color disappeared. The yield was 71% of theoretical, mp 240.5 °C (corrected). The compound could also be recovered by refluxing in glacial acetic acid for several hours followed by recrystallization from ethanol, methanol, water, acetone, or ethyl acetate

D. Crystallization. Single crystals of the colorless and yellow forms of NHP (NDP) were grown from different solvents, namely, ethanol, isopropanol, and acetone for the yellow form of NHP (NDP) and benzene, toluene, cyclohexane, and *n*-hexane for the white form of NHP (NDP). The transition of the yellow form of NHP (NDP) to the white form of NHP (NDP) was studied by dissolving crystals of the yellow form in solvents such as *n*-hexane, benzene, toluene, and cyclohexane. It is critical that all crystallizations take place in polyethylene vials in order to avoid any contact with inorganic cations, e.g., sodium, potassium, or calcium. A typical crystallization procedure for the white form of NHP (NDP) consists of dissolving 5 mg of *N*-hydroxyphthalimide in 20 mL of *n*-hexane (cyclohexane, benzene, toluene), heating the solution for 5 min to 50 °C, cooling the solution to 20 °C, removing all particulate matter through centrifugation at 10000 rpm (Beckman J2-22 centrifuge, 20 °C), and slowly evaporating the solvent over a period of 1 h. However, precautions must be applied to exclude any moisture or unspecified water of unknown purity, and a temperature between 15 and 20 °C must be maintained.

E. Synthesis of Deuterated *N*-Hydroxyphthalimide (NDP). NDP was prepared by exchanging the hydrogen of the *N*-hydroxy group with D_2O under reflux in a N_2 atmosphere for 2 h. The material was crystallized from ethanol or *n*-hexane as described in section C above. The following melting points were determined: 115 °C for the yellow form and 127 °C for the white form of NDP. The NDP was analyzed by GC-MS spectroscopy (HP 6890 Series) and elementary analysis and was evaluated for the amount of deuterium.

F. Synthesis of *N*-Ethoxyphthalimide (Ethoxy-NHP). The ethoxy derivative of NHP (ethyl ether of NHP) was prepared by reacting stoichiometric amounts of NHP (colorless or yellow, 1 mg, 162 mM) and 1-chlorethane (162 mM) or 1-iodoethane in 1,2-dimetyloxyethan or acetonitrile (10 mL) in the presence of pyridine (0.5 mL) at 5 °C in the presence of 4.5-Å zeolites.[17] The reaction with either 1-iodoethane or 1-chlorethane was completed after 15 min. The ethoxy-NHP was extracted with ethanol (20 °C), separated from unreacted 1-chlorethane or 1-iodoethane, suspended in H_2O (20 °C), and extracted again with ethanol. Ethoxy-NHP melts at 113 °C and, upon crystallization from ether or benzene, forms colorless prisms (Table 1). The ethoxy-NHP was analyzed using GC-MS spectroscopy (HP 6890 Series) and elementary analysis. The obtained ethoxy-NHP was identical in composition to that reported by Orndorff and Pratt.[19,20]

Warning: NHP and derivatives thereof are not hazards per se; however, they can cause irritation to the eyes, respiratory system, and skin.

G. Crystallography. Single crystals were mounted on a glass fiber, and all measurements were made on a Rigaku AFC5R diffractometer with a 12-kW rotating-anode generator; graphite-monochromated Cu Kα radiation was used for colorless and yellow NHP and ethoxy-NHP, and Mo Kα radiation was used for the corresponding NDP crystals. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $51.86° < 2\theta < 78.85°$. The data were collected at a temperature of 23 ± 1°C using the $\omega-2\theta$ scan technique to a maximum 2θ value of 120.1°. ω scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.42° and a takeoff angle of 6.0°. Scans of $(1.37 + 0.30 \tan \theta)°$ were made at a speed of $32.0°\ \text{min}^{-1}$ (in ω). The weak reflections $[I < 10.0\sigma(I)]$ were rescanned (maximum of two rescans), and the counts were accumulated to ensure good counting statistics. The structures were solved by direct methods.[21−24] The structure factors computed from the various NHP models, applying equal isotropic temperature factors for all atoms, gave a residual of $R = 0.098$, a value sufficiently low to indicate the overall correctness of the model before refinement. The non-hydrogen atoms were refined anisotropically. Hydrogen-atom positions were located from difference Fourier maps, and a riding model was used in subsequent refinements with fixed thermal parameters $[u_{ij} = {}^{1}/_{2}U_{ij(\text{eq})}]$ for the atoms to which they were bonded. The deuterium atoms were treated crystallographically in the same way as the hydrogen atoms in the refinement. The structural homogeneity of the crystalline NHP and NDP samples

TABLE 1: Crystal Data and Refinement of (A) the Two Colorless Forms of NHP, (B) Yellow NHP and Light Yellow NDP, and (C) Light-Brown NDP and Ethoxy-NHP at $T = 295.5$ K[a]

	(A) Two Colorless Forms of NHP		(B) Yellow NHP and Light Yellow NDP		(C) Light-Brown NDP and Ethoxy-NHP	
empirical formula	$C_8H_5NO_3$, colorless NHP I, needle plates	$C_8H_5NO_3$, colorless NHP II prisms	$C_8H_5NO_3$, yellow prisms	$C_8H_4DNO_3$, light-yellow plates	$C_8H_4DNO_3$, light-brown plates	$C_{10}H_9NO_3$, *N*-ethoxy, colorless needles
mol weight	163.13	163.13	163.13	164.13	164.13	191.19
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic
space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	*Pnma* (No. 62)
Z value	4	4	4	4	4	4
crystal dimens (mm)	0.400 × 0.120 × 0.050	0.300 × 0.100 × 0.040	0.500 × 0.050 × 0.030	0.500 × 0.200 × 0.100	0.650 × 0.300 × 0.100	0.500 × 0.080 × 0.060
a (Å)	11.570(1)	11.565(3)	11.538(1)	11.582(1)	8.3463(9)	7.505(1)
b (Å)	3.761(2)	3.710(5)	3.7005(6)	3.771(2)	5.644(2)	10.619(2)
c (Å)	16.4685(9)	16.421(8)	16.3930(6)	16.485(1)	14.8656(9)	11.885(1)
β (deg)	104.991(6)	104.97(2)	105.254(4)	104.982(7)	96.821(7)	90.0
V (Å)^3	692.3(4)	680.6(4)	675.3(1)	695.4(3)	695.3(2)	947.2(4)
d_{calc} (g·cm^{-3})	1.569	1.598	1.605	1.558	1.558	1.340
d_{meas} (g·cm^{-3})	1.570	1.590	1.601	1.600	1.600	1.345
F(000)	336	336	336	336	336	400
μ(Cu Kα) (mm^{-1})	9.95	9.98	10.20		−	7.99
μ(Mo Kα) (mm^{-1})				11.40	11.40	−
$2\theta_{max}$ (deg)			120.1	50.0	50.0	119.9
no. reflns measured	total 1285 unique 1221	total 1270 unique 1220	total 1248 unique 1183	total 1513 unique 1440	total 1456 unique 1360	total 860
no. obsd reflns [$I > 3\sigma(I)$]	862	860	789	785	884	466
no. variables	130	129	129	130	130	71
reflns/params	6.63	6.60	6.12	6.04	6.80	6.56
GOF[b] on F^2	1.84	1.73	1.69	1.34	1.43	1.72
final *R* indices[c] [$I = 3\sigma(I)$]	R1 = 0.035, wR2 = 0.047	R1 = 0.037, wR2 = 0.048	R1 = 0.042, wR2 = 0.054	R1 = 0.038, wR2 = 0.042	R1 = 0.034, wR2 = 0.040	R1 = 0.043, wR2 = 0.052
P factor	0.03	0.03	0.00	0.03	0.00	0.03
max shift/error in final cycle	0.0000	0.0000	0.0000	0.0000	0.0000	0.09
max peak in final diff map	0.13 e$^-$/Å^3	0.15 e$^-$/Å^3	0.20 e$^-$/Å^3	0.19 e$^-$/Å^3	0.17 e$^-$/Å^3	0.14 e$^-$/Å^3
min peak in final diff map	−0.15 e$^-$/Å^3	−0.18 e$^-$/Å^3	−0.23 e$^-$/Å^3	−0.13 e$^-$/Å^3	−0.12 e$^-$/Å^3	−0.16 e$^-$/Å^3

[a] For both structures, refinements were performed by full-matrix least-squares on F^2. [b] GOF = $\{\sum[w(F_o^2 - F_c^2)^2]/[(\text{no. of reflns}) - (\text{no. of params refined})]\}^{1/2}$. [c] R1 = $\sum||F_o| - |F_c||/\sum|F_o|$, wR2 = $[\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2}$, $w = 1/[\sigma^2F_o^2 + (aP)^2]]$, with $P = (F_o^2 + 2F_c^2)/3$ and $\sigma^2(F_o^2) = [S^2(C + R^2B) + (PF_o^2)^2]/Lp^2$, where *S* is the scan rate, *C* is the total integrated peak count, R is the ratio of the scan time to the background counting time, *B* is the total background count, and Lp is the Lorentz polarization factor.

was assessed by comparing experimental X-ray powder data with simulated powder patterns based on single-crystal data. The final cycle of full-matrix least-squares refinement was based on 789 observed reflections [$I > 3.00\sigma(I)$] and 129 variable parameters and converged (largest parameter shift was 0.0001 times its esd) with unweighted and weighted agreement factors. Additional details of the structure solution and refinement are reported in Table 1. X-ray powder diffraction was carried out using a Rigaku XRD Ultima III 3000 powder diffractometer equipped with a fine-focus X-ray tube using Ni-filtered Cu Kα radiation. The tube voltage and amperage were set at 30 kV and 25 mA, respectively. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted intensities were detected with a NaI scintillation counter, using $\theta-2\theta$ continuous scans at 1.5°/min with a step size of 0.02° from 5° to 40° in 2θ. The instrument was calibrated with a SiO_2 standard. Furthermore, powder diffraction patterns were also calculated from the various single-crystal structures of NHP and compared with the experimental powder patterns.

H. Vibrational Spectroscopy. Raman spectra were recorded using a Fourier transform Raman spectrometer (Bruker RFS 100/S) with an InGaAs detector and a ~300-mW Nd:YAG laser. The spectra were recorded at 2 cm^{-1} resolution with the detector at room temperature (cutoff at ~3450 cm^{-1} by 50 scans). The low-frequency limit of 150 cm^{-1} was imposed by the filters used to eliminate the Rayleigh-scattered radiation at 1065 nm.

Infrared spectra (400−4000 cm^{-1}) were recorded from powdered KBr disks, small crystals, or Nujol dispersions using a Bruker FTIR spectrometer at 1 cm^{-1} resolution at room temperature using 360 scans. Special care was taken in sample preparation to ensure the insolubility of NHP in the mulling medium (Nujol), the absence of water unless it was an essential constituent of the solvents, and the prevention of lattice distortions during pulverization and grinding.[25]

I. Differential Scanning Calorimetry (DSC). DSC experiments were performed using a Perkin-Elmer model DSC-4 differential scanning calorimeter with a 25 mL/min flow of helium as the purge gas. Crystals of NHP and derivatives were heated at a rate of either 5 or 20 °C/min. The instrument was calibrated using indium and mercury.

