4d, 121142-91-4; **5a**, 121142-92-5; **5b**, 121142-93-6; **5c**, 121142-94-7; **5d**, 121142-95-8; OCNSO$_2$Cl, 1189-71-5; H-Gly-OEt·HCl, 623-33-6; H-DL-Ala-OMe·HCl, 13515-97-4; H-DL-Phe-OMe·HCl, 5619-07-8; H-DL-Met-OMe·HCl, 16118-36-8.

Disproportionation of 4-Nitroacetophenone to 4-Aminoacetophenone and 4-Nitrobenzoic Acid

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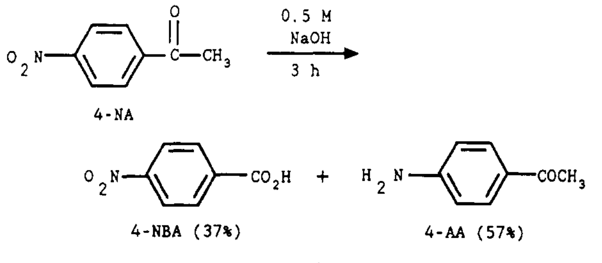
The base-catalyzed aldol condensation of an aldehyde or ketone containing an α-hydrogen involves initial ionization of the α-proton to form an enolate ion, followed by addition to the carbonyl of another molecule of substrate.[1] The Cannizzaro reaction is a disproportionation of an aldehyde lacking an α-hydrogen, to give an equimolar mixture of the corresponding alcohol and acid, usually under strongly basic conditions, the mechanism of which is believed to involve transfer of a hydride ion.[2,3] Aldehydes containing an α-hydrogen may also react via the Cannizzaro pathway when the aldol reaction is slow, although this is rare.[2] We now report an unusual disproportionation reaction of 4-nitroacetophenone (4-NA) in aqueous NaOH, to give 4-aminoacetophenone (4-AA) and 4-nitrobenzoic acid (4-NBA) in high yield. The reaction is interesting for three reasons: (i) 4-NA does not undergo the expected aldol reaction; (ii) the disproportionation reaction is the equivalent of a "Cannizzaro" reaction for 4-NA; and (iii) the mechanism probably involves electron transfer from the initially generated enolate ion of 4-NA.

In a typical run, 4-NA was dissolved in CH$_3$CN and added to an argon-purged solution of 0.5 M NaOH. After 3 h at room temperature, the products were isolated by extraction. The isolated yields of 4-AA and 4-NBA were 57% and 37%, respectively (eq 1), with a recovery yield of ≈70–85%. The structures of the products were confirmed by comparison with the authentic materials, by ^{1}H NMR, IR, and MS. The reaction was found to be strongly base catalyzed, as shown in Figure 1. Below pH 11, the substrate was recovered unchanged. Above approximately pH 13, the conversion of substrate to products was complete within the time of the experiment. Therefore, the appearance of the curves shown in Figure 1 will depend somewhat on the time allowed for reaction. No trace of the expected aldol condensation product(s) was observed in the pH range studied. When air was allowed into the system, the rate of the reaction was retarded, and when pure oxygen was used, the only product observed was 4-NBA. When a freshly prepared solution of 4-NA in aqueous NaOH was transferred to a quartz flat cell and placed in the cavity of a Bruker E200TT ESR spectrometer, strong signals assignable to the radical anion of 4-NA were observed, by comparison with the known spectrum for this species.[4] In lower base strength, the signal was weaker or not observed at all.



(1)

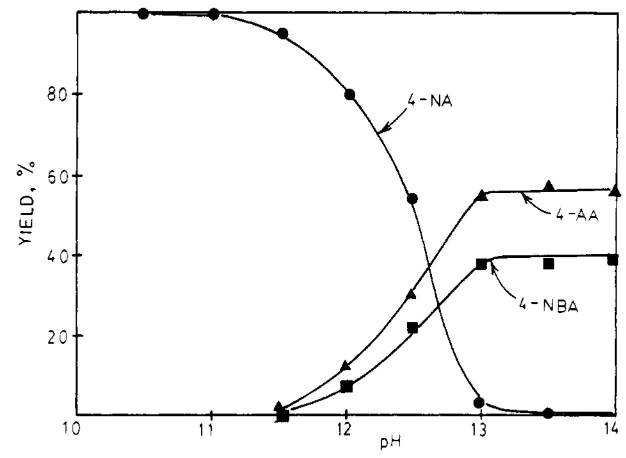
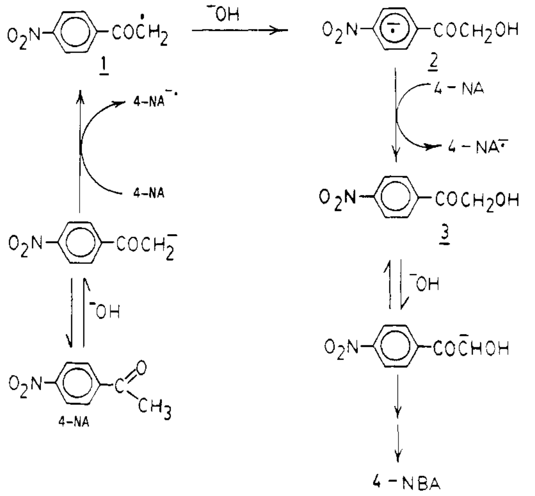


