Photochemical Generation of Superoxide Radicals in Aqueous Solutions

Richard A. Holroyd and Benon H. J. Bielski*

Contribution from the Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973. *Received March 9, 1978*

Abstract: Superoxide (O_2^-) is shown to be readily generated in aqueous solutions with vacuum-UV lamps of simple design. The lamps are microwave-powered rare gas lamps emitting in the wavelength region from 165 to 185 nm. An internal Suprasil coil contains the aqueous solution. Photolysis of an oxygen-saturated formate solution yields O_2^- at an initial rate of 5–20 μM/s depending on lamp design. The O_2^- is identified by its ESR and ultraviolet absorption spectrum and also by its rate of decay in acid and base. The yield of O_2^- is dependent on photolysis time, microwave power, and oxygen concentration, but is independent of formate concentration. Hydrogen peroxide is formed as a secondary product. A mechanism is proposed and shown to account for the results by comparison to computer calculations. Superoxide can also be formed in good yield by photolysis of hydrogen peroxide solutions. The photolysis of air-saturated water at pH 2 results in hydrogen sesquioxide. These lamps provide a convenient source of superoxide radicals which will facilitate studies of the reactions of this biologically important species.

Introduction

The aim of the work described here was to develop a convenient and inexpensive method of generating aqueous solutions of superoxide (O_2^-) in order to facilitate studies of its chemistry and biochemistry. In recent years interest in superoxide has grown rapidly as evidenced by numerous papers, meetings, and reviews on this topic.[1-3] The interest stems from a need to understand the biological role of O_2^-: its toxicity toward cell structures[4] and role in diseases.[5,6] The individual chemical reactions that may be responsible for such effects have not yet been identified, and a convenient source of this reagent may help the investigation of its chemistry.

Various methods have been used in the past for the generation of O_2^-. These include enzymatic, electrochemical, photochemical, and pulse radiolysis. The merits and disadvantages of each have been discussed elsewhere.[7,8] The pulse radiolysis method,[9] previously employed in this laboratory with a stopped-flow spectrophotometer, has the disadvantage that it requires a source of ionizing radiation such as a Van de Graaff accelerator. However, vacuum-UV photolysis has an effect similar to radiation in that water is dissociated into H and OH radicals:

$$H_2O + h\nu \rightarrow OH + H \quad (1)$$

The quantum yield of reaction 1 is 0.33 at 184.9 nm and 0.72 at 147 nm.[10]

The quantum yield of O_2^- should be equal to twice the quantum yield of reaction 1, since in the presence of oxygen, H atoms are converted to O_2^- (reaction 2). Also the addition of formate is known from pulse radiolysis studies to convert oxidizing OH species to the reducing species CO_2^-. In the presence of oxygen these also convert to O_2^- (reactions 4 and 5):[11-14]

$$H + O_2 \rightarrow HO_2 \rightleftharpoons H^+ O_2^- \quad (2)$$

$$H + HCOO^- \rightarrow H_2 + CO_2^- \quad (3)$$

$$OH + HCOO^- \rightarrow H_2O + CO_2^- \quad (4)$$

$$CO_2^- + O_2 \rightarrow CO_2 + O_2^- \quad (5)$$

In earlier studies, superoxide was detected in the flash photolysis of aqueous formate–oxygen solutions[15] and in the flash photolysis of hydrogen peroxide solutions.[16] The formation of O_2^- in the photolysis of water at 184.9 nm was also demonstrated through the use of superoxide dismutase.[17]

The formation of O_2^- in good yield requires, first, the use of ultraclean solutions to prevent destruction of O_2^- by impurities. Second, the solution is buffered at high pH which shifts the equilibrium in reaction 2 toward O_2^-. This lengthens its lifetime since O_2^- does not react with itself at a measurable rate. Third, a lamp is used which emits strongly at or near the absorption edge of water; that is, the extinction coefficient of water must be large enough so that light is not absorbed by solutes but not too large so that sufficient penetration into the solution is obtained.

