

Solvated Electrons in Organic Chemistry Laboratory

Predrag-Peter Ilich,* Kathleen R. McCormick, Adam D. Atkins, Geoffrey J. Mell, Timothy J. Flaherty, Martin J. Bruck, Heather A. Goodrich, and Aaron L. Hefel

Division of Molecular and Life Sciences, Loras College, Dubuque, Iowa 52001

*Peter.Ilich.07@gmail.com

Nenad Juranić

Department of Biochemistry and Molecular Biology, Mayo Foundation, Rochester, Minnesota 55905

Suzanne Sealeem

Department of Natural Sciences, Mathematics and Computers, Central State University, Wilberforce, Ohio 45384

A solvated electron is a powerful reagent (1), capable of reducing benzene derivatives in a solution at the liquid ammonia temperature ($-33.4\text{ }^{\circ}\text{C}$). The early reports on this type of reaction date back to the mid-1930s (2), but it was Alexander Birch who subsequently refined it and expanded it, earning the honor of having the reaction named after him (3). In a typical Birch reaction, an alkali metal in liquid ammonia releases solvated electrons that, in the presence of a proton source, transform an aromatic ring into a nonconjugated 1,4-cyclohexadiene derivative (4). The position of the carbon atoms reduced in this multistep radical–radical anion reaction is influenced by the type of benzene ring substituents. Electron-donating groups ($-\text{OR}$, $-\text{CR}$) show preference for the vinyl carbon (Figure 1A), while electron-withdrawing groups ($-\text{C}=\text{O}$) prefer the allyl carbon position of the product (5) (Figure 1B). Another factor apparently influencing the mechanism and outcome of the reaction is the source of protons; typically, this is ethanol, ammonium chloride, or ammonia.

The solvated electrons, that is, “free” electrons unbound to any particular nucleus, are unusual chemical entities that are rarely studied in the undergraduate science curricula. The interactions of unbound electrons with proximal solvent molecules give rise to a strong absorption of light, $\epsilon_{1500} = 50000\text{ L mol}^{-1}\text{ cm}^{-1}$ at $\lambda_{\text{max}} = 1500\text{ nm}$ (1a), causing a strong coloration of alkali–ammonia solutions (see the supporting material, Figure S2). Solvated electrons can initiate other types of reduction reactions of which the best known is the reduction of 3-methoxy-17 α -hydroxy-17-acetyl-1,3,5-estratriene-20-ketal in the course of the preparation of the oral contraceptive steroid norethindron. The reaction earned the principal author, Carl Djerassi, fame (6) and arguably changed the world in the second half of the 20th century. Our interest in the Birch-type reactions has been 2-fold: (i) to learn how to implement and optimize the use of solvated electrons as a reducing agent in second-year organic chemistry laboratory and (ii) to learn how to control this agent through the addition of potential electron scavengers to the reaction mixture. We used a benzyl alcohol derivative as a reductive substrate in liquid ammonia. With a proper control of the proton supply, solvated electrons in this type of reaction

induce dehydroxylation at the benzyl carbon while preserving the aromatic character of the benzene ring (7) (Figure 2).

However, the effectiveness of solvated electrons and the availability of protons in the reaction solution result in frequent over-reduction of the substrate (6). A need to control the effectiveness of solvated electrons is important in organic chemistry laboratory and essential in the chemistry of living systems. Formation, transfer, and recombination of free electrons with electron acceptors are the essential stages of the most important biochemical reactions: photosynthesis and respiration. It is also the basis of the process causing aging and death. Electron scavengers can intercept, interfere with, and tone down the reductive power of solvated electrons. An electron scavenger is an electron acceptor: a molecule with a higher electron affinity than other reagents.

With this idea in mind and with the electron affinities obtained using electronic-structure calculations, we selected and tested a number of common organic compounds for their ability to compete for solvated electrons in a Birch-type reaction given in Figure 2. Through trial and error, with the help of NMR spectroscopic analysis, and using arguments supported by electronic-structure calculations, we created an original and interesting experiment suitable for chemistry and biochemistry majors.

Experiment

Chemicals

All chemicals were standard grade and used without purification: (i) the substrate, 2-amino-1-phenylethanol (APE), (ii) the scavengers, lithium and sodium 3,5-dinitrobenzoate, benzenetetracarboxylic dianhydride, 2,4-dinitrophenylhydrazine, *N,N*-dimethylaniline, and 4-methoxyaniline, (iii) the principal reagents, Li pellets and ammonium hydroxide, and (iv) other common chemicals, NaOH, HCl, LiOH, CaCl_2 , and MgSO_4 . Extraction of the product and NMR spectroscopic measurements were carried out in 99.8% deuterated chloroform, CD_3Cl .