J. Scanning Electron Microscopy. The morphologies of the various NHP crystal forms were characterized by imaging the Au-coated crystals at a voltage of 20 or 7 kV using a scanning electron microscope (JEOL 6400).[26]

Results and Discussion

Crystallization and Morphology. The yellow crystalline form of NHP was obtained from solutions containing ethanol, methanol, acetone, water, and acetic acid, strong hydrogen-bond-forming solvents. The colorless crystalline form of NHP (NHP I) was formed from solvents such as cyclohexane, benzene, toluene, and xylene, which are typically weakly interacting solvents. The colorless form of NHP could also be recovered by recrystallization of the yellow form of NHP from solvents such as cyclohexane, *n*-hexane, benzene, and xylene (all water-free). The crystals formed during recrystallization revealed the same crystallographic unit-cell dimensions and space groups as those formed by the synthesis technique. Attempts to obtain the colorless form of NHP by recrystallization of the yellow form from ethanol, water, and glacial acetic acid were unsuccessful. It was possible to grow colorless prismatic crystals by dissolving the yellow form in water at an elevated temperature and then cooling to 20 °C. However, these crystals were not the same as those obtained from either xylene or benzene. Although NHP is only slightly water-soluble, colorless NHP crystals of NHP (NHP II) of the same shape as those obtained from the synthesis could be extracted from benzene solutions containing 10% (v/v) water. The synthesized colorless crystals (NHP I) had a melting point of 237.5 °C, whereas the crystals formed in solvents containing water had a melting point of 240.5 °C.

Inspections of the morphology of the colorless and yellow crystals of NHP (Figure 1B and C) using a polarizing microscope confirmed the monoclinic symmetry revealed by the parallel extinction from the basal plane of the colorless NHP I single crystals. Double refraction was found to be very strong from the synthesized colorless crystals (NHP I); however, the double refraction was significantly reduced from the crystals formed in xylene-containing water (0.1−15% v/v). The crystals formed in solvents containing water appeared as prismatic needles. Differences were also seen in the crystal structure and molecular packing of the crystals produced in water-containing solvents. The colorless NHP was found to be optically negative, with a large optical angle and weak dispersion (blue > red). In contrast, crystals of the yellow form exhibited a different habit plane and appeared as flattened and elongated crystals rather than the orthopinacoidal or prismatic shape of the colorless forms. The angles of the yellow form appear to be identical to those of the colorless NHP I form. However, the yellow crystals show pleochroism: in the yellow form, one or both of the rays are normal to the *b* axis and exhibit a yellow color as previously described,[17] whereas in the colorless crystals, the rays vibrate parallel to the *b* axis and exhibit no color. A table of angles can be found in the Supporting Information (S1).

SEM Examinations of the Various NHP and NDP Crystal Forms. Presented in Figure 2 are SEM images of the various crystals forms of NHP and NDP. Crystals of the colorless forms of NHP I and NHP II are shown in Figure 2A,B. Thin, flat, rectangular crystals with sharp morphological faces characterize the colorless form of NHP I. These NHP I crystals show striations running along the long crystal axis, and with increasing electron-beam current, cracks occur parallel to this axis. NHP II crystals recovered from 10% (v/v) water/90% (v/v) benzene solution (Figure 2B) are columnar in shape with rounded edges and fracture normal to the crystal axis. These colorless NHP II crystals resemble the yellow form of NHP in morphology (Figure 2C), and this form also fractures normal to the long crystal axis but the fractures are sharper and less irregular. The morphologies of the two deuterated NHP forms are shown in Figure 2D,E. The light-yellow form takes on the appearance of thin rectangular platelets, but the light brown form reveals a more massive layered structure.

Crystal Structures of Colorless and Yellow *N*-Hydroxyphthalimide. The two crystalline NHP morphological modifications crystallize in the same monoclinic space group $P2_1/c$ (No. 14) and have similar cell dimensions (Table 1). The refined atomic positions for both forms of NHP are reported in Supporting Information S2, including intermolecular bond lengths, non-close contacts, bond angles, and conformational angles. Listed in Table 2 are the structural parameters of the colorless form (obtained from dry unpolar solvents, e.g., benzene) and the yellow form (obtained from, e.g., dry ethanol, isopropanol) of NHP. Good-quality refinements for both crystal forms were obtained and further substantiated by analysis of the thermal parameters from the X-ray study (see Supporting Information S2). The molecular vibrations are reasonably well described by the rigid body model; however, the hydrogen atoms and, to a lesser extent, the carbonyl oxygens do exhibit slightly enhanced thermal motions. Perhaps ORTEP[27] best illustrates the slightly enhanced motions of the oxygen atoms, which are out of the plane of the molecule (Figure 1A).

Given in the Supporting Information (S3) are the patterns of the closest nonbonded contacts and lists of intermolecular contacts for the two NHP structures, along with the hydrogen atoms of the phenyl ring and the carbonyl oxygens of neighboring molecules.

A significant feature of the structures is the conformation of the *N*-hydroxyl group involved in the hydrogen bond to an adjacent NHP molecule. The molecule, in turn, is hydrogen-bonded to O(3) of yet another NHP molecule farther along the *b* axis, forming a chain. The hydrogen-bond geometry for the yellow form is as follows: O(2)−H(1)···O(3) forms an angle of 185°, and the intermolecular distances are O(3)···O(1) = 2.675(3) Å and H(1)···O(1) = 1.70(4) Å. The corresponding values for the colorless form of NHP are as follows: O(2)−H(1)···O(3) forms an angle of 159°, and the intermolecular distances are O(3)···O(1) = 2.695 Å, and H(1)···O(1) = 0.975 Å (Table 3). The above information confirms the existence of a loosely linked network of NHP molecules along the *b* axis, vibrating in a manner that can be described as rigid-body motions. At room temperature, the atoms intrinsic to the ring system undergo a slightly enhanced motion that is both directional and vibrational. The terminal atoms undergo interactions of a weak nature, suggesting that these interactions are not the only controlling factor in determining the magnitude of the additional thermal motions. All of the NHP and NDP structures are centrosymmetric and contain equal numbers of molecules in the unit cell, with the exception of ethoxy-NHP, for which only one form was found. No intermolecular contacts or special packing motifs appear significant in the colorless and yellow NHP forms, apart from the intermolecular hydrogen bonds and the different conformations of the isoindole-1,3-dione ring. This indicates that the primary mode of molecular association of NHP and NDP in these crystals is van der Waals or dipole−dipole interactions. It can be seen from Table 3 that only a few closest-bonded contacts are within the accepted lengths and angles for hydrogen bonding for both the NHP and NDP forms. Generally, the NHP molecules pack in a herringbone motif, with contacts except those of hydrogen bonding between the hydrogens of the phenyl ring and the face of the aromatic ring in a neighboring molecule (Figure 3, Figure 1 in Supporting Information S3). These contacts are between nearly perpendicular NHP molecules in the *a* and *c* directions, whereas the hydrogen-bond network is extended along the *b* axis and is stabilized by dispersive $\pi\cdots\pi$ interactions. There are layers stacked in the *c* direction, where the only contacts are between

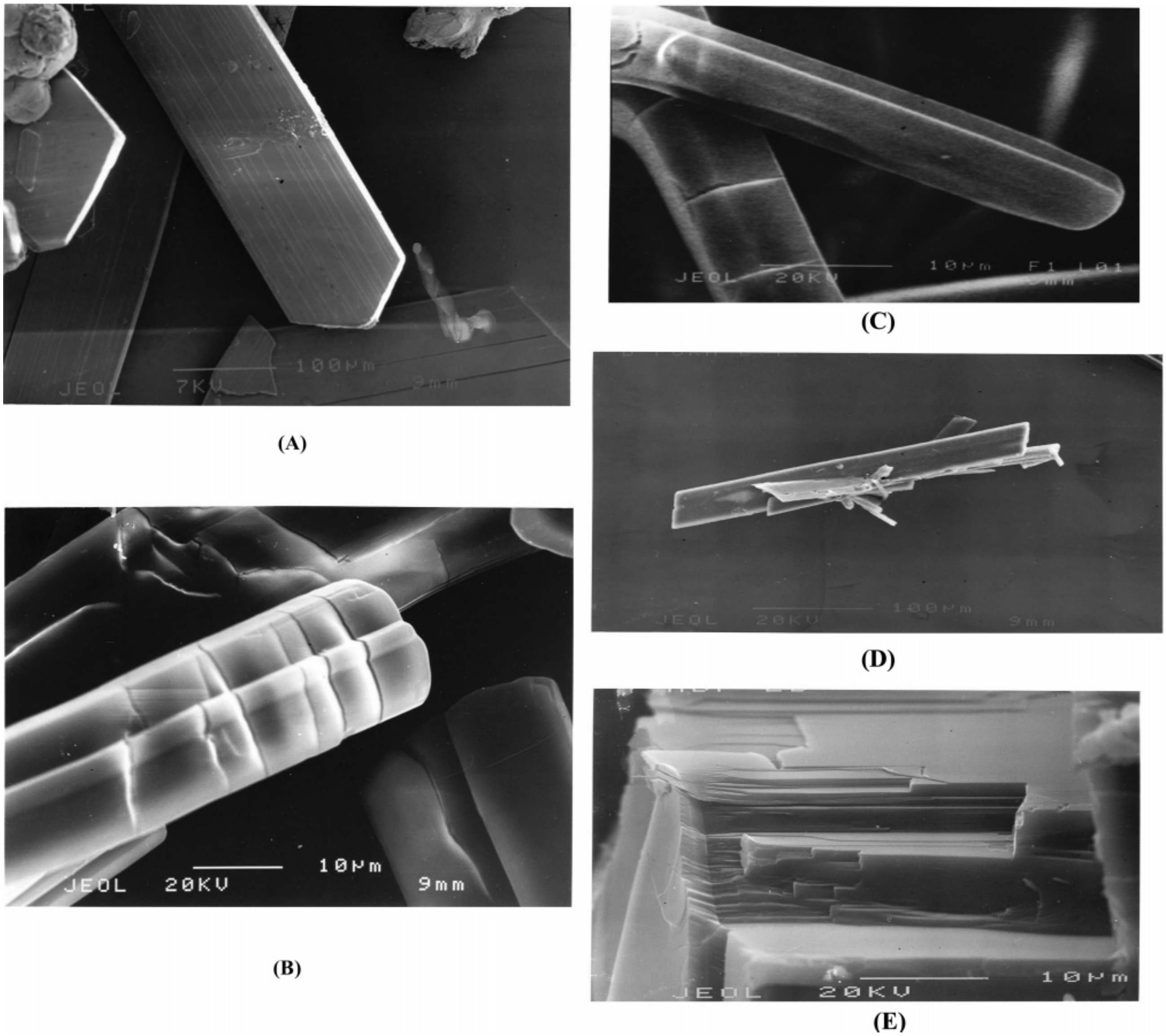

Figure 2. Various SEM images of the different polymorphic forms of NHP: (A) colorless NHP I, (B) colorless NHP II, (C) yellow NHP, (D) light-yellow NDP, and (E) light-brown NDP.

aromatic hydrogens. The geometry of the C−H····O angles is also indicative of hydrogen bonding. The hydrogen-bond pattern of the deuterated forms of NHP is certainly different from that of the undeuterated forms. Accordingly, a strong intramolecular deuterium−nitrogen bond is observed in both deuterated forms, in addition to the very strong intermolecular hydrogen bonds observable in both the light-yellow and light-brown NDP forms (Figure 4).