Experimental Section

Vacuum-UV Lamps. Most of the lamps used in this study consisted of an outer jacket (of either quartz or Pyrex) and an internal coil or loop made of Suprasil tubing (Figure 1). (Note: Eye protection is recommended if quartz outer jackets are used.) The water to be photolyzed flows through the tubing inside the arc and is surrounded by the plasma discharge. The "window" is the wall of the inner coil which has an area of 20 cm^2. The vacuum-UV light passing through the window is totally absorbed in the 0.5 cm^3 of water in the coil. Alternately the lamps may have a flat Suprasil end window which can be immersed in the aqueous solution. The lamps are first evacuated to 10^{-6} Torr and baked at 400 °C for 48 h. They are then filled with either a few torr of Ar or a medium pressure (10–100 Torr) of Xe. In some lamps a small amount of N_2 is added. The lamps are powered by a 100-W microwave generator (KIVA Model MPG-4M) with an Evenson-type cavity. The microwave generator operates either dc or pulsed (70–800 Hz). The lamp emission spectra are recorded on a McPherson Model 218 spectrophotometer.

Chemicals. Since the decomposition of O_2^- solutions is catalyzed by small traces of metal, it is essential that all chemicals be highly and carefully purified.[9] No metal instrument or vessel can be used. The sodium formate, phosphate, and EDTA are recrystallized prior to use. The water is distilled and then treated by a Milli-Q reagent grade water system. The solutions are stored in quartz vessels.

Analysis. For kinetic and spectral studies the yields of O_2^- were measured using a Durrum Model D 110 stopped-flow fast kinetics spectrophotometer[9] at λ 260 nm where ϵ 1925 M^{-1} cm^{-1}.[18] In this instrument the effluent from the lamp mixes with an equal volume (0.5 cm^3) of acid in order to lower the pH and follow the O_2^- decay. The yield of O_2^- is calculated from the initial minus final absorbance. Since O_2^- solutions are relatively stable at high pH,[18,19] solutions can also be photolyzed as they flow through the lamp. The O_2^- in the effluent stream is then assayed spectrophotometrically at 260 nm. This method is convenient for testing the output of different lamp designs and parameters. Hydrogen peroxide was assayed by the iodide method.[20] The ESR spectrum of O_2^- was recorded at 95 K on a Varian Model 4500 ESR spectrometer.

Results

Figure 2 shows the absorption spectrum of O_2^- formed by photolysis with an Ar lamp. The solid line represents the O_2^-

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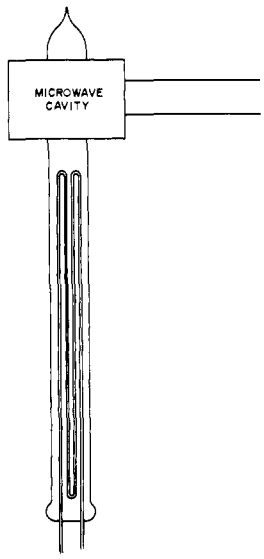

Figure 1. Rare gas filled vacuum-UV lamp design. Outer jacket is quartz (or Pyrex), inner tube is 60 cm of 0.1 cm i.d. Suprasil quartz.

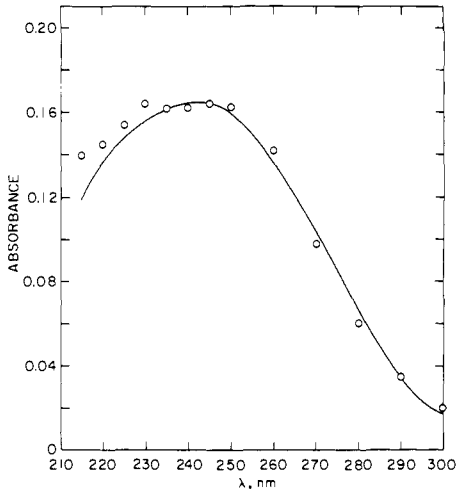

Figure 2. Absorption spectra of product formed in the vacuum-UV photolysis of an oxygen-saturated aqueous solution of 0.01 M formate; 10-s exposure in Ar lamp at 50 W power. ⊙, photolysis; solid line is spectrum of O_2^- from ref 11.

