Free Radicals in Nucleophilic Aromatic Substitution of N-tert-Butyl-2,4,6-trinitrobenzamide

by

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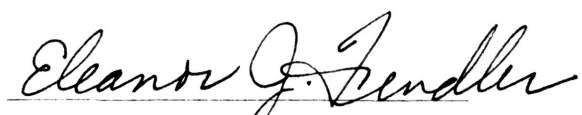
Submitted in Partion Fulfillment of the Requirements of the University Undergraduate Fellows Program

1978 - 1979

Approved by:



Eleanor J. Fendler Ph.D.

April 1979

ABSTRACT

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The nucleophilic aromatic substitution of N-tert-butyl-2,4,6-trinitrobenzamide (NtBB) has been carried out in dimethylsulfoxide in the presence and absence of sodium cholate under photolytic and nonphotolytic conditions. The formation of at least two free radicals was observed in the formation and decomposition of the intermediate 1-hydroxy sigma-(or Meisenheimer-)complex(es) of NtBB in the absence of oxygen. The obtained results are compared and contrasted with those for other nucleophilic aromatic substitutions in which free radicals have been observed.

ACKNOWLEDGEMENTS

I would like to express my deepest thanks to Dr. Eleanor J. Fendler for the guidance and the many lessons I have learned through her. I would also like to thank Steven Rosenthal for his help and many explanations.

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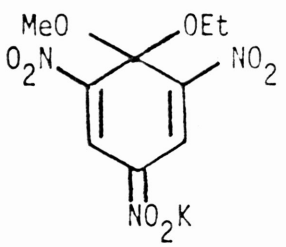
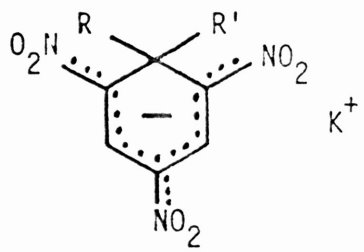
INTRODUCTION

The reactions between nucleophiles and aromatic species with electron withdrawing substituents to form highly colored solutions have been observed for nearly a hundred years.[1,2] In 1902, Meisenheimer[3] obtained red salts by treating either 2,4,6-trinitroanisole with potassium ethoxide or 2,4,6-trinitrophenetole with potassium methoxide. Since both products gave the same mixture of picryl ethers upon acidification, he argued that the two products were identical and assigned them the structure 1 in which the negative charge is localized on the para nitro group. Relatively recent research employing instrumental techniques, however, has demonstrated that the structure of this and



1



2

similar salts is best represented by structure 2 in which the 1-carbon atom has been rehybridized from sp^2 to sp^3, the substituents R and R' lie in a plane perpendicular to that of the rehybridized cyclic structure and the negative charge is delocalized over the nitro groups. Salts of this type, which are -complexes, have become commonly termed Meisenheimer complexes. The structures of many of these compounds have been

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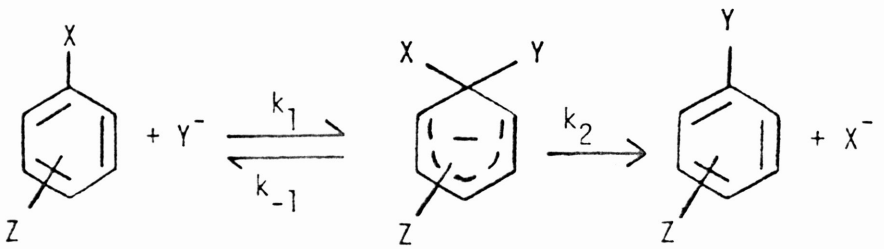
established by ^{1}H nmr spectroscopy,[4-11] x-ray crystallography,[12-14] and/or other physical methods.[15] As evidenced by the large number of reviews,[16-21] a considerable amount of recent research has been directed toward elucidation of the structures and mechanisms of formation and decomposition of these complexes. This surge of interest is, at least in part, due to the fact that the Meisenheimer complex provides compelling evidence for the bimolecular S_N2Ar mechanism for nucleophilic aromatic substitution reactions involving substrates activated by electron withdrawing substituents. Since nucleophilic aromatic substitution has been extensively reviewed recently,[22-29] only a brief summary will be given here.