Figure 1. Plot of yield of 4-AA and 4-NBA as a function of pH of the aqueous (NaOH) portion of the solution (≈30% CH$_3$CN) after 3-h reaction at 22 ± 2 °C.

Scheme I



Neither 4-nitrobenzophenone nor 4-nitrobenzaldehyde underwent the above reaction when dissolved in aqueous NaOH, showing that the process requires the presence of ionizable α-protons. In addition, acetophenone itself failed to undergo the disproportionation, indicating the requirement of the nitro group. However, 3-nitroacetophenone did react to give 3-aminoacetophenone and 3-nitrobenzoic acid, although the rate of reaction was substantially slower than for 4-NA.

Addition of 1,4-dinitrobenzene or 4-nitrobenzonitrile, both excellent electron acceptors, to the reaction mixture resulted in a decrease in the yield of 4-AA (from 58% to 30%) but the yield of 4-NBA was unchanged. When 4-nitrobenzonitrile was used, a new product, 4-aminobenzonitrile, was observed (yield 30%) in the product mixture.

Our studies of the chemistry of photogenerated nitrobenzyl carbanions[4-6] have shown that, when photogener-

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[1] March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 829–834.

[2] Reference 1, pp 1117–1119.

[3] Ashby and co-workers have proposed a single electron transfer pathway for both the Cannizzaro and aldol condensation reactions: (a) Ashby, E.; Coleman, D.; Gamasa, M. *J. Org. Chem.* **1987**, *52*, 4079. (b) Ashby, E. C.; Argyropoulos, J. N.; Meyer, G. R.; Goel, A. B. *J. Am. Chem. Soc.* **1982**, *104*, 6788.

[4] Muralidharan, S.; Wan, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1142.

ated in aqueous solution, *p*-nitrobenzyl carbanions readily "eject" electrons. In addition, we have recently established[7] that even non-nitro-substituted carbanions, when generated in aqueous solution, can also "eject" electrons provided that there is a good electron acceptor in solution. Furthermore, nitroarenes in general are known to be oxidants of carbanions in strongly basic solution.[8] These observations coupled with the above results indicate that the mechanism of reaction of 4-NA in aqueous NaOH probably involves initial electron transfer from its enolate ion to the unionized substrate (Scheme I). It is known that 4-NA is an excellent electron acceptor[4] and its radical anion has a lifetime of several minutes in aqueous base. However, in order to reduce 4-NA to 4-AA, a total of six electrons is required. This implies that sequential transfer of electrons to 4-NA and its subsequently derived partially reduced products from the enolate ions is involved. The details of the mechanism beyond the initial electron-transfer step are probably complicated. However, a reasonable pathway (Scheme I) is attack of the radical **1** by hydroxide ion in the medium, to give a new radical anion **2**, which transfers its electron to 4-NA, resulting in 2-hydroxy-4′-nitroacetophenone (**3**). The enolate ion of **3** can now undergo a similar series of steps, which eventually oxidizes the carbonyl moiety to carboxyl (with loss of the extra carbon in the form of carbon dioxide). When an authentic sample of **3** was dissolved in aqueous NaOH and allowed to react over 3 h, 4-NBA was formed in ≈65% yield. However, the expected reduction product in this case (2-hydroxy-4′-aminoacetophenone) was not observed. In hindsight, this was not unexpected since 2-hydroxy-4′-nitroacetophenone would be expected to be oxidized by nitro compounds in basic solution due to its readily ionizable α-methylenes. The identity of the reduced products has not been completely determined, but the isolation of a good yield of 4-NBA in the reaction is consistent with the mechanism proposed in Scheme I.