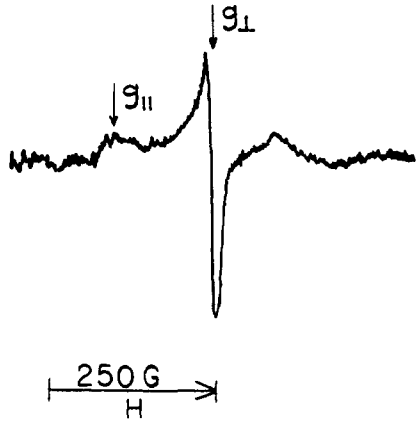

Figure 3. ESR spectrum of O_2^- formed in the photolysis of oxygen-saturated 0.02 M formate solution at pH 11.7, $g_\perp = 2.006$, $g_\parallel = 2.103$; sample at 95 K.

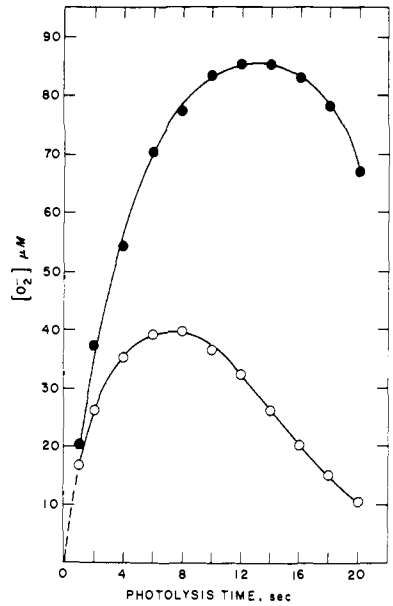

Figure 4. Yield of O_2^- as a function of photolysis time for an Ar lamp (pressure = 1 Torr) operated at 50 W. Solution contained 0.01 M formate at pH 11.2; ○, air saturated; ●, O_2 saturated.

spectrum obtained by radiolysis of this solution.[18] There is good agreement between the two spectra expect for the slightly higher absorbance at wavelengths below 230 nm in the photolysis case which is attributed to interference by H_2O_2.

The decay rate of the O_2^- was determined with the stopped-flow spectrophotometer. The decay follows second-order kinetics and the observed rate constants are 2.7×10^4 M^{-1} s^{-1} at pH 8.3 and 8.7×10^5 M^{-1} s^{-1} at pH 2.0. These values are in good agreement with the values of 2.4×10^4 and 9.5×10^5 M^{-1} s^{-1} determined at these pHs in a radiolysis study.[18,19]

The ESR spectrum of O_2^- at 95 K is shown in Figure 3. This spectrum was obtained by flowing an oxygen-saturated aqueous solution of 0.02 M formate at pH 11.7 through an Ar lamp (pressure 1 Torr) and freezing the effluent. The spectrum is an asymmetric singlet quite similar to that obtained in ice.[21,22] We find the low-field parallel feature at $g_\parallel = 2.103$ and the more intense perpendicular component at $g_\perp = 2.006$.

Effect of Variables. Typically the yield of O_2^- as a function of photolysis time first increases, passes through a maximum, and then decreases, as shown in Figure 4. The yield of O_2^- is the observed yield at the end of the photolysis and is not corrected for spontaneous decay. Decay is minor since k_{obsd} is about 10 M^{-1} s^{-1} at the pH used (11.5). Increasing the initial oxygen concentration enhances the initial rate of O_2^- formation slightly and increases the maximum yield considerably. For oxygen-saturated formate solutions, concentrations of O_2^- greater than 200 μM are attained at the maximum (Tables I and II). The yield of peroxide is small initially but increases rapidly at later times, as is shown in the final columns of the tables. The ratio $[O_2^-]/[H_2O_2]$ is large initially and steadily decreases with time to values less than one.

The time at which the superoxide yield reaches a maximum varies from lamp to lamp and is attributed to differences in absorbed light intensity. Where the initial rate is high (20 μM/s for the data shown in Figure 4), the maximum is attained in ~13 s. Where the initial rate is lower, as for the 30-Torr Xe lamp (Table II), the maximum is attained at 80 s. (The absorbed light intensity is also a function of the penetration depth—see Discussion.)