Nucleophilic substitution reactions with aromatic substrates are generally of three types:[30] (1) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile; (2) reactions catalyzed by very strong bases and proceeding through aryne intermediates; and (3) reactions in which the aromatic ring is activated by electron withdrawing groups ortho and para to the leaving group. Not unexpectedly, the currently accepted reaction mechanisms for each of these reaction types differ considerably.

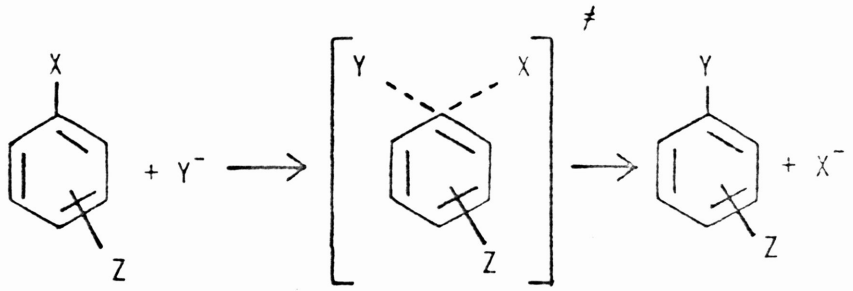
This review shall deal specifically with the mechanism for the third reaction type. In general, the accepted mechanism for reaction in the third category is given by equation 1. S_N2Ar (bimolecular nucleophilic aromatic) mechanism; synonomous terms in use for this mechanism



(1)

include the addition-elimination, the intermediate complex, and the activated complex mechanism. The aromatic system must be activated toward nucleophilic attack by electron withdrawing (Z) substituents. In the case of nitro groups, the substituents also stabilize the intermediate -complex 3 via delocalization of negative charge.

An alternative mechanism, proposed earlier for reactions of this type, involves synchronous bond making by Y and bond breaking by X (equation 2). Both mechanisms are compatible with the observed bi-

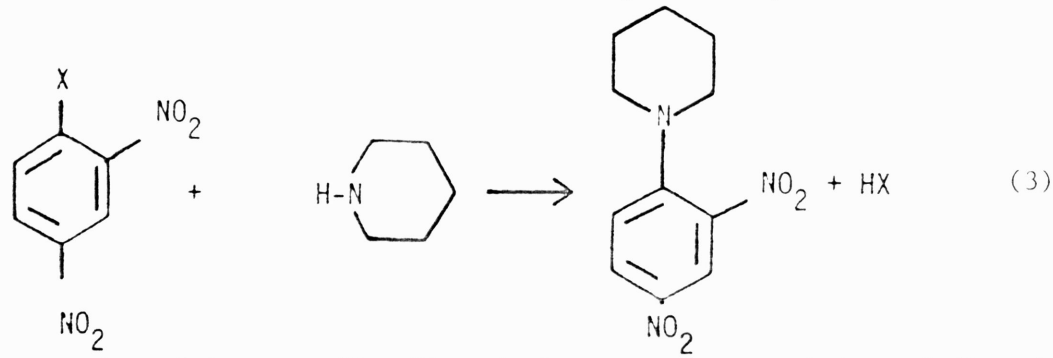


(2)

molecularity of the reaction, i.e. first order dependence upon both ArX and Y. Evidence[21,30,31] for the former mechanism(equation 1) includes: (1) the isolation and subsequent characterization of the σ-complex by instrumental methods such as ^{1}H nmr spectroscopy, x-ray crystallography, ir, and uv-visible spectrophotometry; and (2) a wealth of information from kinetic and thermodynamic studies. However, a considerable body of other evidence has been accumulated which is only compatible with the two step mechanism (equation 1).