Experimental Section

^{1}H NMR spectra were recorded at 90 MHz in $CDCl_3$. IR spectra were recorded by using NaCl plates. ESR spectra were recorded on a Bruker E200TT spectrometer in quartz flat cells. Solutions were transferred to the cell via a syringe and purged with argon prior to study. All reactions were carried at 22 ± 2 °C.

All the compounds used in this study were commercially available, with the exception of 2-hydroxy-4′-nitroacetophenone (**3**), which was prepared by refluxing 2-bromo-4′-nitroacetophenone in aqueous solution in the presence of $AgNO_3$. The purity of all the compounds used was >95%, as determined from their ^{1}H NMR spectra.

2-Bromo-4′-nitroacetophenone. To a cooled (ice bath) and stirred solution of 5 g (30 mmol) of 4-nitroacetophenone (Aldrich) in 200 mL of glacial acetic acid was added dropwise 5.1 g (32 mmol) of reagent grade bromine. After addition (≈30 min), the solution was poured into ice water, which gave a mass of precipitate. The solid was collected on a funnel and air-dried, to give crude 2-bromo-4′-nitroacetophenone (6 g; 82%; mp 92 °C, lit.[13] mp 98 °C).

2-Hydroxy-4′-nitroacetophenone (3). A solution of 5 g (20.6 mmol) of 2-bromo-4′-nitroacetophenone and 5 g (30 mmol) of $AgNO_3$ in 250 mL of H_2O and 150 mL of acetone was refluxed for 4 h with stirring. After cooling, the solution was filtered to remove insoluble material, and the filtrate was extracted twice with 150-mL portions of CH_2Cl_2. The crude solid obtained was recrystallized twice from 50% EtOH, to give 2 g (54%) of pure **3** (mp 118–120 °C; lit.[13] mp 121 °C).

Disproportionation Reaction of 4-NA. In a typical run, 100 mg (0.61 mmol) of 4-NA was dissolved in 50 mL of reagent grade CH_3CN and added with stirring to 200 mL of 0.5 M NaOH (100 mmol), which was continuously purged with a stream of argon. After several minutes, the solution turned yellow and became successively darker in color over the period of the reaction. The solution was kept away from light. After 3 h at 22 °C, the solution developed a deep orange color. It was extracted twice with 100-mL portions of CH_2Cl_2, which on evaporation gave ≈47 mg (57%) of pure 4-AA (mp 103 °C, lit.[14] mp 105–107 °C; identical with an authentic sample by ^{1}H NMR, IR, and MS). The aqueous layer was acidified with 10% HCl and extracted twice with 100-mL portions of CH_2Cl_2, which on evaporation gave ≈37 mg (37%) of pure 4-NBA (mp 235–237 °C, lit.[14] mp 239–241 °C; identical with an authentic sample by ^{1}H NMR, IR, and MS).

When oxygen was used in place of argon, the solution never took on the dark orange color observed above over the period of the reaction. Direct extraction of the solution with CH_2Cl_2 gave no observable product by ^{1}H NMR. Extraction of the acidified solution gave only 4-NBA (≈75 mg; 74%). The pH dependence of the reaction shown in Figure 1 was determined by carrying out the reaction in different pH's for 3 h and analyzing the ratio of products and substrate by integration of ^{1}H NMR spectra.

Disproportionation of 2-Hydroxy-4′-nitroacetophenone (3). A solution of 100 mg (0.55 mmol) of **3** in 50 mL of CH_3CN was mixed with 150 mL of 0.5 M NaOH with stirring and continuous purging with a stream of argon. The solution was allowed to stand for 3 h under argon, which was then diluted with 100 mL of distilled H_2O and acidified to pH ≈ 1 with 10% HCl. Extraction of this solution with CH_2Cl_2 followed by evaporation of the solvent gave ≈60 mg (65%) of 4-NBA. The ^{1}H NMR spectrum of the material obtained after complete removal of the water of the aqueous portion proved to be complex and was not studied further.

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Nickel(II)–Lithium Aluminum Hydride Mediated Reduction of Carbon–Sulfur Bonds[†,1]

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A number of organonickel compounds are thiophilic, and several systems are known to be active desulfurization agents.[3,4] To illustrate this, $LiAlH_4$ in the presence of Ni(COD)(bpy) reduces dibenzothiophene and related compounds into desulfurized products.[4] We recently re-

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[†] Dedicated to Professor Kung Tsung Wang on the occasion of his 60th birthday.

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