Reduction of Benzophenone by a Lithium Dialkyl Amide Containing β-Hydrogen Atoms Does Not Proceed by Electron Transfer

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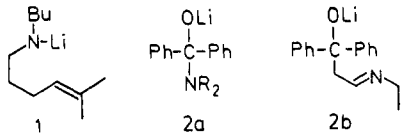
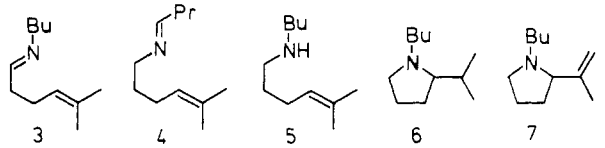
The reduction of benzophenone to benzhydrol by lithium dialkyl amide bases, a reaction studied for 2 decades, was originally postulated to occur via a concerted β-hydride process.[2] Recent studies that focused on the reduced products formed from benzophenone and other ketones have suggested that electron transfer from the base to the ketone could be the first step in such a reduction.[3] In the latter studies somewhat harsh conditions were employed,[4] and qualitative evidence for electron-transfer processes was obtained. Since the reactions of carbonyl compounds and their derivatives with lithium dialkyl amide bases are among the most fundamental modern synthetic organic reactions, we have applied a mechanistic probe, *N*-lithio-*N*-butyl-5-methyl-1-hex-4-enamine (**1**), in a study of the reduction of benzophenone. Our



1 2a 2b

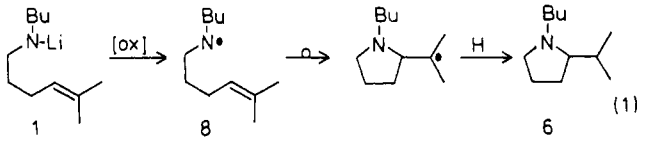
results show that electron transfer from the amide base does not occur in this reaction.

We envision three possible primary pathways for reduction of benzophenone by a lithium dialkyl amide base containing β-hydrogen atoms. β-Hydride transfer and electron transfer followed by radical disproportionation have been mentioned. The third path would involve nucleophilic attack of amide at a carbonyl carbon to give **2a** followed by homolysis of the N–C bond and radical disproportionation.[5] Treatment of benzophenone with probe **1** in tetrahydrofuran (THF) or THF containing hexamethylphosphoramide gave good yields of the reduction product, benzhydrol, and imines **3** and **4** from oxidation of probe **1**, but



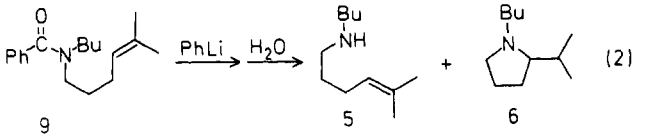
3 4 5 6 7

no trace (<0.1%) of cyclic products **6** or **7**.[6a] Cyclic products would be expected if **1** had been oxidized to radical **8** by electron transfer or by nucleophilic addition–homolysis since radical **8** cyclizes (eq 1).[7]



1 8 6 (1)

Despite the negative evidence against aminyl radical formation, it could be possible that the aminyl radical was formed but that it disproportionated or underwent other reactions faster than it could cyclize. Fortunately, our ability to generate a tetrahedral intermediate by addition of phenyllithium to a benzamide disproved this possibility. We have observed that *N*,*N*-diisopropylbenzamide reacts with phenyllithium in THF at 25 °C to give good yields of benzophenone or triphenylcarbinol depending on the ratio of the reactants;[8] during the reaction the benzophenone ketyl was observed by ESR spectroscopy.[10] When benzamide **9**, which incorporates the probe moiety, was treated with phenyllithium, we found that *N*-butyl-2-isopropylpyrrolidine (**6**) was formed in significant yields in addition to the parent acyclic amine **5** (eq 2).[6b] Benzhydrol was not formed (<2%) in these reactions,



9 5 6 (2)

and we did not detect any (<0.1%) formation of imines **3** and **4**. A control reaction showed that pyrrolidine **6** was not formed when amine **5** was treated with our commercial phenyllithium.

The formation of pyrrolidine **6** suggests that a tetrahedral intermediate formed by addition of phenyllithium to benzamide **9** decomposed at least in part by a homolytic process since other pathways to radical **8** seem unlikely. These results show that benzophenone reduction by amide base **1** via nucleophilic addition–homolysis is not possible. Also, since the radicals formed by electron transfer and by nucleophilic addition–homolysis as well as the reaction milieu in each case should be essentially equivalent, we conclude that the electron-transfer pathway for reduction of benzophenone by **1** does not obtain.