There are some significant differences in some of the covalent bond angles and lengths of the colorless and yellow forms and both deuterated forms (Table 2). There are also noticeable structural changes in the colorless and yellow forms of NHP with respect to differences in the bond angles, conformational angles, and bond lengths (Table 2 and Supporting Information S4). Differences can also be detected in the packing efficiencies, densities, and dihedral angles between the planes of the six-membered ring (phenyl) and the fused five-membered ring (isoindole-1,3-dione). The packing efficiency also accounts for the differences: the packing efficiency of the colorless form is 0.6072 with a density of 1.569 g/cm^3, and the packing efficiency of the yellow form is 0.6222 with a density of 1.604 g/cm^3. The corresponding values of the light-yellow and light-brown forms of NDP are 0.6272 and 1.55 g/cm^3 and 0.6370 and 1.56 g/cm^3, respectively.

In both NHP forms, the six carbon atoms of the phenyl ring approach coplanarity, but the atoms of the isoindole-1,3-dione ring are significantly nonplanar. In the colorless form, the distances of the carbonyl carbons from the best plane through the atoms of the isoindole-1,3-dione ring range from −0.0192 to 0.0219 Å, with O(1) and O(2) lying −0.0655 and −0.1132 Å from the plane, respectively. For the yellow form, the corresponding distances range from 0.0209 to −0.0224 Å, with O(1) and O(2) lying 0.0646 and 0.2051 Å from the plane, respectively. The "bowing" effect of the carbonyls in the isoindole-1,3-dione ring has been reported for quinones and also for halogenated quinones.[28] The mean deviation of the isoindole-1,3-dione ring from planarity is 0.0176 Å for the yellow form and only 0.0163 Å for the colorless form (NHP I). The nitrogen is out of the plane by 0.0219 ± 0.0018 Å in the colorless NHP form (NHP I) and by −0.0244 ± 0.0026 Å in the corresponding yellow form. The oxygen of the colorless form (NHP I) is out of the plane by −0.156 Å, and that of the yellow form is out of the plane by 0.0121 Å. In general, the dihedral angle between plane 3 [defined by O(1), C(1), N(1), C(2), O(3), C(3), C(4),

TABLE 2: Structure Parameters for (A) Colorless NHP I, (B) Colorless NHP II, (C) Yellow NHP, (D) Light-Yellow NDP, and (E) Light-Brown NDP

	intramolecular distances (Å)				
bond	A	B	C	D	E
O(2)−N(1)	1.381(2)	1.370(2)	1.370(3)	1.380(3)	1.379(2)
O(2)−H(1) or O(2)−D(1)	0.97(3)	1.00(1)	1.03(4)	0.98(4)	0.95(3)
O(1)−C(1)	1.20(2)	1.210(4)	1.212(3)	1.200(3)	1.216(2)
O(3)−C(2)	1.288(3)	1.209(2)	1.202(3)	1.217(3)	1.205(2)
C(1)−N(1)	1.404(3)	1.375(3)	1.385(4)	1.405(3)	1.379(3)
C(2)−N(1)	1.371(3)	1.392(9)	1.405(4)	1.379(3)	1.400(3)
C(2)−C(3)	1.487(3)	1.489(1)	1.491(4)	1.484(3)	1.490(3)
C(1)−C(8)	1.489(3)	1.482(3)	1.429(4)	1.491(3)	1.480(3)
C(8)−C(3)	1.386(3)	1.390(3)	1.392(4)	1.386(3)	1.388(3)
C(3)−C(4)	1.367(3)	1.365(3)	1.369(4)	1.378(3)	1.380(3)
C(4)−C(5)	1.395(3)	1.389(2)	1.390(4)	1.384(4)	1.394(3)
C(5)−C(6)	1.376(4)	1.380(4)	1.383(5)	1.378(4)	1.383(3)
C(6)−C(7)	1.387(3)	1.389(4)	1.393(4)	1.392(4)	1.386(3)
C(7)−C(8)	1.377(3)	1.368(2)	1.372(4)	1.379(4)	1.378(3)
C(7)−H(5)	0.94(2)	0.965(3)	0.98(3)	1.01(3)	0.99(2)
C(6)−H(4)	0.93(2)	0.971(2)	1.01(3)	0.99(3)	1.03(2)
C(5)−H(3)	1.00(3)	0.94(3)	0.95(3)	0.93(3)	0.96(2)
C(4)−H(2)	0.92(2)	0.92(3)	0.92(3)	0.95(3)	0.96(2)

	angles (deg)				
bond angle	A	B	C	D	E
O(2)−N(1)−C(1)	122.4(2)	119.1(2)	122.7(2)	122.7(2)	121.0(2)
O(2)−N(1)−C(2)	121.6(2)	123.0(4)	121.5(2)	121.5(2)	123.0(2)
C(1)−N(1)−C(2)	114.1(2)	113.2(4)	113.9(2)	114.0(2)	113.9(2)
O(1)−C(1)−N(1)	125.4(2)	123.9(5)	125.2(3)	125.4(2)	125.4(2)
O(1)−C(1)−C(8)	131.0(2)	130.3(2)	131.0(3)	130.8(2)	129.8(2)
N(1)−C(1)−C(8)	103.6(2)	103.7(1)	103.9(2)	103.8(2)	104.9(2)
C(1)−C(8)−C(3)	108.9(2)	106.6(4)	108.5(2)	108.7(2)	108.5(2)
C(1)−C(8)−C(7)	129.8(2)	120.4(1)	129.9(3)	129.7(2)	129.8(2)
C(2)−C(3)−C(8)	108.1(2)	106.9(2)	108.7(3)	108.5(2)	108.4(2)
C(2)−C(3)−C(4)	130.0(2)	107.9(3)	130.0(3)	129.9(2)	130.2(2)
C(8)−C(3)−C(4)	121.9(2)	120.4(2)	121.3(3)	121.6(2)	121.4(2)
O(3)−C(2)−N(1)	125.5(2)	124.7(3)	125.1(3)	125.2(2)	125.2(2)
O(3)−C(2)−C(3)	129.5(2)	129.7(2)	130.0(3)	129.9(2)	131.0(2)
N(1)−C(2)−C(3)	105.0(2)	103.9(2)	104.8(2)	104.9(2)	103.9(2)
C(8)−C(7)−C(6)	117.0(2)	117.6(3)	117.2(3)	116.9(3)	117.3(2)
C(3)−C(4)−C(5)	117.1(2)	117.4(3)	117.5(3)	117.0(3)	117.0(2)
C(4)−C(5)−C(6)	121.0(2)	121.9(3)	120.7(3)	121.3(3)	121.4(2)
C(5)−C(6)−C(7)	121.7(2)	120.2(4)	121.7(3)	121.5(3)	121.3(2)
C(3)−C(8)−C(7)	121.3(2)	121.0	121.6(3)	121.6(2)	121.6(2)
N(1)−O(2)−H(1)	106.0(2)	113.1(2)	106.0(2)	107.0(2)	110.0(2)

TABLE 3: Hydrogen-Bonding Schemes and Dimensions of NHP and NDP Forms

compound	angle (deg)	hydrogen bond[a] (Å)
colorless NHP	N(1)···O(1)−H(1) = 122 O(1)···H(1)−O(3) = 159	O(1)−H(1) = 0.9705^{1} O(3)−H(1) = 1.77(3)^{2} O(3)−O(1) = 2.694(2)^{2}
yellow NHP	N(1)···O(1)−H(1) = 122 O(1)···H(1)−O(3) = 185(4)	O(1)−H(1) = 1.095^{1} O(3)−H(1) = 1.70(4)^{2} O(3)−O(1) = 2.675(4)^{2}
light-brown NDP	N(1)···O(1)−D(1) = 110(3) O(1)···D(1)−O(3) = 156(3)	D(1)−N(1) = 1.92(3)^{1} O(3)−Δ(1) = 1.75(3)^{2}
light-yellow NDP	N(1)···O(1)−D(1) = 107(3) O(1)···D(1)−O(3) = 160(3)	D(1)−N(1) = 1.97(4)^{1} O(3)−D(1) = 1.75(4)^{2}
colorless NHP, benzene/water 90%/10% (v/v)	N(1)···O(1)−H(1) = 120(5) O(1)···H(1)−O(3) = 167.7(4)	O(1)−H(1) = 1.035^{1} O(3)−H(1) = 1.78(1)^{2} O(3)−O(1) = 2.697(6)^{2}
colorless NHP, water	N(1)···O(1)−H(1) = 112(3) O(1)···H(1)−O(3) = 167(8)	O(1)−H(1) = 0.9708^{1} O(3)−H(1) = 1.76(3)^{2} O(3)−O(1) = 2.674(2)^{2}

[a] Symmetry operators. Intramolecular hydrogen bonding: (1) x, y, z. Intermolecular hydrogen bonding: (2) $-x$, $^{1}/_{2} + y$, $^{1}/_{2} - z$.

C(5), C(6), C(7), and C(8)] and plane 1 [defined by C(1), N(1), C(2), C(3), and C(8)] is 0.86° for colorless NHP, and the dihedral angle between plane 3 and plane 2 [defined by C(3), C(4), C(5), C(6), C(7), and C(8)] is 1.57°. The corresponding value for these planes in the yellow form is only 0.45°. In addition, the *N*-hydroxyl oxygen in the isoindole-1,3-dione ring for the yellow form is significantly out of the best plane by −1.19°, but for the colorless form (NHP I), it is out of the plane by only 0.06°; however, the carbonyl oxygens are considerably out of the plane. In this respect, a minimum change in molecular structure change appears to afford changes that alter the orientation of the N−O−H moiety, illustrated schematically in Figure 5A,B. Figure 5 shows the two twist conformations of the five-membered ring and the different orientations of the N−O−H group for the (A) colorless and (B) yellow forms of NHP. This structural change also affects the packing of the various forms of NHP shown in Figures 3 and 4.