The yield of O_2^- at short times is approximately linearly dependent on microwave power (Table II). The dependence becomes sublinear at higher power and at longer times. The

Table I. Photolysis of Formate Solutions with Ar Lamps[a]

lamp Torr	lamp W	[formate], mM	[oxygen], mM	photolysis time, s	yields[a] O_2^-, μM	yields[a] H_2O_2, μM
1.0	50	10	1.28	2	38	
1.0	50	10	1.28	15	110	
1.0	20	10	1.28	10	37	
1.0	100	10	1.28	10	96	
1.0	50	0	0.25	8	11	
1.0	50	1	0.25	8	49	
1.0	50	10	0.25	8	49	
1.0	50	50	0.25	8	54	
1.0	50	100	0.25	8	57	
10.0	20	20	1.28	2	25	0
10.0	20	20	1.28	5	60	58
10.0	20	20	1.28	10	110	110
10.0	20	20	1.28	30	190	480
10.0	20	20	1.28	50	220	930

[a] Measured concentration of product in lamp.

Table II. Photolysis with Xe Lamps

lamp Torr	lamp W	photolysis time,	yields[a] μM	yields[a] H_2O_2, μM
Oxygen-Saturated, 0.02 M Solution				
1.0	50	10	59	36
7.5	60	2	15	0
7.5	60	10	59	20
7.5	60	30	61	42
7.5	60	80	60	240
30.0	50	3	30	14
30.0	50	10	68	54
30.0	50	30	140	180
30.0	50	80	220	400
30.0	50	120	200	560
44.0	50	10	128	
200.0	50	10	117	
0.8 (5% N_2)	50	8	55	49
30.0	10	5	5	
30.0	20	5	8	
30.0	40	5	18	
30.0	80	5	46	
Air-Saturated, 0.15 M Hydrogen Peroxide Solutions (pH 10.6)[a,b]				
7.5	60	10	25	
7.5	60	20	37	
7.5	60	40	80	
7.5	60	100	176	

[a] Measured concentration of product in lamp at end of run. [b] At this lower pH a larger decay of O_2^- is expected.

O_2^- yield is independent of formate concentration from 1 to 100 mM.

The factor in lamp construction which influences the yield of O_2^- most is surface area of the window. Most of the lamps used had window areas of 20 cm^2. Lamps of greater area produce proportionately more O_2^-. Another factor affecting the output is pressure of rare gas. For a Xe lamp the yield of O_2^- increases with pressure between 5 and 40 Torr and then levels off above 40 Torr (Table II). The lamp design makes no provision for cooling of the solution; consequently, for very long runs the solutions become warm and this causes oxygen dissolution and bubbles which interfere with the spectrophotometric measurements. Individual lamps have been used over periods of months; in general, lamps made of all quartz proved more reliable than those with Pyrex outer walls.

Spectra. The first absorption band of water has a maximum at 150 nm in the liquid phase, which is considerably blue shifted compared to the vapor phase.[23] The absorption spectrum of liquid water in the region of interest is shown in Figure 5A. The presence of oxygen is reported to enhance the absorption slightly at long wavelengths (red shift).[24] The solutes OH^- and $HCOO^-$ also absorb in this region.[25] As shown in Figure 5A, absorption by $HCOO^-$ is significant at wavelengths above 180 nm. Absorption by OH^- is weak except at very high pH.

The emission spectrum of the Xe lamp at 30 Torr with a Suprasil window is shown in Figure 5B; there is a continuum extending from the Suprasil cutoff to 195 nm with a maximum at 172 nm. For a nongettered lamp filled with 1 Torr of argon, many lines are observed between 165 and 193 nm due to adventitious impurities[26] (Figure 5C). The lines below 170 nm are strongly absorbed near the window and do not contribute significantly to the O_2^- yield. The line at 193 nm (due to carbon) is not absorbed significantly. The useful lines are those between 170 and 182 nm. The output of these lamps as measured by the initial O_2^- formation rate is $4 \pm 2 \times 10^{15}$ quanta/s.