If electron transfer does not occur when benzophenone is treated with lithium dialkyl amides, then what in these reactions leads to the benzophenone ketyl that can be observed[3c] by ESR spectroscopy and implicated[3a] by formation of ketyl coupling products? Benzophenone ketyl could be formed in secondary reactions. After initial β-hydride reduction of benzophenone, the lithium benzhydrol salt could be deprotonated by amide base to give the benzophenone dilithium dianion, and the aldol-like products (like 2b) should suffer retroaldol reactions to supply benzophenone. The benzophenone dianion and benzophenone will react to give ketyl.[11] Preliminary rate studies support this possibility.[12]

Thus, benzophenone does not react with a lithium dialkyl amide base containing β-hydrogen atoms by an electron-transfer process. Reduction of benzophenone occurs by β-hydride transfer, and ketyl apparently is formed in secondary reactions. The implication of our results is important enough to emphasize. Oxidant-derived radical anions could be formed in secondary processes in other reductions by lithium dialkyl amides. Further, much of the evidence accumulated to date supporting electron transfer to organic compounds by bases or nucleophiles has involved the observation of oxidant-derived radical anions; this type of study would appear to be dangerous. We would suggest that many of these conclusions must now be reevaluated and that *our results vitiate any elec-*

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(6) (a) Probe **1** (0.1 N) in THF was added to 1 or 10 equiv of benzophenone at 25 °C; after 4 h the reaction mixtures were quenched and analyzed by GC (tetradecane standard). Imines **3** and **4** were formed in 35–44% total yield. In several runs with a 1:1 reactant ratio, the yield of benzophenone was 39–51% and that of benzhydrol was 36–43%. Similar results were obtained when the reaction mixtures contained 0.2 M hexamethylphosphoramide (HMPA). (b) Benzamide **9** (0.1 or 0.5 N) in THF was treated with 1–5 equiv of phenyllithium in cyclohexane/ether at −78 or 25 °C. After 4–30 h at 25 °C the reactions were quenched. The GC yields of **5** and **6** (tetradecane standard) were 100 ± 3%; the ratio **5**:**6** was 17:1.
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tron-transfer scheme deduced solely from the observation of ketyls arising from the reactions of aryl ketones with reagents that can serve as hydride donors and bases.

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Gas-Phase ^{13}C NMR Spectra and Exchange Kinetics of *N,N*-Dimethylformamide

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Recently, gas-phase NMR kinetic studies of *N,N*-dialkyl-substituted formamides have appeared.[1-3] The simplest molecule of this type, *N,N*-dimethylformamide, presents special problems due to the temperature-independent magnetic equivalence of the ^1H dimethylamino resonances in the gas phase.

The present study reports gas-phase ^{13}C NMR spectra of *N,N*-dimethyl-$^{13}C_2$-formamide (DMF), consistent with first-order exchange rates attributable to the internal rotation process, which are ca. 6.7 times faster than corresponding solution values. The gas-phase value of the free activation energy, $\Delta G^{\ddagger}$ is 19.4 (0.1) kcal/mol, approximately 1.5 kcal/mol lower than values obtained for the neat liquid and solutions in CCl_4, and is consistent with a process having a transition state with greater steric requirements than the molecule's equlibrium configuration.[1,2]

We recently obtained ^1H spectra of DMF at 500 MHz at 23 °C for a sample containing 1100 torr of SF_6 and DMF at its vapor pressure (ca. 0.8 torr) which showed a single resonance (2.88 ppm relative to gaseous Me_4Si, 5.7-Hz fwhm) for the dimethylamino proton resonances. The line widths of the formyl proton resonance was 5.8 Hz. Previous attempts to resolve the ^1H dimethylamino resonances of gaseous DMF at 100 and 360 MHz were also unsuccessful.[3,4] In contrast, in a 10% solution in CCl_4, at 500 MHz the dimethylamino resonances are separated by 83.15 Hz. In order to determine if the suprising magnetic equivalence of the dimethylamino proton resonances in the gas phase is due to rapid exchange or structural factors, we investigated the gas-phase ^{13}C spectrum of DMF.