The colorless NHP form (NHP I) exhibits a twist angle of approximately 1.6°, which represents a considerable change from the conformal twist of the nonplanar isoindole-1,3-dione ring (Figure 5A). This results in the N−O−H oxygen being out of the plane by approximately 0.16 Å. The twist angle for the yellow form is 0.05° and results in the N−O−H oxygen being out of the plane by only 0.012 Å (Figure 5B). If such a rotation were to occur in solution, virtually no energy barrier would be encountered, although the rotation is apparently dependent on the nature of the solvent. Of course, the crystal structure of the yellow form locks the twisted ring conformation, particularly in the case of the carbonyls and the oxygen in the N−O−H group. The structure is locked in such a manner that a molecular reorganization would be required to accomplish such a change and produce the colorless form. This might be one reason why it is not possible to change the yellow form to the colorless form by refluxing or crystallizing the yellow form in apolar solvents. However, it is possible to transform the colorless form to the yellow form in polar solvents, especially primary alcohols and water. Accordingly, the conformations of the isoindole-1,3-dione ring, especially the bowing of the carbonyls in both NHP forms, do not allow intramolecular hydrogen bonding with the *N*-hydroxyl moiety. This is because the distance and conformational angles between the oxygen of either carbonyl and the hydrogen of the N−O−H group are unfavorable for both NHP forms. The dynamics of the twist of the torsion angles of the isoindole-1,3-dione ring does not permit a close approach to the N−O−H group unless a proton has been removed and a salt formed, and then, the solutions tend to be red-shifted.[15] The unit cell reveals some noticeable differences in the molecular packing of the colorless (NHP I) and yellow NHP and NDP forms, presented in Figures 3 and 4. The crystal lattice of light-yellow NDP is quite different from those of yellow and colorless NHP (NHP I and NHP II). The lattice is more open and, consequently, not as closely packed as in the undeuterated forms; however, it does follow the same motif as discussed for colorless NHP (NHP I). The light-brown NDP more closely resembles the yellow NHP form, but the NDP forms are different with respect to color, melting point, crystal shape, and fracture characteristics. SEM images of the fracture characteristics are shown in Figure 2.

Further inspection and analysis of the packing and orientation of the colorless and yellow forms of NHP reveal a lattice for each crystal structure in which the long molecular axis is roughly parallel to the *c* axis. Although the arrangements of the NHP molecules in the two crystal types are quite different, the space groups are the same and the lengths along the *b* axis are similar. In the colorless form, the four molecules in the unit cell are arranged in a “tail-to-tail” fashion, with the benzene portion of the NHP molecule and the isoindole-1,3-dione ring forming a

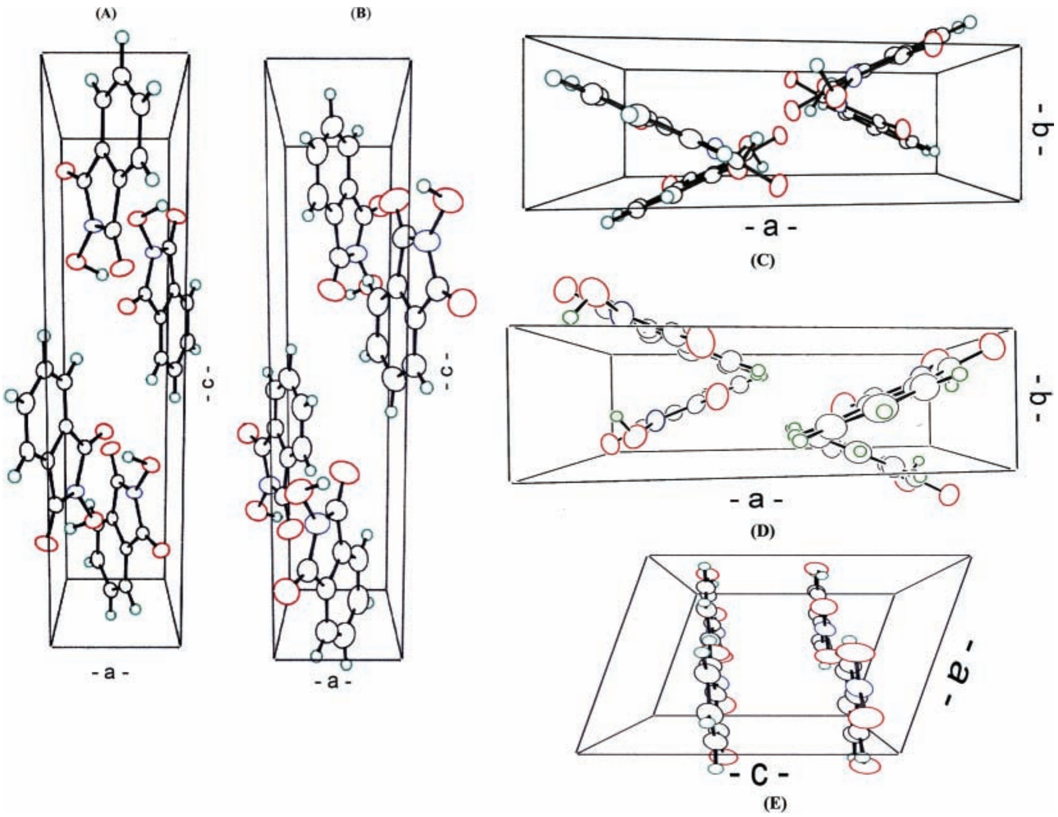

Figure 3. Orientation and packing of the NHP molecules in the monoclinic lattice for (A) colorless NHP I and (B) yellow NHP, orientation in the *ab* plane projection of (C) the colorless form of NHP I and (D) the yellow form of NHP, and (E) projection in the *ac* plane of both forms of NHP. $b = y$, $z = a$, which are the optical axes (Note: The optical axes are $x \parallel a^*$, $z \parallel c$, and $y \perp xz$ plane).

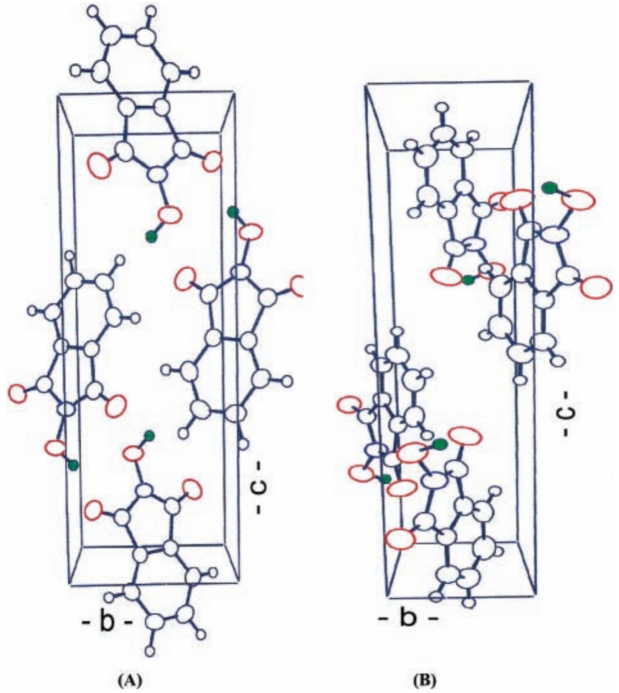

Figure 4. Packing of the two NDP forms: (A) light-yellow and (B) light-brown.

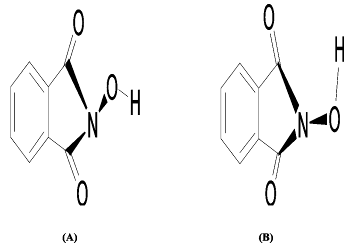

Figure 5. Schematic equilibrium structures of the colorless (A) and yellow (B) forms of NHP according to the crystal structures.

“plow”-like structure with an opening angle of ~55°. The hydroxyls of the N−O−H group face each other along the direction of the *b* axis. The symmetry-related plane of the other dimer of colorless NHP I is separated by ~3.95 Å (Figure 1C in Supporting Information S3). The yellow crystal form is also a structure with two layers along the *c* axis; each layer contains two NHP molecules arranged in pairs in a “head-to-head” fashion. Here, the N−O−H group of the isoindole-1,3-dione and the five-membered ring face each other, resulting in a plow with an angle of 46° and a distance between the symmetry planes on the order of 3.55 Å (Figure 1D in Supporting Information S4). The molecules are seen to alternate in orientation, whereas in the dimer of colorless NHP I (Figure 1C in Supporting Information S3) the molecules form ribbons, with the ribbons adopting a “herringbone”-like pattern. The tail-to-tail and head-to-head arrangements of the NHP molecules in the crystals are portrayed in Figure 3E, showing a displacement of the yellow NHP molecules along the *b* axis. The angle of inclination to the *ac* plane in the colorless form is 60°, compared to ~53° in the yellow form.

The differences between these crystals are also seen in the powder diffraction patterns calculated from the single-crystal X-ray data for each NHP reported here (Figure 6). Experimental powder diffraction patterns of gently ground samples of the various NHP forms were compared. The powder diffraction patterns of neither the colorless nor the yellow NHP show noticeable differences in intensity and 2θ positions from those calculated from single-crystal diffraction analysis. Care must be taken when grinding the colorless crystals of NHP (NHP I)

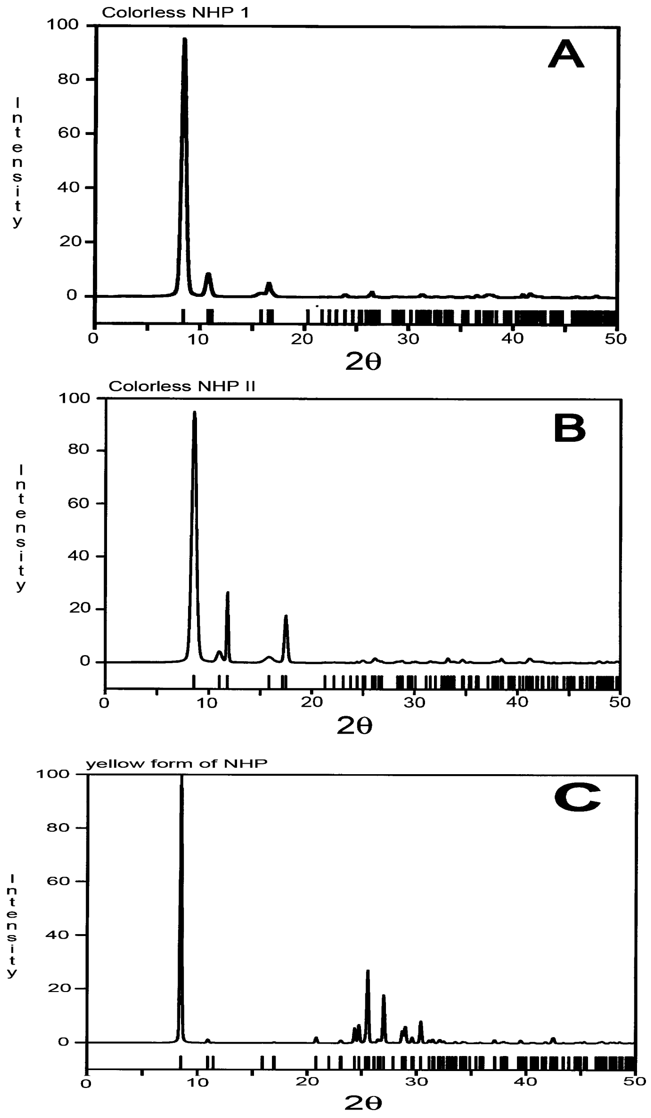

Figure 6. Powder diffraction patterns obtained from (A) the colorless NHP I form, (B) the yellow NHP form, and (C) the colorless NHP II form. Sticks represent a simulated diffraction powder pattern of NHP based on the determined crystal structure.