Liquid Ammonia Production

We obtained liquid ammonia by distillation of ammonia solution (28–30% *m/v*). The two products, water and ammonia,

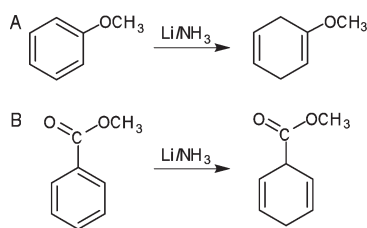


Figure 1. Birch reduction of methoxybenzene (A) and methyl benzoate (B).

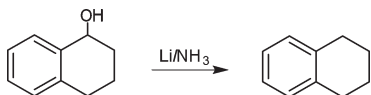


Figure 2. Reductive dehydroxylation of benzyl alcohol derivatives with solvated electron created by a reaction of elementary lithium with liquid ammonia.

were collected in separate traps at two different temperatures (Figure 3; supporting material, Figure S5). This operation has to be carried out in a well-ventilated hood.

Reduction Reaction

After a sufficient volume of ammonia has been collected ($\sim 15\text{--}20\text{ mL}$), it is transferred quickly to a ceramic or glass bowl with thick walls (to slow down heat exchange between the liquid ammonia and the room environment) and used to dissolve the substrate. The substrate, 2-amino-1-phenylethanol, APE, is suitable because (i) it contains the benzyl alcohol functionality, the primary target of the reduction reaction, and (ii) it is closely related to a large and physiologically important class of natural and synthetic α -methylphenethylamines (8). APE, commercially available as a quaternary ammonium salt, readily dissolves in liquid ammonia. The lithium pellets, whose addition causes instantaneous intense deep-purple coloration of the liquid ammonia solution (supporting material, Figure S2), have to be vigorously broken with a glass rod. At the beginning of the reaction, the temperature inside the reaction vessel is $50\text{--}60\text{ }^\circ\text{C}$ higher than the boiling point of liquid ammonia ($-33.4\text{ }^\circ\text{C}$) so the whole reaction takes no longer than 6–10 min. As the liquid ammonia evaporates quickly at room temperature the reaction has to be carried out in a well-ventilated hood. The end of the reaction is easily recognized: as the ammonia evaporates the deep-purple color of the NH_3 -solvated electrons disappears, leaving an off-white paste of the reduction product.

Partially Inhibited Reduction Reaction

The inhibited reaction is carried out in the same manner except that a small quantity of a selected electron scavenger is added and dissolved in liquid ammonia prior to the addition of the substrate and lithium pellets. The visual cues of these reactions are immediate and striking from the onset to the end. The deep-purple solution at the onset of the noninhibited reaction is replaced by a reddish-brown coloration in case of an inhibited reaction (supporting material, Figures S2 and S3). At the end, instead of an off-white paste product of the noninhibited reaction, a honey-gold, strong violet, or a pitch black suspension is obtained in an inhibited reaction. Depending on the character and the quantity present in the solution, the electron scavenger will either mildly interfere with the reduction

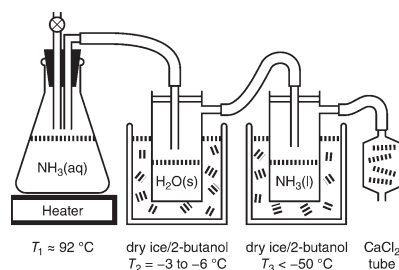


Figure 3. Laboratory setup for small-scale production of liquid ammonia.

of the APE substrate or completely react with the solvated electrons and leave the substrate unchanged (Figure 4).

At this point, we introduced a simplification to the procedure: we skipped the potentially lengthy separation of the product mixture into components and subsequent purification of the product and used NMR spectroscopy to analyze the whole reaction pot. We dissolved the product paste in a small quantity of water at a pH ~ 8 to ensure that the amines are in neutral form and extracted the reaction with 5 mL of CDCl_3 . After the separation of the bottom layer and drying with MgSO_4 , the CDCl_3 solution is carefully decanted (or filtered through a fine glass-wool plug) into an NMR tube up to ca. 0.65 mL mark. In this way, we were able to significantly simplify and speed up the experimental procedure, at the expense of few milliliters of wasted CDCl_3 . (For a larger scale operation, a simple procedure combining acidification and microdistillation can be used to recover most of the deuterated solvent.)