Lamps containing a small percentage of N_2 in an inert gas at a total pressure of 1 Torr emit two lines at 174.3 and 174.5 nm. These are at a nearly ideal wavelength to be absorbed and yet penetrate a significant distance into the water. However, the output of such a lamp is less[27] and lamps of this type were found to produce less O_2^- than either the nongettered Ar lamp or the Xe lamps.

Discussion

The results show that considerable amounts of superoxide are formed in oxygen-saturated formate solutions by a short exposure with a rare gas filled lamp. Hydrogen peroxide is a secondary product since its yield is small initially and the ratio $[O_2^-]/[H_2O_2]$ decreases monotonically with time.

The maximum of the continuum emission from the Xe lamp is at a wavelength which is strongly absorbed by water; where $k = [H_2O] \times \epsilon = 700\ cm^{-1}$. Similarly there are strong emission lines in the Ar lamp in this region. Thus the results are attributed to the photochemical decomposition of water; that is, the main primary process is, as stated earlier, dissociation into H and OH. However, it is clear from Figure 5 that solutes may absorb a fraction of the light at longer wavelengths. Absorption by formate results in dissociation into HCO and OH; the HCO dissociates into H and CO.[28] Absorption by OH^- is known to produce OH and e_{aq}^-.[29] Solvated electrons react rapidly with O_2 to form O_2^-.[30] Thus the result of absorption by OH^- (important only at very high pH) or by $HCOO^-$ would be the same as reactions 1-5. It has been pointed out that oxygen enhances light absorption by water at wavelengths above 185 nm and this is attributed to direct formation of a charge transfer complex.[24] To the extent that the complex

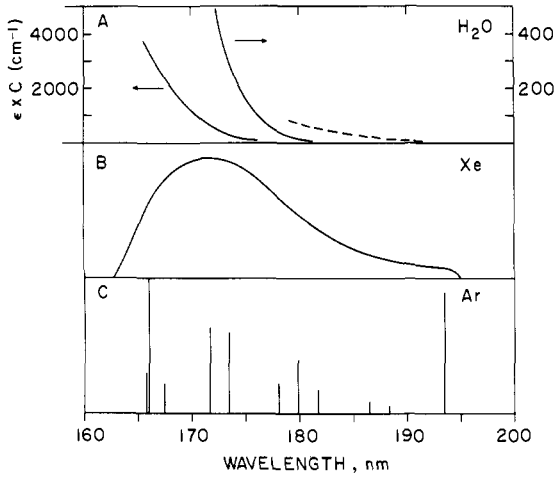

Figure 5. Spectra: (A) absorption spectrum of liquid water (solid lines) and 0.02 M formate (dotted lines) (ref 25); (B) emission spectrum from Xe lamp at 30 Torr; (C) emission spectrum from an "ungettered" Ar lamp at 1 Torr.

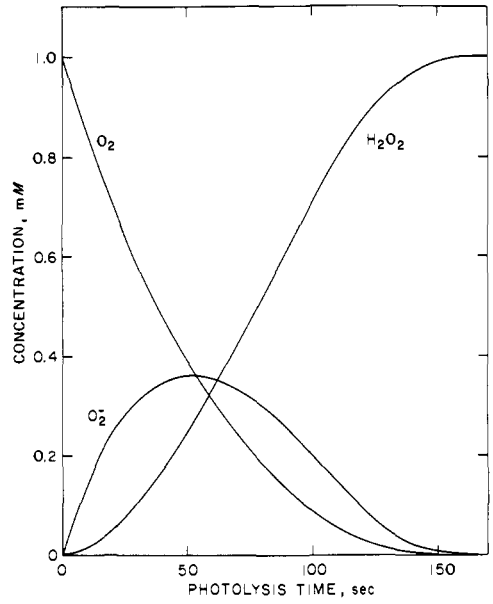

Figure 6. Computer-calculated curves showing concentration of O_2, O_2^-, and H_2O_2 as a function of photolysis time. See text for mechanism and values of rate constants. Calculation is for a 0.02 M formate solution and an absorbed light intensity of 20 μEinsteins/L·s.

dissociates it would form OH and O_2^- and the result again would be the same as in the mechanism given.