in the presence of water (moisture) or contamination with alkali ions, because, with time, they will transform to the yellow form.[15]

Furthermore, the colorless and yellow forms of NHP often crystallize concomitantly, e.g., if the crystallizing matrix consists of water/benzene (10%/90%, v/v) or of xylene that is not water-free. Using a polarizing microscope, the NHP crystals (colorless NHP II) can be separated manually because the two forms have different habit planes and a distinction can be made between the colors and the morphology. (Note: The yellow form crystallizes in prisms, the colorless form in needles). Because of their importance as an oxidation mediator, the colorless NHP forms in aqueous media[9,12−14] were analyzed and their structures were determined (Table 3, Supporting Information S5). Close inspection of colorless NHP II reveals virtually the same twisted conformation of the five-membered ring as seen in the previous colorless NHP crystals (NHP I), schematically shown in Figure 5A. However, there are noticeable differences between these two colorless forms in packing efficiency (0.607 vs 0.6127) and in the orientation of the NHP molecules in the unit cell (Figure 7, Figure 1 in Supporting Information S5). The twist conformation and other dimensions are all very similar, although no twinning takes place in NHP II molecules. They are arranged in layers, i.e., phenyl-stacked layers along the *c* axis, and hydrogen-bonded along the *b* axis; each layer contains four NHP II molecules arranged in pairs head-to-tail, with the isoindole-1,3-dione ring as the head and the phenyl group as the tail. A transformation of the NHP II structure to the yellow NHP structure requires a slip along the *c* axis so that the NHP molecules in adjacent layers become mixed or the NHP molecules re-form along the long molecular axis, i.e., the *c* axis, and retain the same symmetry ($P2_1/c$).

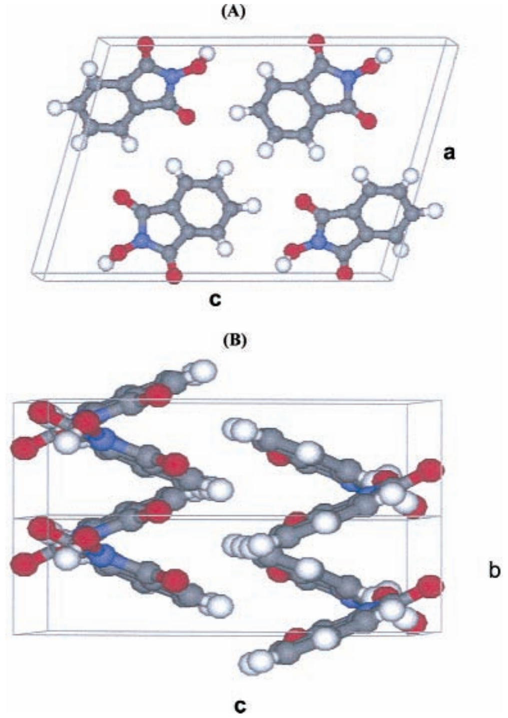

Figure 7. Crystal structure of the colorless NHP II form showing (A) the *ac* plane ($y = b$) and (B) the *cb* plane. Note: The optical axes are $x \parallel a^*$, $z \parallel c$, and $y \perp xz$ plane.

Neither in this investigation nor in previous studies have any intermediate structural forms of NHP been revealed. Only the yellow and colorless (white) forms shown in Figure 2A,B have been encountered. Although the transformation between the colorless and yellow forms can readily take place, the reverse transformation has not proved possible. The same transformation criteria exist for the second colorless form, NHP II. It is also possible that more NHP forms exist that depend on the solvent composition and the nature of the solvent as well as the temperature.[29]

There is no available information on the transformation path as to how the yellow form develops from the colorless form, and despite the hydrogen-bonding network along the *b* axis, an intermediate rearrangement might be possible. This would assume that the rearrangement takes place after the hydrogen bonds are broken because of the solvent, moisture conditions, or mechanical stress but that the stacking of the rigid phenyl rings remains undisturbed.

It would, therefore, seem reasonable that the transformation proceeds along the [110] and [1$\bar{1}$0] directions, the same directions as found in the irreversible melting process. Upon examination of Figure 5A and B, it would appear that the yellow form might be derived from the colorless form by shifting the molecules of the same layer after breaking the hydrogen bonds and also rotating by ~55°. The mechanism would also require a relaxing of the twisted conformation of the isoindole-1,3-dione ring in colorless NHP I to form the yellow conformation. Such an operation would cause a rapid rearrangement of the five-membered ring system and realign the hydrogen bonding between the molecules of each layer of the now yellow form, parallel to (110) or $(1\bar{1}0)$. The operation would provide a partial explanation for the formation of the cracks and corrugations that appear after a period of time on the surfaces of the colorless NHP I form. The cracks form when the material is exposed to air, moisture, or grinding and subjected to optical observation during the melting process. A visible color change, from colorless to yellow, occurs when the colorless NHP I form (in the literature referred to as the "white form") undergoes a grinding operation. The grinding process itself is not the cause of the color change—this is a result of the exposure of newly formed crystallite surfaces to the atmosphere. When the colorless form was ground in benzene, xylene, or hexane, the colorless form was retained. When these crystallites were subsequently examined using X-ray powder diffraction and Raman spectroscopy, the preceding results were confirmed.

Another colorless form of NHP, prismatic in shape, obtained from water and quite different from all other morphologies, was reported by Miao et al.[30] This form more closely resembles the yellow form of NHP, although it was described as being colorless and having a packing efficiency of 0.623. However, the unit-cell dimensions, the angle β, and the density were different from those of the colorless form of NHP II reported here; the covalent bond lengths and angles were similar but not identical. In addition, the orientation, packing, and simulated powder diffraction pattern shown in Figure 7 are different. No solvates were found, except for the NHP dimer, which crystallizes from watery solutions with one molecule of water in the unit cell.[31]

Preliminary calculations with a MIDI split-valence double-ζ basis set (G-31G) at the HF−SCF level (Gaussian 03)[32] for unsolvated single NHP molecules in the gas phase with imposed symmetry indicated that the conformations observed in the unsolvated NHP forms both correspond to local minima. The conformations observed at 20 °C for the colorless form were found to be energetically more favorable than those of the yellow form by 0.51 kJ/mol. According to Gavezzotti and Filippini[33] applying the 6-exponential potential approach to the colorless and yellow NHP forms, values of approximately −6.5 kJ/mol (colorless NHP I) and −5.0 kJ/mol (yellow NHP) were obtained. These values are just within the range expected to display the differences between the polymorphs.[34] The values obtained for the crystal densities (yellow, 1.604 g/cm^3; colorless, 1.565 g/cm^3) and the packing coefficients (yellow, 0.661; colorless, 0.6104) are consistent with the ordering of the lattice energies.

None of the structures of NHP showed any significant overlap between the benzene unit and the five-membered isoindole-1,3-dione ring, but extensive stacking was revealed. The yellow structure was shown to exhibit a degree of overlap with adjacent isoindole-1,3-dione fragments of the NHP because of its head-to-head arrangement. This caused both a different orientation and a reduction in distances along the *c* axis, which is the long prismatic crystal axis. There are also interactions with the isoindole-1,3-dione fragment, which tilts toward benzene and has a tilt angle larger than that of the colorless form. This was also seen in the light-brown NDP crystal. There was no π-complexing or charge-transfer interaction in the crystals, which was supported by the UV spectrum of the yellow NHP crystals. The observed changes in UV absorption of the colorless and yellow forms can be attributed to small differences in the stacking and orientation of the phenyl rings within the different NHP crystals.

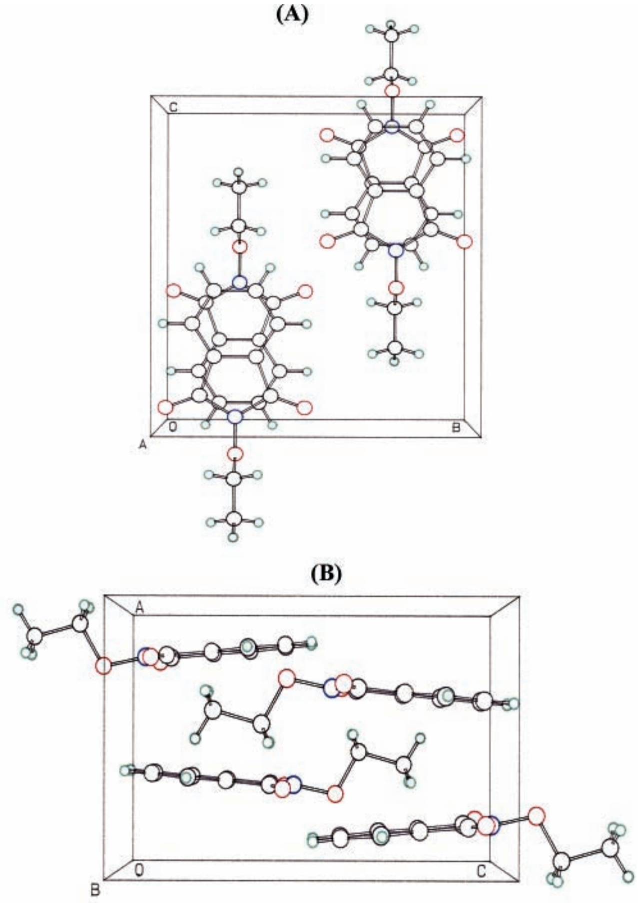

Figure 8. Molecular packing of ethoxy-NHP in the orthorhombic unit cell (*Pnma*) showing (A) the stacking of the phenyl moiety and (B) the orientation of the phenyl rings with respect to the ethoxy groups upon rotation of 90°.

The structures shown in Figure 5A,B might imply a steric interference with the coplanarity of the phenyl ring and the iso-1.3-indole ring. Consequently, destabilization of either the five-membered ring or the phenyl ring can occur when an intramolecular hydrogen bond is formed with either oxygen atom of the carbonyls. Of course, this would only be possible in suitable solvents. Another minor factor likely to be important is steric inhibition of resonance in the isoindole-1.3-dione ring. Assuming the formation of an intramolecular hydrogen bond between the hydrogen of the N−O−H group and the oxygen atom of one of the carbonyls, such an arrangement would be accompanied by a distortion of the aromatic phenyl ring. This would suggest a dipolar resonance structure, and to avoid such a distortion, intermolecular hydrogen bonds would form to stabilize the structures. These should be thermodynamic minimum structures. However, such a structure was not observed in the Raman spectra and is not consistent with the bond lengths and dihedral angles determined from the crystal structures.