Hazards

Most chemicals, 2-amino-1-phenylethanol, benzenetetracarboxylic dianhydride, 2,4-dinitrophenylhydrazine, *N,N*-dimethylaniline, 4-methoxyaniline, CaCl_2 , and MgSO_4 , require no special precaution beyond the standard safety measures. LiOH and NaOH (solid) and HCl (liquid) are highly caustic substances and should be handled with special care. Skin contact with CDCl_3 should be avoided. Ammonia, released from the ammonia solution and liquid NH_3 , is a highly pungent vapor and should not be inhaled, though limited exposure is not known to cause shorter or longer term health hazards. Dry lithium and sodium 3,5-dinitrobenzoate, when subjected to strong mechanical stress, can detonate, though no danger is present under the conditions of this experiment (0.1–0.01 g, dissolved in liquid ammonia). The stock container with elementary lithium (metal pellets kept in benzene) is potentially the most hazardous chemical and should be handled by the instructor; however, the quantity of Li distributed for each experiment ($< 0.04\text{ g}$) is small enough that the hazard is minimal. All chemicals should be properly stored prior to the experiment, handled with due care during the experiment, and disposed of properly after the experiment.

Results and Discussion

NMR Spectra

There are several lines in the ^1H and ^{13}C NMR spectra reporting the loss of the alcohol group through the reduction with Li/NH_3 . The alcohol carbon resonance is easiest to read: it is a distinct line around 74.1 ppm in the proton-decoupled ^{13}C

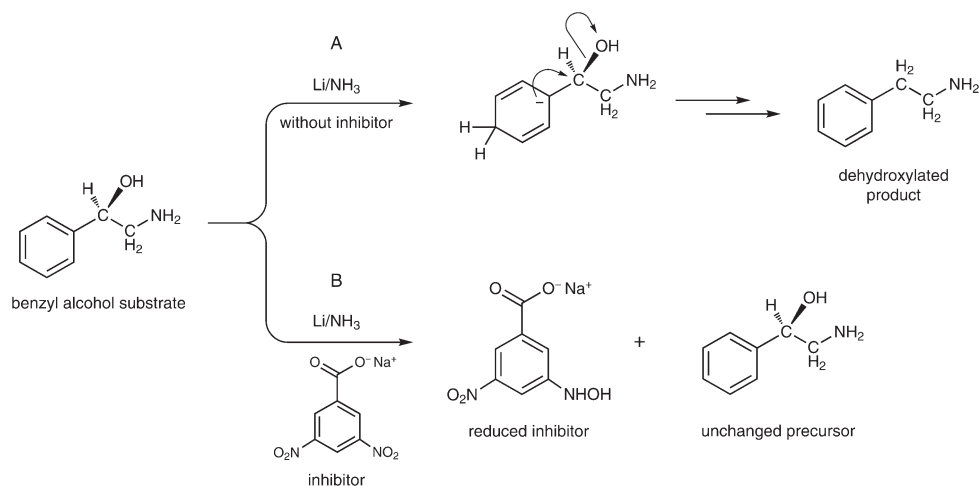


Figure 4. Reductive dehydroxylation of APE to phenylethaneamine (A). The same reaction in the presence of a competitive electron scavenger, Na-3,5-dinitrobenzoate, leaves APE unchanged (B).

spectrum of the substrate (Figure 5A), which disappears in the course of a complete reduction with Li/NH₃. The line shifts to the 40 ppm region, as expected for the 2-phenylethaneamine product (Figure 5B).

The reduction reaction carried out in the presence of electron scavengers shows the formation of other species but also retention of the ¹³C—O line in the ¹³C NMR spectrum of the reaction product. The ¹H spectra of the substrate and products of this reaction offer a number of resonances, but the proton NMR spectrum of APE is relatively complex due to the anisotropic character of the ethane C2 protons and the presence of the geminal and vicinal nuclear spin—spin coupling (see the supporting material).

Electron Scavenging

Electron scavengers were added to the reaction mixture with the goal to capture a fraction of the solvated electrons and in this way interfere with and tone down the reductive dehydroxylation of the substrate. We selected several aromatic molecules as potential scavengers and ranked them on the basis of their calculated electron affinities. We used the Windows version Gaussian-03W suite of programs (9) to calculate the total electronic energy of the neutral and radical anion forms of each potential scavenger. The electron affinity, EA (10), is found as the difference between the energies of the radical anion form and the neutral form, multiplied by −1 (see the supporting material):

$$EA = -[E(\text{radical anion}) - E(\text{neutral molecule})]$$

The electron affinities, calculated at a coarse level, clearly separate the potential scavengers into two groups. One group, the dinitrobenzene and dianhydride derivatives, shows a significant stabilization with the addition of an electron, with electron affinities over +100 kJ/mol. We label this group as “high” electron affinity compounds. The other group of compounds, amino and alkoxy derivatives, is predicted by our calculations to become destabilized by more than 200 kJ/mol following the addition of an electron. Accordingly, we label them as “low” electron affinity compounds. The substrate/scavenger molar ratios in our experiments ranged from 1:1 to 25:1. The qualitative results of our EA calculations are compared with the on—off evidence of each scavenger (20% molar) to interfere with the reductive dehydroxylation of APE by a solvated electron (Table 1).