A sample containing 25 μL of 99% ^{13}C-enriched DMF (MSD isotopes) and 1000 torr of SF_6 in a 6 cm long, 20 mm o.d. tube was used to obtain rate data. The high SF_6 partial pressure ensured first-order rates. On the basis of RRKM calculations and previous gas-phase studies of amides,[1,3] the transition to second-order kinetics for this system is expected at pressures below ca. 10 torr. All ^{13}C NMR measurements were made with a Nicolet 4.8T spectrometer with ^{13}C observation at 50.307 917 MHz. Proton-decoupled gas-phase spectra were acquired in an unlocked mode. Decoupler powers of 2.5 W were supplied to the sample between and 8.5 W during the acquisition pulse, respectively. Typically 2000 free induction decays were acquired and stored in 2 K to produce frequency domain spectra with signal/noise ratios of ca. 50/1. Acquisition times were typically 256.25 ms/transient with a 2.75-s delay and a 90° pulse angle (50 μs). At 50° T_1 values for the up- and downfield ^{13}C resonances are 0.29 (8) and 0.25 (3) s, respectively.[5] Temperatures were controlled with a 0.1 °C pyrometer. The temperature was calibrated at 10-deg intervals with a copper–constantan thermocouple placed in a nonspinning tube, under the same experimental conditions, i.e., decoupling power and repetition rate, used to obtain rate data.

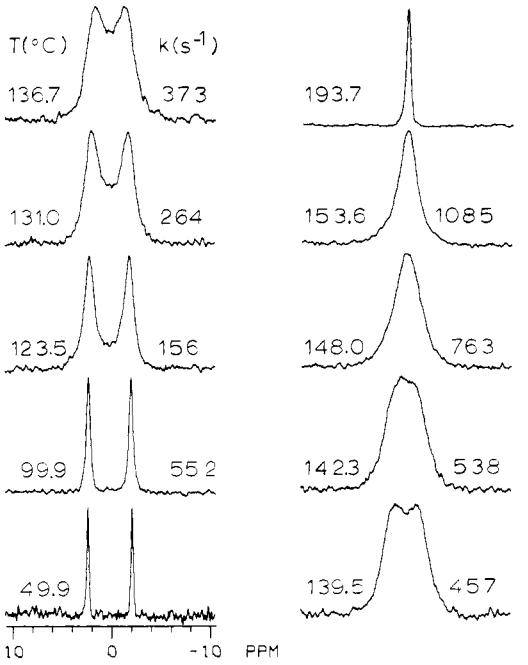

Figure 1. Gas-phase ^{13}C NMR spectra of *N,N*-dimethyl-$^{13}C_2$-formamide. Spectral acquisition parameters are described in the text.

Rates were calculated with the computer program DNMR5,[6] which uses a nonlinear least-squares regression analysis to obtain the best fit of the experimental spectrum. All free induction decays were multiplied by an exponential line-broadening factor of 8.0 Hz, after zero filling to 4K. The digital resolution was 1.95 Hz/point. Typically 900 experimental points were used in the analysis of each spectrum. The effective line-width parameter, T_2, was measured at 30 °C and between 180 and 200 °C and was estimated assuming a linear temperature dependence at each temperature where experimental rate data were obtained. A limiting chemical shift difference of 228.0 ± 2 Hz was obtained at 30.0 °C. Within our experimental uncertainty limits, limiting ^{13}C chemical shifts for gaseous DMF are not temperature dependent. Each spectra was analyzed as an AX system with a $^3J_{^{13}C-^{13}C}$ coupling constant of 1.92 Hz, which was measured for a liquid sample containing ca. 1% DMF in D_2O.

Figure 1 displays temperature-dependent gas-phase ^{13}C spectra of DMF and associated rate constants obtained from the analysis described above. The coalescence temperature for the ^{13}C resonances occurred at 142.3 °C. Analysis of the temperature dependence of 15 rates obtained between 109.3 and 156.4 °C yielded the following kinetic parameters: $E_{act}(\infty)$, 20.5 (0.3) kcal/mol; $\Delta H^{\ddagger}$, 19.7 (0.3) kcal/mol; $\Delta S^{\ddagger}$, 1.0 (0.8) cal/(mol K); $\Delta G^{\ddagger}_{298}$, 19.4 (1) kcal/mol. The small entropy value observed in this experiment is consistent with previous results obtained for similar molecules in the gas phase.[1,2] Previous ^{13}C liquid kinetic studies that employed line-shape analysis and application of the Forsen–Hoffman spin-saturation method reported a $\Delta H^{\ddagger}$ of 20.39 kcal/mol,[7,8] in good agreement with a ^1H line-shape analysis[9] and variable field coalescence measurements.[10] Faster gas-phase exchange rates and lower gas-phase $\Delta G^{\ddagger}$ values are consistent with a process proceeding via a transition state with greater steric requirements than the equlibrium conformation.[1,2] Dilution studies that varied the mole fraction of DMF from 1 to 0.167 in CCl_4

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