Ethoxy-NHP. Ethoxy-NHP is the only NHP compound that, upon crystallization, forms an orthorhombic structure, space group *Pnma* (No. 62), and where the crystallites take the shape of small colorless needles. Attempts at crystallization to obtain a yellow modification of ethoxy-NHP by applying ethanol, acetone, etc., always resulted in a colorless crystalline material. Illustrations of the NHP ethoxy molecule are presented in Figure 8. Good-quality refinements were obtained for both crystal forms and were further substantiated by an analysis of the thermal

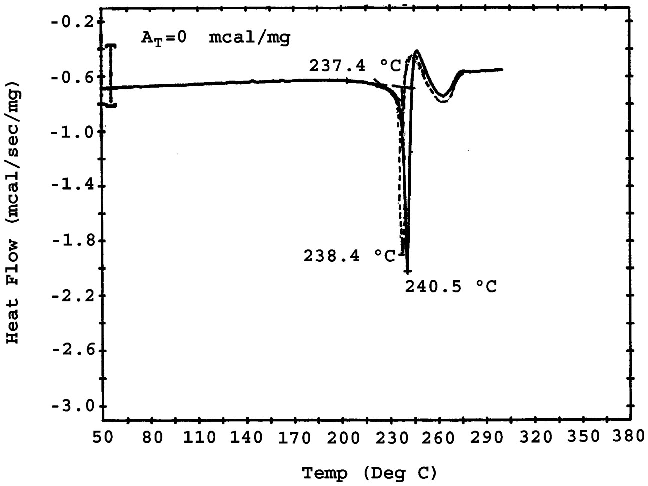

Figure 9. Differential scanning calorimetry (DSC) results for the colorless form of NHP I (blue line) and the yellow form of NHP (broken line).

parameters employing an X-ray study (Supporting Information S6). In the refinement, hydrogen atoms were constrained to idealized positions with C−H = 0.945 Å and with isotropic temperature factors 1.18 times those of the attached C atoms. The rigid-body model was used to describe molecular vibrations apart from the hydrogen atoms and, to a lesser extent, the carbonyl oxygens that show slightly enhanced thermal motions. The motions are perhaps best illustrated by an ORTEP plot, which exhibits the thermal motions of the out-of-plane oxygen atoms. The ethyl ether molecule of NHP is located on a mirror plane of the lattice. The mirror plane also includes the N−O−C−C chain and bisects the two rings of the NHP group. The eight carbon atoms of the NHP unit are coplanar, with the nitrogen being displaced 0.045 Å from the plane. This displacement is on a site opposite the plane of the oxygen atoms, i.e., the carbonyl oxygens are displaced by 0.054 Å and the ether oxygen atom is displaced by 0.103 Å, which creates a 3.44° dihedral angle (C−N−C/C−C−C) in the five-membered ring. There are no other unusual or significant intermolecular contacts and the packing results from head-to-tail stacking of the planar rings along the direction of the needle axis. At present, it is not possible to convert the colorless ethoxy-NHP form to the yellow form by varying the solvent composition. The colorless ethoxy-NHP conformation resembles the colorless NHP conformation (NHP I).

Thermochemistry. DSC measurements revealed melting points of 238.4 and 240.5 °C (Figure 9) for the colorless and yellow forms of NHP, respectively. However, the colorless crystals of NHP obtained from water and from a mixture of benzene and water (90%/10% v/v) both melt at 238.5 °C. When the colorless and yellow NHP crystal forms were mixed, the DSC results showed a melting point of 238.5 °C regardless of the ratio of colorless to yellow crystals. Upon melting, the crystalline and pulverized forms of NHP decompose irreversibly[35] with a color change to brownish-black and finally to a tar-like material. Because of the poor thermal stability of the crystals, precise thermodynamic data could not be obtained. The enthalpies of melting obtained from the DSC experiments are 5.81 and 5.40 kJ/mol for the colorless and yellow NHP forms, respectively. The NDP forms have melting points similar in relationship to those of NHP, although the melting points are much lower (115 and 177 °C, with enthalpies of melting of 7.81 and 7.25 kJ/mol for the NDP light-yellow and light-brown forms, respectively).

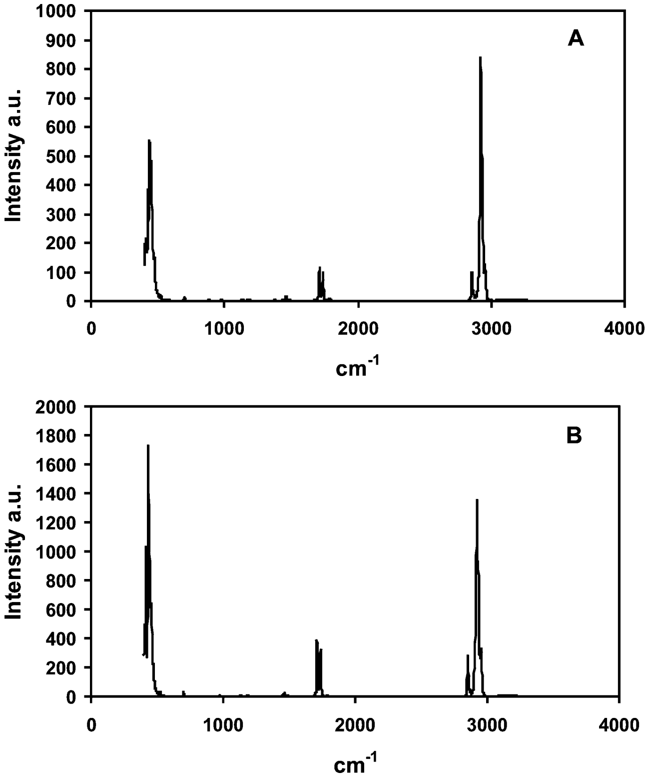

Figure 10. Comparison of the crystalline infrared spectra of (A) the colorless form of NHP-1 and of the yellow form of NHP (B).

A hot-stage examination of single crystals of both forms of NHP and of those obtained from mixed solvents was inconclusive. Deterioration started at 156 °C for all NHP forms, and severe reaction fronts developed along the [110] direction and the symmetry-related [1$\bar{1}$0] direction. It was also found that the conversion rate of the colorless form to the yellow NHP form is highly dependent on the temperature and the nature of the solvent. At room temperature, both NHP forms are stable and can be stored for an indefinite period of time, in the absence of moisture or cations, e.g., Na^+, K^+, Me^{2+}, and ammonia. The initiation of the transformation of the colorless form to the yellow form occurs over a broad temperature range (90−120 °C), but when nucleation occurs, the colorless form undergoes an irreversible rearrangement and forms yellow NHP.

Vibrational Spectroscopy. Raman and infrared spectroscopies were employed to investigate the effects of the solvent on the crystallization and molecular conformation of three types of NHP. For the solid-state structures of NHP at room temperature, the molecule occupies a C_1 site; however, the symmetry could also be close to C_{2v} as shown in Table 2. For C_{2v} symmetry, the internal modes of the isolated molecule can be classified as $8A_1 + 7B_1 + 3A_1 + 3B_2$, where A_1 and B_1 are in-plane modes. There are four NHP molecules per unit cell, and if factor-group splitting takes place, each molecule will vibrate. These vibrations will subsequently give rise to four modes in the unit cell. The similarity of the infrared and Raman frequencies demonstrates that, for the different colored forms, most of the factor-group splitting of the internal modes is not significant. Presented in Figures 10 and 11 are the infrared and Raman spectra of the two forms, and the similarities and differences between the colorless and the yellow forms are quite apparent. This displays the fact that the two different forms of vibrational spectroscopy exploit different properties of the molecules. Infrared spectroscopy requires a change in the dipole moment and is, therefore, sensitive to the more polar motions of the molecule. Raman spectroscopy, on the other hand,

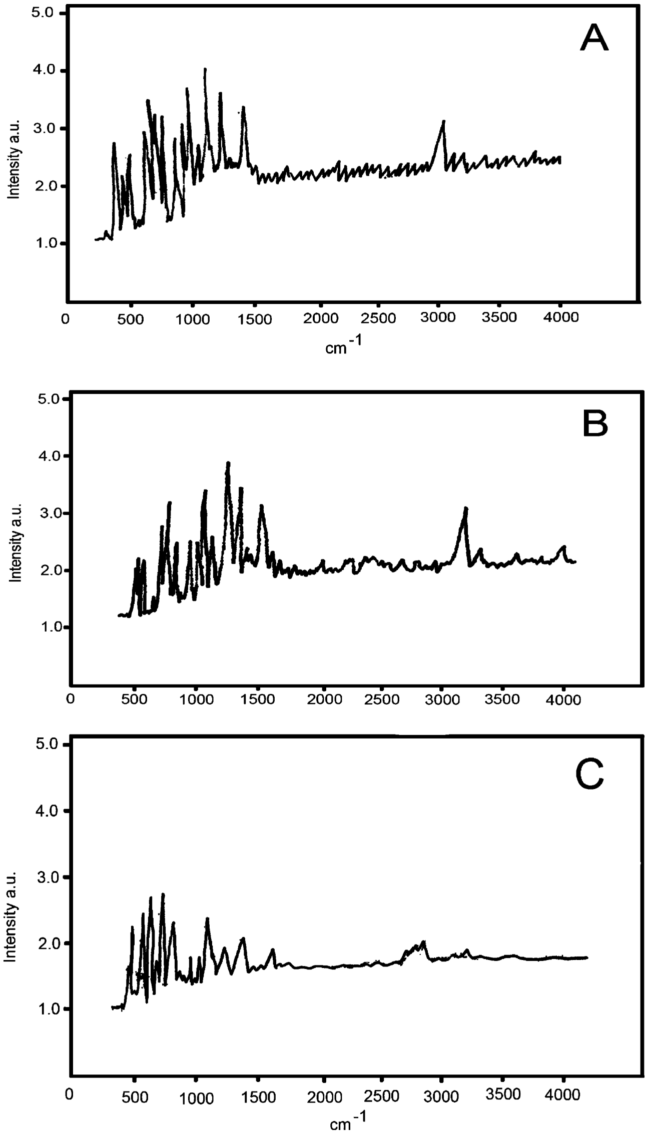

Figure 11. Raman spectra of (A) the crystalline colorless form of NHP I, (B) the crystalline yellow form of NHP, and (C) the crystalline colorless form of NHP II.

requires a change in polarizability and is more sensitive to the nonpolar motions of the NHP molecule. There are noticeable differences between the values for the Raman peaks of the colorless and the yellow NHP forms at positions of 877, 2680, 1614, 1618, 1155, and 650 cm^{-1}, in both peak shape and magnitude. There are also differences between colorless NHP forms I and II at, e.g., 3400, 3130, 2680, 1995, 1706, 1585, 1155, and 880 cm^{-1}, as well as significant differences in the low-frequency region (Table 4 and Figure 11). The spectra of the colorless form contain a single band at 1718 cm^{-1}, but the yellow form shows a triplet structure at 1706, 1690, and 1680 cm^{-1}. All of these frequencies are lower than those observed for the carbonyl group in the corresponding non-hydrogen-bonded NHP forms at 1732−1735 cm^{-1}. It can also be seen that the ν(C=O) frequency peak at 1718 cm^{-1} is noticeably higher in magnitude in the yellow form than in the colorless form, indicating that, at this frequency, the hydrogen-bonding contribution is lower. In the yellow form, the splitting of the C=O stretching mode into a triplet occurs because of the combined effects of intermolecular hydrogen bonding, an intermolecular hydrogen bonding angle of 185°, the packing efficiency in the yellow crystals, and a closer intermolecular distance for the O(1)^i and O(1)^j atoms. As a consequence, a decrease in molar volume was observed compared to that of the colorless form because intermolecular hydrogen bonding brings the NHP molecules into closer contact than van der Waals interactions.