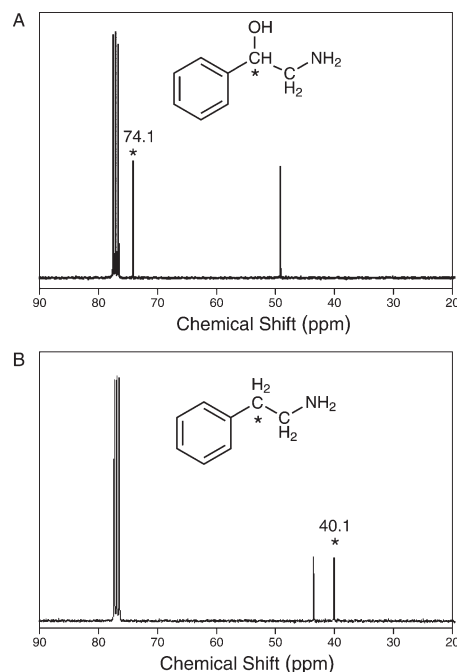
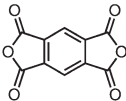
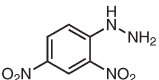
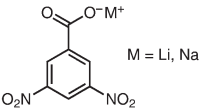
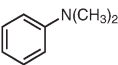
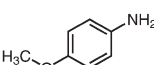


Figure 5. ¹³C NMR spectra of APE (A) and its reduction product (B).

It appears that these results are in line with our qualitative understanding of organic chemical reactivity: the aromatic compounds containing one or more electron-withdrawing groups are able to capture (and retain) an electron and act as effective scavengers. The electron-donating groups, on the other hand, significantly reduce the ability of an aromatic ring to accept an extra electron and are ineffective as scavengers of solvated electrons in this reaction. It is likely that the ability of materials to capture solvated electrons depends on more than one parameter, but the calculated electron affinities seem to be a good first indicator.

This project is probably too labor intensive to be completed within a single period of a second-year organic chemistry lab course. We assigned it to chemistry and biochemistry majors who were enrolled in a one-semester organic synthetic project course; prior to this project, they all completed one year of general

Table 1. Comparison of Five Aromatic Compounds for the Ability to Absorb an Electron and the Effectiveness To Inhibit the Reductive Dehydroxylation of APE

Scavenger	Electron Affinity	Reaction Outcome
(a) 	High	Reaction inhibition
(b) 	High	Reaction inhibition
(c) 	High	Reaction inhibition
(d) 	low	Partial or no inhibition
(e) 	low	Partial or no inhibition

chemistry lab and one or two semesters of organic chemistry lab. All of our students found this project interesting and engaging; they diligently tended to the liquid ammonia production line and, through numerous suggestions and little changes, increased the efficiency of the procedure. They seemed to particularly appreciate the direct and simple use of the NMR analysis. Instead of breaking and extending each batch into a 2–3 week sequence (the synthetic part, the separation and purification, the NMR sample preparation, the spectra recording and the data analysis), this exercise teaches them how to prepare a sample directly from a reaction mixture and record, read, and interpret the NMR spectroscopic results in one lab period. With the possibility to broaden the NMR spectroscopic analysis and the molecular modeling-based structure–activity analysis this experiment can be used to generate one or two additional laboratory projects for chemistry majors.

Conclusion

This project combines an unusual chemical concept (unbound, solvated electron), an efficient and versatile organic reaction (Birch-type reduction), and different laboratory procedures and techniques (preparation of liquid ammonia, handling of elementary lithium and in situ creation of solvated electrons) and teaches how to use the NMR spectroscopy in a direct and relatively easy way. With the addition of electronic-structure calculations and the analysis of electron affinities of potential

reaction inhibitors, this experiment ties together an interesting wet-lab procedure, an advanced instrumental analysis, and an a priori quantitative view of chemical reactivity into an approach that we hope will become a standard in undergraduate chemistry education. We have found the project most beneficial to upper-level students majoring in chemistry or biochemistry.

Acknowledgment

P.-P.I. would like to thank the Chemistry Program, Loras College, Dubuque, IA, for providing a microcomputer workstation and the Iowa Science Foundation (Grant No. ISF 04-13) for awarding the funds for purchasing the molecular-modeling software. All routine NMR analyses were done using a Bruker Avance 300 MHz spectrometer, purchased with the NSF funds awarded to Dave Speckhard, Loras College (MRI-0116699, 2001). All authors acknowledge the help of Ed Maslowsky, Loras College, with the liquid ammonia production setup.

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Supporting Information Available

Instructor notes, with the analysis and assignment of the ^1H NMR spectra of the substrate and reaction products, and an outline of the electronic structure calculation procedure; student instructions with a detailed description of the glassware, quantities of the reagents, procedures for conducting the experiment and analyzing the ^{13}C NMR spectra, and questions pertaining to this experiment; a detailed list of chemicals and associated hazards. This material is available via the Internet at <http://pubs.acs.org>.