The fact that σ- or Meisenheimer complexes exist and have been isolated does not "prove" that they are intermediates in nucleophilic aromatic substitution reactions. For example, the observed relative reactivities of halides as leaving groups is unreasonable if the reaction were a one-step displacement (equation 2), since the leaving

group order would be I>Br>Cl>F, as in aliphatic S_N2 reactions. However, for the reaction[31] given in equation 3, the rate is 3300 times faster when X=F than when X=I. Additionally, rate constant dependence on substituents is Br>Cl>$-SO_2C_6H_5$>$-OC_6H_4NO_2$-p>I with only a five-fold difference in reactivity between Br and K, indicating that leaving groups which are similar in electronegativity but different in other chemical structures are similar in reactivity. This phenomenon



(3)

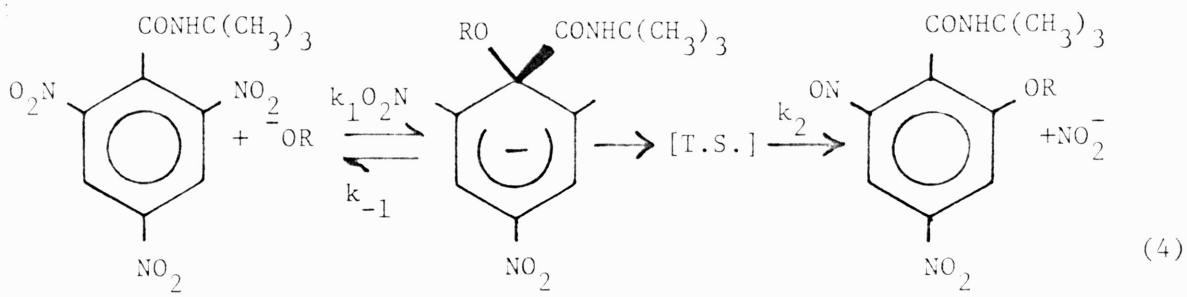
(abscence of an "element effect") and the greater reactivity of flourinated aromatics indicate a two-step mechanism in which expulsion of the leaving group is not involved in the rate limiting first step. The second step does become rate limiting when the nucleophile is highly reactive, when the intermediate complex is stabilized and/or when the leaving group is poor.[32]

Due to their importance in nucleophilic aromatic substitution (vide supra), it is not at all suprising that Meisenheimer complexes are currently the subject of a considerable amount of research using a wide variety of techniques. The majority of the earlier detailed studies were carried out on adducts of strong bases (e.g. ^-OH, ^-OR) with nitro-substituted benzenes. Subsequently, cyclohexadienylides of benzenes with less strongly electron withdrawing groups (e.g., -CN, $-COCF_3$, $-COCH_3$, -CONHR, $-SO_3R$) were investigated. More recent work

has involved adducts composed of a wide variety of nucleophiles and aromatic compounds, including intramolecular complexes. Among the aromatic and heteroaromatic compounds known to form Meisenheimer complexes are naphthalenes, anthracenes, azulenes, pyridines, pyrimidines, S-triaxines, pyridine-N-oxides, thiophenes, serenophanes, furans, purines, benzofuroxans, and tropones.[15] Nucleophiles utilized range from hydride, sulfite, alkoxide, cyanide, and hydroxide ions to carbanion, amines, halomethyl anions, and organometallic compounds.[15,27,30] Additionally, the employment of a wide variety of reaction conditions is yielding information on the effects of added salts, reactant concentration or strength, solvent or mixed solvent systems, light temperature, free radical, isotopic replacement, and added surfactants.

In recent years, various species, for example: σ-complexes, charge transfer complexes, anion radicals, dianions, dianion radicals, free radicals, carbocations, carbanions, and arynes, have been postulated to be involved in the reactions of aromatic compounds with nucleophiles.[33] In 1970 Bunnett and Gloor[34] first postulated a $S_{RN}1$ mechanism for nucleophilic substitution of non-activated aromatic compounds. Subsequently, Shein[33] and other workers reported evidence for free radical formation of deactivated aromatic compounds in the presence of nucleophiles using nmr spectroscopy and other techniques (see reference 33 for a review of this literature).

The interaction of hydroxide and methoxide ion with N-tert-butyl-2,4,6-trinitrobenzamide (NtBB) results in the equilibrium formation of the hydroxy adduct and the methoxy adduct, respectively,



(4)

R = H, CH_3, or CH_2CH_3

The rate constants for the attainment of the equilibria as well as for the subsequent formation of nitrite ions were determined at different lyate ion concentrations. Additionally, the structures of the complexes were established unequivocally using proton nuclear magnetic resonance spectroscopy.[10]

Biomolecular nucleophilic aromatic substitution reactions in the presence of micellar surfactants have been investigated and reviewed. Included are: studies on attack by both anionic and neutral nucleophiles, the use of both benzenoid and naphthalenoid substrates, measurement of rates of complex formation and decomposition, employment of cationic, anionic, and neutral surfactants as well as phospholipids, and determination of binding constants, CMC's, and thermodynamic parameters from kinetic data.