When the colorless crystalline forms were gently ground, the infrared and Raman spectra of the resulting material were virtually the same as those recorded for the crystalline yellow form. Upon grinding of the crystals of the yellow form, some peaks became so severely blurred and broadened that they were no longer distinguishable as individual peaks, e.g., peaks at 3126, 3095, and ∼2273−2050, and all peaks between ∼1680 and 1790 cm^{-1} became one broad peak at 1690 cm^{-1}. When the single-crystal form and powdered samples of the colorless and yellow forms were immersed in Nujol, the infrared spectra were virtually identical. The differences in the infrared and Raman spectra for the crystalline colorless and yellow NHP forms and the deuterated (NDP) forms are clearly seen in the Raman spectra (Figure 11). In Table 4, tentative assignments of the observed peaks in the Raman spectra for the various crystalline forms are presented in support of the differences found in the vibrational structure of the colorless and yellow forms.

It is apparent from the Raman spectra that all crystalline forms of NHP and NDP lack the ν(OH) and ν(N−O−H) vibrations, which are close to ∼3300 cm^{-1} in the unassociated state. Because of the extensive hydrogen bonding, the frequency falls to ∼1686 cm^{-1} in the yellow NHP form and to 1720 cm^{-1} in the colorless form. This can be reconciled as a lengthening and weakening of the original O−H bond formation, where the hydrogen is at a greater distance from the donor and consequently closer to the acceptor. It can, therefore, be concluded that an increase in mechanical anharmonicity of the H bond lowers the stretching frequency without influencing the O−H distance.

For both forms, from the point of view of hydrogen bonding, it can be seen from the Raman spectra that the important vibrational frequencies are those associated with the carbonyls of the isoindole-1,3-dione moiety and the hydrogen of the N−O−H(D) group mode. Both the hydrogen and the deuterium are involved in intermolecular hydrogen bonding. The frequencies of the C=O stretching mode observed for the crystalline colorless and yellow forms give rise to different Raman spectra (Figures 11), i.e., spectra that are shifted toward lower frequencies. Shifts in the vibrational frequencies of the Raman spectrum are noted for the triplet of the yellow form to 1685 cm^{-1}, for the singlet of the colorless form to 1717 cm^{-1}, and for both forms to ∼1350 cm^{-1}. Vibrational modes for strong and nearly symmetrical hydrogen bonds have $3 \times 3 - 5 = 4$ normal modes, of which ν_{2a} and ν_{2b} are doubly degenerate. This is also the case for the out-of-plane ν_{2b} and ν_r frequencies found in the 400−900 cm^{-1} region. It seems that the O−H···O angle of the intermolecular hydrogen bonding is responsible for the differences in the positions and intensities at these frequencies for both forms of NHP and NDP. The preceding findings appear to be the cause of the differences in the frequency range from 500 to 1000 cm^{-1} and the weak (900 cm^{-1}) and strong (1500 cm^{-1}) hydrogen-bond regions found in both NHP forms. The in-plane bending mode for β(C−OH) occurs at very low frequency and is observed at 475 cm^{-1} for the colorless form and at 460−465 cm^{-1} for the yellow form. There is also a twist motion present in the yellow form at ∼600 cm^{-1} only. It would appear that, for the yellow form, the hydrogen bonding is responsible for this frequency value, because for the unassoci-

TABLE 4: Analysis of the Observed Frequencies (cm^{-1}) in the Raman Spectra of Colorless NHP I and II, Yellow NHP, Light-Yellow NDP, and Light-Brown NDP

vibration mode	colorless NHP I	colorless NHP II	yellow NHP	light-yellow NDP	light-brown NDP
υ(C−H)	3190	3195	3200	3150	3042
υ(C−H)	3090	3088	3042, 3019	3030, 3010	3015, 3000
υ(C═O)	1718	1720	1685, 1706	1713, 1708	1682
δ(C−H)	1450	1450	1453	1597	1591
β(O−H)	1350 (1327)	1349 (1327)	1345 (1327)	1425	1405, 1415
β(O−H)	1351 (1360)	1351 (1359)	1317	1405	1400
υ(C−O)	1300	1290	1300 (1290)	1120	1135
υ(C−C)	1200 (1150)	1200	1200 (1145)	1000	1005
υ(C−OH)	1050	1045	1045	826	800
ϕ(CC)	1000	1001	975	965	960
γ(O−H)	770 (750)	750	725	850	810
β(O−H)	650, 690, 700	645, 690	650, 600	630	591
ϕ(CC)	510	508	550	500	650
β(C−OH)	475	470	465	480	490
β(C═O) + β(C−C)	455	451	438		
γ(O−H)	770 (750)	750	725		
β(O−H)	700, 690, 650	645, 690	650		
	−		600, 550		

ated N−O−H groups of the molecule, the out-of-plane deformation (N−O−H···O) would occur at ~700 cm^{-1} (weak H-bond).

The lowering of the carbonyl frequency in both forms of NHP is indicative of strong hydrogen bonding. However, the values of the vibrational frequencies observed for the N−O−H stretching vibration are lower than would be expected in a non-hydrogen-bonded system. Further quantitative analysis is in progress to support these findings, including inelastic neutron-scattering experiments. In addition, the frequencies of the O−H in-plane and out-of-plane bonding were found to be high for both NHP forms, and these observations support the formation of hydrogen bonds.

The vibrational results are consistent with previous inelastic neutron scattering (INS) experiments.[36] Particularly, the bands observed in the 50−120 cm^{-1} region can be assigned to the stretching and deformation modes associated with intermolecular hydrogen bonding of the C═O and C−O···H units in the NHP crystals. The frequencies below 120 cm^{-1} in the INS spectra for both NHP forms also belong to external modes, e.g., librations about the principal crystallographic axes, as well as to translational and phonon modes.[37] A tentative thermal motion analysis on the basis of the obtained crystallographic parameters of the colorless NHP I form and the yellow form was performed to calculate the components of the librational and translational tensors for all non-hydrogen atoms of the molecule.[38] The librational frequencies were computed by the method of Cruickshank[39] by applying the appropriate eigenvalues of the L tensor and the corresponding moments of inertia. The frequencies of the modes for the colorless NHP I form were observed at 41 and 45 cm^{-1} at 14 K,[35] and those for the yellow form were found at 71, 85, and 98 cm^{-1}, where the latter was observed as a strong band in the far-infrared region (Paradies, H. H., unpublished results). Using the X-ray structures and applying the normal convention that the moments of inertia follow the order $I_c \geq I_b \geq I_a$, the calculated values for colorless NHP I are $I_c = 4.98 \times 10^{-45}$, $I_b = 3.15 \times 10^{-45}$, and $I_a = 1.98 \times 10^{-45}$ kg m^2, and the corresponding values for the yellow form are $I_c = 4.90 \times 10^{-45}$, $I_b = 3.0 \times 10^{-45}$, and $I_a = 1.93 \times 10^{-45}$ kg m^2. Taking these inertia values into account and assuming the shape of the bands in the low-frequency region to be expressed as (amplitude)^2(radians)$^2 \times 10^4$, it can be shown that these frequencies belong to the librations and translation along the principal crystallographic axes.

Conclusion

Two crystalline forms of NHP, one colorless and the other yellow, were characterized by analyzing their crystal structures and Raman spectra. The intermolecular hydrogen-bond networks along the *b* axis were similar, but differences were observed in the O(2)−O(3) distances. Other differences were found in the twist conformation of the five-membered isoindole-1,3-dione ring, the effective packing, and the O(2)−H(1)···O(3) hydrogen-bond angle. Infinite molecular chains along the *b* axis were also revealed, albeit without hydrogen-bond interactions between the phenyl rings. The layer-to-layer separations between the colorless NHP form and the yellow form of NHP were found to be about 3.56 and 3.41 Å, respectively.

The crystalline yellow form of NHP exhibits a strong absorption band at 575 nm, whereas the colorless NHP form does not. The various NHP forms decompose[35] at temperatures considerably below the melting point; therefore, it was not possible to carry out solid-state transition experiments

Although single-crystal−polymorphic transformations of molecular crystals are known and well-documented, it would appear from the results of this study that a transformation is possible only in the presence of a solvent. The miscible solvents contain small amounts of water and can be maintained at a specified temperature. The yellow NHP form is a product derived from the colorless NHP form, and the yellow NHP form assembles along a particular crystallographic plane, the *ab* plane of the colorless form. This involves no change in crystal symmetry, no alteration in the order of attachment of the hydrogen bonds, only a small change in molecular volume, and a minor alteration in the arrangement of the intermolecular hydrogen-bonding pattern. The only significant change is an alteration in the hydrogen-bond angles from 154° to 184°. There is also a possibility that the transformation takes place through an amorphous intermediate stage.

The irreversible conversion of the colorless crystalline form to the yellow crystalline form is more like a dynamic isomerism[40] than a polymorphic transformation. The criterion for polymorphism[1] requires a dynamic equilibrium difference in the solution structures of NHP; however, this criterion is not met.[41] There might be NHP species in solution that, although different in detailed structure from their counterparts, the colorless and yellow NHP forms, roughly correspond to these species. For example, in terms of identical intermolecular hydrogen-bonding networks, the twists of the isoindole-1,3-dione ring are different for the colorless and yellow NHP molecules. On this basis, the colorless and yellow NHP forms can be seen as isomeric species rather than polymorphs. There might be NHP species in solution that, though different in detailed structure from their counterparts, the colorless and yellow forms, roughly correspond to these species. The crystalline NHP forms and their various crystal morphologies also give rise to questions as to crystal growth, i.e., the effects of the solvent on the growth kinetics of different specific morphologies.[5,42,43]

Acknowledgment. The authors acknowledge the support, critical discussions, and advice on use of the IR instrumentation by Dr. Neil M. Boag.