Therefore it is assumed that the mechanism includes reactions 1-5. Because of the high intensity, oxygen will be depleted especially near the window. Thus reaction 6, presumed to have a rate constant of 10^{10} M^{-1} s^{-1},[30] will convert O_2^- to peroxide. Finally termination (reaction 7) will also occur:

$$H + O_2^- \rightarrow HO_2^- \text{ (peroxide)} \quad (6)$$

$$CO_2^- + CO_2^- \rightarrow HCOO^- + CO_2 \quad (7)$$

In order to compare with experiment the concentrations of O_2, O_2^-, and H_2O_2 based on this mechanism were calculated as a function of time by numerical integration of the coupled rate equations. The calculation was done on a PDP-11 computer using the Runge-Kutta method.[31] Steady state assumptions were made for [H], [OH], and $[CO_2^-]$. The values of rate constants are as follows: $k_2 = 1.6 \times 10^{10}$,[11] $k_3 = 1.5 \times 10^8$,[12] $k_4 = 2.5 \times 10^9$,[13] $k_5 = 2.4 \times 10^9$,[14] $k_6 = 1.0 \times 10^{10}$ (assumed), and $k_7 = 5.0 \times 10^8$ M^{-1} s^{-1}.[32]

A typical calculation based on this mechanism is shown in Figure 6. As a result of numerous calculations it was shown that the mechanism predicts the following: (1) The yield of O_2^- will reach a maximum in the reaction zone equal to 36% of the initial oxygen concentration (460 μM for oxygen saturated). (2) Eventually the O_2^- will be completely converted to peroxide. (3) The initial rate of O_2^- formation will be increased 47% by increasing the initial oxygen concentration fivefold. (4) The time at which the O_2^- maximum occurs is inversely proportional to the absorbed light intensity, and increased by increasing the oxygen concentration.

These predictions are to be compared to the following experimental results: (1) The maximum observed yield of O_2^- is 220 μM for photolysis of an oxygen-saturated formate solution and the yield of O_2^- at the maximum increases with oxygen concentration, but not proportionately. (2) The yield of O_2^- does in time eventually decrease (Figure 4) and large yields of peroxide are observed (Table I). (3) Increasing the oxygen concentration fivefold enhances the initial rate of O_2^- formation (roughly 20%). (4) The maximum occurs at a longer time if the oxygen concentration is increased (Figure 3). The differences for different lamps are attributed to differences in absorbed light intensity.

Quantitative agreement of the calculations with the results is not expected for several reasons. One is the depth of the photolysis zone. At the maximum in the Xe emission, 99% of the light is absorbed within 28 μm path length or within 11% of the aqueous volume. Shorter wavelengths will be absorbed in a smaller volume and the resultant high absorbed intensity will result in rapid conversion to peroxide. Longer wavelengths will be more penetrating. The observed maximum yield of 200 μM indicates that in this lamp about one-half of the 0.5 cm^3 of water is actually irradiated. Another reason not to expect quantitative agreement is that concentrations are not uniform as assumed. Oxygen will be less and product concentration will be greater near the window; however, diffusion will tend to even this effect out near the window and some mixing by convection will occur as the photolysis progresses. Another complication which has been ignored is photolysis of products. There is practically no emission by these lamps between 195 and 300 nm. However, hydrogen peroxide could be photolyzed by emission around 195 nm. Apparently this is minor since large yields of peroxide build up during photolysis.

Other Systems. This paper has been concerned primarily with the photolysis of formate solutions. Another interesting system is the photolysis of hydrogen peroxide solutions in which H and OH are converted to O_2^- via reactions 8 and 9:[33,34]

$$H + H_2O_2 \rightarrow OH + H_2O \quad (8)$$

$$OH + H_2O_2 \rightarrow HO_2 + H_2O \quad (9)$$

As shown in Table II the yield of O_2^- is linear with time. There is no back reaction since ample quantities of peroxide may be added. However, it is necessary to work at lower pH because of the instability of peroxide in base. At the lower pH the second-order disappearance of O_2^- becomes significant and there will be some loss of O_2^- during photolysis by this reaction.