The formation and decomposition of a variety of Meisenheimer complexes have been investigated in both aqueous and non-aqueous micellar solution (vide supra). However, no dipolar aprotic solvents, such as dimethylsulfoxide (DMSO), have been employed as the primary solvent nor have any naturally occurring surfactants, such as bile acids or salts, been used in these studies. The main purpose of this research is to elucidate the role of free radicals in the reaction of

NtBB in DMSO solution in the presence of bile salts (see Appendix). This reaction system can be considered to be a relevant model for related physiological reactions occurring in or near membranes and other similar biological structures as well as for some phases of digestive processes.

EXPERIMENTAL

Reagents and Materials

N-tert-butyl-2,4,6-trinitrobenzamide (NtBB) was prepared employing procedures reported in the chemical literature.[10,35] Two elutions of the crude product through a column of neutral alumina with benzene-methanol (90/10, v/v) followed by recrystallization from benzene-petroleum ether (bp 40-60°C) yielded white crystals melting at 238-239°C (lit.[35] 234-235°C).

The hydroxy complex of NtBB was prepared by the addition of 0.25 ml (0.5 mmol) of 2.00 M aqueous potassium hydroxide (BDH) to a warm solution of 0.1495 g (0.5 mmol) of tert-butylamine in 0.90 ml of dioxane. The dark red crystals whech appeared after ca. 2 minutes were removed by filtration under dry nitrogen and were washed with dry benzene and anhydrous ether. After drying in vacuo over P_2O_5, the crystalline product contained approximately 0.5 mol dioxane of crystallization (by ^1H nmr integration). Anal. (analysis performed by Galbraith Laboratories, Inc., Knowville, Tenn.) Calcd. for $C_{11}H_{13}N_4O_8K \cdot 0.5C_4H_8O_2$: C, 37.9; H, 4.16; N, 13.6; K, 9.50. Found: C, 35.26; H, 3.83; N, 13.22; K, 10.04.

Sodium cholate, NaC, (Sigma Chemical Co.) was dried to constant weight at 60°C and 1 torr over P_2O_5. The obtained ^1H nmr spectra indicated no impurities and were in excellent agreement with those in the literature.[36]

Stock solutions of NtBB and the corresponding hydroxy complex used for spectral studies and kinetic measurements were prepared by

accurately weighing out a dry, solid sample of the appropriate compound on Ainsworth 21 N or Mettler analytical balances and dissolving it in dry DMSO in a volumetric flask. Dilute solutions were prepared by volumetric dilution. These solutions were either made up immediately prior to use or stored in the dark under refrigeration to prevent decomposition.

Spectroanalyzed reagent DMSO (Fisher) was dried over freshly activated Linde Type 4A molecular sieves and stored under nitrogen. All water (H_2O) used in this study was doubly distilled. All other reagents and solvents used were the best available reagent grade materials.

Fremy's salt was prepared from reagent peroxylamine disulfonate and sodium carbonate in doubly distilled deionized water.[37]

Methods and Techniques

The epr spectral data were obtained using a Varian E-109 spectrometer with direct data-link to a computer. The e-line data were determined with a field-frequency lock at different modulation amplitudes and ambient temperature. The computer adjusts a marker which aligns repetitive scans thereby obviating line-broadening due to magnetic field drift. The scan range is contained in 2048 data bits, and spectra are automatically shifted according to the marker and recorded on drums of the Sigma 2 computer.

Simulations have been done by generating stick-spectra upon which are superimposed the appropriate line shapes. G-values were determined based on Fremy's salt solution(2.0055-2.0057 gauss).