Supporting Information Available: List of the angles of the colorless and yellow forms of NHP determined by polarizing microscopy and the morphology of the NHP crystal (S1); tables providing details of the refined positions of the colorless NHP I and yellow forms of NHP and equivalent isotropic thermal parameters, anisotropic displacement parameters, and least-squares planes for NHP (S2); tables listing torsion or conformational angles of the two NDP forms, close contacts, intermolecular distances, and least-squares planes (S4); list of crystallographic details of colorless NHP II, fractional atomic coordinates, equivalent isotropic thermal parameters, and anisotropic displacement parameters at 20 °C (S5); and tables listing refined fractional atomic coordinates, equivalent isotropic thermal parameters, and anisotropic displacement parameters at 20 °C for ethoxy-NHP (S6). Crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon: Oxford, 2002. (b) Dunitz, J. D.; Bernstein, J. *Acc. Chem Res*. **1995**, *28*, 193. (c) Davey, R. J. *Chem Commun*. **2003**, 1463. (d) Desiraju, G. *Crystal Engineering, The Design of Organic Solids*; Elsevier: Amsterdam, 1989; pp 285−299. (e) Bernstein, J.; Desiraju, G. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; pp 471−518. (f) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res*. **1995**, *28*, 193.

(2) (a) Barton, J. H. *Science* **2000**, *287*, 1933. (b) Engelberg, A. P. *J. Law Technol.* **1999**, *39*, 389.

(3) (a) Bernstein, J. *J. Phys. D* **1993**, *26*, B66. (b) Wöhler, F.; Liebig, J. *Ann. Pharm*. **1832**, *3*, 249.

(4) (a) Paradies, H. H. U.S. Patent 5,604.206, 1997. (b) Paradies, H. H. U.S. Patent 5,254,728, 1995. (c) Hanna, S. B.; Schneider, B.; Paradies, H. H. U.S. Patent 5,266,723 1993. (d) Paradies, H. H.; Thies, M.; Hinze, U.; Schneider, B. Molecular Structures of the Enantiomers of Ibuprofen, X-ray Reflectivity from Insoluble Layers, and Their Interfacial Chirality in Solution. *International Symposium on Molecular Chirality, Kyoto* (Japan), May 23−27, 1994; pp 151−155. (e) Paradies, H. H.; Thies, M.; Düme, U. *Pharmaceutical Manufacturing International, The Pharmaceutical Review of Pharmaceutical Technology Research and Development*; Barnacal, P. A., Ed.; Sterling Publications Ltd.: London, 1993; pp 141−145. (f) Zhang, Y.; Grant, D. J. W. *Acta Crystallogr*. **2005**, *C61*, m435.

(5) (a) Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M. J. *J. Am. Chem. Soc*. **2005**, *127*, 16802. (b) Amato, I. *Chem. Eng. News* **2007**, *105*, 27.

(6) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (b) Etter, M. C.; Siedle, A. R. *J. Am. Chem. Soc*. **1983**, *105*, 641.

(7) (a) Cohn, L. L. *Ann. Chem*. **1880**, *205*, 295. (b) Gazz Errera, G. *Chem. Ital.* **1894**, *24*, 469. (c) Lach, B. *Chem. Ber*. **1883**, *16*, 1780. Brady, O. L.; Baker, L. C.; Goldstein, R. F.; Harris, S. *J. Chem. Soc.* **1928**, 529.

(8) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. *Angew. Chem., Int. Ed*. **2001**, *40*, 222.

(9) (a) Einhorn, C.; Einhorn, J.; Marcadal, J.; Pierre, J. L. *J. Chem. Soc., Chem. Commun*. **1997**, 447. (b) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520. (c) Tabushi, I.; Yazaki, A. A. *J. Am. Chem. Soc.* **1981**, *103*, 7371. Tabushi, I.; Yazaki, A. A. *J. Am. Chem. Soc.* **1979**, *101*, 6456. (d) Masui, M.; Ueshima, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun*. **1983**, 479. (e) Masui, M.; Hara, S.; Ueshima, T.; Ozaki, S. *Chem. Pharm. Bull*. **1987**, *31*, 4209.

(10) (a) Kaneda, K.; Haruna, S.; Imanaka, T.; Kawamoto, K. *J. Chem. Soc., Chem Commun.* **1990**, 1467. (b) Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett*. **1991**, 1. (c) Maurahashi, S. I.; Oda, Y.; Naota, T.. *J. Am. Chem. Soc*. **1992**, *114*, 7913. (d) Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn*. **1995**, 68, 17. (e) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem*. **1993**, 58, 6421. (f) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, 67 (8), 2671. (g) Yang, G.; Zhang, Q.; Miao, H.; Tong, X.; Xu, J. *Org. Syn. Lett.* **2005**, *7* (2), 263.

(11) Kaneda, K.; Ueno, S.; Imanaka, T.; Shiumotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem*. **1994**, 2915.

(12) *Chem. Eng. News* **2001**, *99*, 25.

(13) Saito, J.; Takayama, M.; Matsuura, T. *J. Am. Chem. Soc*. **1990**, *112*, 883.

(14) Tezuka, T.; Narita, N. *J. Am. Chem. Soc*. **1979**, *101*, 7413.

(15) The colored forms of NHP crystals obtained from aqueous solutions in the presence of Na^+ or K^+ change in morphology and unit-cell dimensions. The K^+ salt of NHP, for example, has unit-cell dimensions of $a = 8.35$ Å, $b = 5.634$ Å, $c = 14.841$ Å, $\beta = 96.802°$, $V = 692.0$ Å^3, and $d = 1.48$ g/cm^3 and crystallizes in space group $P2_1/n$ (No. 14) as light orange plates. In contrast, the thin dark red needles of the sodium salt of NHP (from ethanol) crystallize in the monoclinic space group $P2_1/n$ with cell dimensions of $a = 15.032$ Å, $b = 37.609$ Å, $c = 13.319$ Å, $\beta = 67.49°$, $V = 6956.07$ Å^3, and $d = 1.56$ g/cm^3 (Paradies, H. H., 1999, unpublished results).

(16) (a) Carpino, L. A. *J. Am. Chem. Soc*. **1957**, *79*, 98. (b) Ames, D. E.; Grey, T. F. *J. Chem. Soc*. **1955**, 3518.

(17) Roderick, W. R.; Brown, W. G. *J. Am. Chem. Soc*. **1957**, *79*, 5196.

(18) (a) Paradies, H. H. U.S. Patent 5,434,302, 1995. (b) Paradies, H. H. U.S. Patent 5,248,815, 1996. (c) Paradies, H. H. *Proceedings of the 1st European Congress of Chemical Engineering*, Florence, Italy, 1997; International Congress of Chemical Engineering Europe-1; p 2655.

(19) Orndorff, W. R.; Pratt, D. S. *Am. Chem. J.* **1912**, *47*, 98.

(20) Bauer, L.; Miarka, S. V. *J. Am. Chem. Soc*. **1956**, *79*, 1983.

(21) Gilmore, C. J. *J. Appl. Crystallogr.* **1984**, *17*, 42.

(22) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr*. **1964**, *17*, 781.

(23) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; The Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2A. Cromer, D. T. *International Tables for X-ray Crystallography*; The Kynoch Press, Birmingham, England, 1974; Vol. IV, Table 2.3.1.

(24) Sheldrick, G. M. SHELXS86. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: Oxford, U.K., 1985; pp 175−189. To solve structure, SHELXS97; to refine structure, SHELXL97.

(25) (a) Threlfall, T. L. *Analyst* **1999**, *120*, 2435. (b) Bugay, D. E. *Adv. Drug. Deliv. Res*. **2001**, *48*, 43.

(26) Faunce, C. A.; Quitschau, P.; Paradies, H. H. *J. Phys. Chem*. **2003**, *107*, 2214.

(27) Johnson, C. K. *ORTEP II: A Fortran Thermal Ellipsoid Program for Crystal Structure Illustrations*; Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1978.

(28) Bernstein, J.; Cohen, M. D.; Leiserowitz, L. In *The Chemistry of Quinoid Compounds*; Patel, S., Ed.; Wiley: London, 1976; Part 1, Chapter 2.

(29) Another colorless NHP form was obtained at 4 °C from 90% *n*-hexane/10% ethanol (v/v). This form crystallizes in a triclinic unit cell with two molecules in the unit cell ($P\bar{1}$) with $a = 8.485$ Å, $b = 10.038$ Å, $c = 10.046$ Å, $\alpha = 115.72°$, $\beta = 94.28°$, $\gamma = 104.7°$, and $d = 1.607$ g/cm^3 and with two molecules in the unit cell. The crystals are twinned with the (010) axis normal to the twin axis, and this is considered to be a consequence of the monoclinic-to-triclinic phase transformation displacing the phase transformation seen at 4 °C (Paradies, H. H., 2000, unpublished results).

(30) Miao, F. M.; Wang, J. L.; Miao, X. S. *Acta Crystallogr*. **1995**, *C51*, 712.

(31) The symmetric dimer form of NHP ($[NHP(OH)_2]_2 \cdot H_2O$) crystallizes as a hydrate from aqueous solutions at room temperature in colorless prisms or dipyramids. The dimensions of the unit cell are $a = 6.896$ Å, $b = 10.0229$ Å, $c = 8.0101$ Å, $\beta = 106.71°$, $V = 547.2$ Å^3, and $d = 1.724$ g/cm^3; space group $P2_1/c$ (No. 14) (Paradies, H. H., 2001, unpublished results).

(32) Frisch, M.; Trucks, J. G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, Iyengar, J. M.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, N.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, K. D.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen,

W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 3.0*, Gaussian, Inc., Pittsburgh PA, 2003.

(33) Gavezzotti, A.; Filippini, G. *J. Phys. Chem.* **1994**, *98*, 4831.

(34) Gavezzotti, A.; Filippini, G. *J. Am. Chem. Soc*. **1995**, *117*, 12299.

(35) The determined decomposition products are phthalic acid, phthalic diamide, and butyric diamide.

(36) Paradies, H. H.; Paradies, F. B.; Parker, S. F. *ISIS Rep.* **2002**, 12587.

(37) Chen, F. P.; Prasad, P. N. *J. Chem. Phys*. **1977**, *66*, 4341.

(38) Bellows, J. C.; Stevens, E. D.; Prasad, P. N. *Acta Crystallogr*. **1978**, *B34*, 3256.

(39) Cruickshank, D. W. J. *Acta Crystallogr*. **1956**, *9*, 1005.

(40) McCrone, W. C. In *Physics and Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds., Interscience: New York, 1965; Vol. 2, Chapter 8.

(41) (a) Reichelt, H. M. Phil. Thesis, University of Salford, Salford, U.K., 2006. (b) Hinze, U. Diploma Thesis, University of Applied Sciences, Südwestfalen, Germany, 1992.

(42) (a) Wells, A. F. *Phil. Mag*. **1946**, *37*, 184. (b) Wells, A. F. *Phil. Mag.* **1946**, *37*, 21. (c) Wells, A. F. *Discuss. Faraday Soc*. **1949**, *5*, 197. (d) Lahav, M.; Leiserowitz, L. *Chem., Ing. Sci*. **2001**, *56*, 2245.

(43) (a) Srinivasan, K.; Sherwood, J. N. *Cryst. Growth Des*. **2005**, *5*, 1359. (b) Weissbuch, I.; Leiserowitz, L.; Lahav, M. *Cryst. Growth Des*. **2006**, *6*, 625.