The photolysis of oxygen-saturated water at low pH in the absence of other solutes leads to the formation of H_2O_3. In this system the OH radicals react with the HO_2 radicals (reaction 2):

$$OH + HO_2 \rightarrow H_2O_3 \quad (10)$$

The first-order decay rate of H_2O_3 formed by photolysis of a solution at pH 2.16 was observed to be 0.86 ± 0.8 s^{-1}. This is in good agreement with the rate constant obtained in a pulse radiolysis study at this pH.[35]

Summary

The reactions of O_2^- as well as other species can be readily investigated by the use of rare gas filled vacuum-UV lamps in combination with a stopped-flow spectrophotometer or ESR spectrometer. The best lamp design is that shown in Figure 1. A lamp of this type filled with 7.5 Torr Xe produces only moderate yields of O_2^- but is advantageous because almost no peroxide is formed at short photolysis times. The medium-pressure (30–200 Torr) Xe lamp is recommended where large yields of O_2^- are desired. The argon-filled lamps are more intense when first prepared but may change with time since the output depends upon impurity lines.

Acknowledgments. The authors wish to thank H. Schwarz, who made several helpful suggestions, and K. Walther and P. Roman for the fabrication of the quartz lamps. They also wish to express their gratitude to D. Schlyer, who made the vacuum-UV monochromator available to us. This research was carried out at Brookhaven National Laboratory under contract with the U.S. Department of Energy and supported by its Division of Basic Energy Sciences and NIH Grant 1 R01 GM23656-01.

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Palladium-Assisted Intramolecular Amination of Olefins. Synthesis of Nitrogen Heterocycles

Louis S. Hegedus,* Gary F. Allen, Joseph J. Bozell, and Edward L. Waterman

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received March 2, 1978*

Abstract: 2-Bromoanilines were converted to 2-allylanilines by treatment with π-allylnickel halide complexes. These were cyclized to 2-methylindoles or to quinolines by treatment with palladium chloride under both stoichiometric and catalytic conditions. 2-Aminostyrene was converted to indole. The cyclization is thought to proceed by a palladium-assisted nucleophilic attack on the olefin of the allyl group.

Introduction

In recent years, organometallic reagents have been used in the synthesis of a variety of heterocyclic ring system. Indoles, benzofurans, and phthalides were prepared from *o*-iodoanilines, *o*-halophenols, or *o*-halocarboxylic acids, respectively, by treatment with copper acetylides.[1] Intramolecular oxymercuration of 2-allylcyclohexanols led to both cyclohexane fused pyrans and furans after reduction.[2] The cyclization of γ,δ-unsaturated alcohols was also studied.[3] A similar oxymercuration was used to convert 2′-hydroxychalcones to aurones using mercury(II) acetate in Me_2SO.[4] The same procedure converted *o*-allylphenols to 2-methyl-2.3-dihydrofurans.[5] Ring closure by mercury was also used to form the heteroyohimbane ϵ ring.[6] Chromanocoumarans were synthesized by the reaction of 2-*H*-chromenes with *o*-chloromercuriphenols.[7]

Indoles were prepared from 2-chloro-*N*-methyl-*N*-allylaniline,[8] and oxindoles from 2-chloro-*N*-alkyl-*N*-acrylanilide[9] by treatment with tetrakis(triphenylphosphine)nickel. Indoles and isoquinolines were prepared from similar substrates using a palladium catalyst[10] (Heck arylation conditions[11]). Acrylic acid diallylamides were cyclized to a mixture of pyrrolidones and *N*-acylpyrroles by treatment with $PdCl_2$ or $RhCl_3$.[12] π-Allylpalladium complexes were intermediates in the palladium-catalyzed cyclization of amino olefins to alkaloid ring systems such as ibogamine, mesembrine, and actinobolamine.[13] Divinylpiperadines were synthesized by the Pd(II)-catalyzed reaction of butadiene with imines,[14] while imidazolones, dihydroxyoxadiazinones, and tetrahydrotriazinones were synthesized by the $PdCl_2$-catalyzed reactions of isonitriles with α-amino acid esters, α-hydroxy acid hydrazides, and α-amino acid hydrazides.[15]

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