The same cell configuration of the standard Fremy's salt solution and the sample solution was used to quantitate the number of spins in the sample (for Fremy's salt $\varepsilon_{248nm} = 1690$).[37]

All solvents and solutions used in the epr studies were degassed on an Ace-Burlitch inert atmosphere high-vacuum line via at least three freeze-pump-thaw cycles and saturated with argon. The epr samples were prepared by mixing the appropriate volumes and concentrations of NtBB in argon-saturated DMSO with DMSO followed by argon-filled syringe transfer to a vacuum line tube to which the appropriate stock solution of NaC in DMSO was added. Argon-saturated water was added immediately. Time of mixing was accurately monitored using a stopwatch. A 1/4 mm thick quartz flat cell mounted in the epr cavity was filled with the solution under argon using a syringe. The times from mixing of the epr scans were recorded.

All solutions were isolated from any extraneous source of light at all times, and the background monitored for the determination of the presence or absence of radicals in the flat cell prior to irradiation. Epr spectra were obtained approximately 5 minutes after addition of NaC to the NtBB.

Irradiation of the samples was carried out using a 250 watt xenon lamp (with an ir filter) placed 62.5 cm from the front of the epr cavity. A convex planar focusing lens was used to focus the beam on the center of the epr cavity.

A Photovolt Aquatest II, Model 702 coulometer, designed specifically for Karl Fischer titrations[38] of water, was used to determine

the water content of solids, solvents, and solutions. The instrument read out directly in micrograms of water, required no standardization, and was operated only with standard (Photovolt) reagents.

UV-visible spectra were recorded on a Cary Model 14 recording spectrophotometer under argon in matched 1 cm pathlength quartz cells with teflon stoppers. The spectra were recorded against an appropriate reference (blank) solution identical in composition to the sample solution except for the absorbing species of interest.

The 60 MHz ^{1}H nmr spectra were obtained using a Varian Associates A-60A and T60 spectrometers at an ambient probe temperature of 32.5±0.5°C. and 37.0±0.5°C ,respectively. The 100-MHz spectra were obtained using a Varian Associates HA-100 spectrometer at an ambient probe temperature of 31.0±0.5°C. Chemical shifts on the δ scale were measured in ppm relative to TMS (δ= 0 ppm).

The ^{1}H nmr spectra were determined on solutions in DMSO-d_6 (Aldrich, 99.5 atom % D) in both air-saturated and degassed argon-saturated solutions. For irradiated samples, the spectra were recorded one minute and 35 seconds after 3 minutes of irradiation under the same photolytic conditions as utilized for the flat cell in the epr cavity. The ^{1}H nmr spectra of the *in situ* generated complex were obtained by dropwise addition of small amounts of a concentrated (0.50 M) solution of sodium cholate in DMSO-d_6 to a *ca.* 0.19 M solution of NtBB in DMSO-d_6 and observing the spectral changes at each cholate concentration with time.

RESULTS AND DISCUSSION

Nucleophilic aromatic substitution of N-tert-butyl-2,4,6-trinitrobenzamide (NtBB) by hydroxide ion in H_2O and methoxide ion in methanol has been postulated to proceed according to equation 4. In the presence of sodium cholate (NaC) in dimethylsulfoxide (DMSO), the reaction mechanism proceeds involving the same intermediate species (see Figure 1). In all of these media, the products are a substituted aromatic compound and nitrite ion. Since it is improbable that a relatively stable 2,2- or 4,4- complex would be an intermediate involved in the formation of these products, an investigation of free radical species was carried out in this system.

In order to probe the role of free radicals in nucleophilic aromatic substitution in general, interactions and reactions of NtBB with NaC were investigated in the absence of oxygen under photolytic and non-photolytic conditions. The reactions were carried out in DMSO solution which approximates the micro-environment in biological systems to a greater extent than aqueous media. No free radical formation was exhibited by either NtBB or NaC in the presence of light; however, in NaC solution varying from 0.0025 M to 0.20 M concentrations, the formation of free radicals was apparent (Figure 2).

The epr spectra for the free radical species formed both before and after light have been determined and simulated (Figures 3-6). Since the hydroxy-Meisenheimer complex of NtBB under these conditions (0.20 M NaC and 1.0 M H_2O) is formed with a rate constant of $k = 1.0 \times 10^{-2}$ sec^{-1}, it has been postulated that this complex is the intermediate

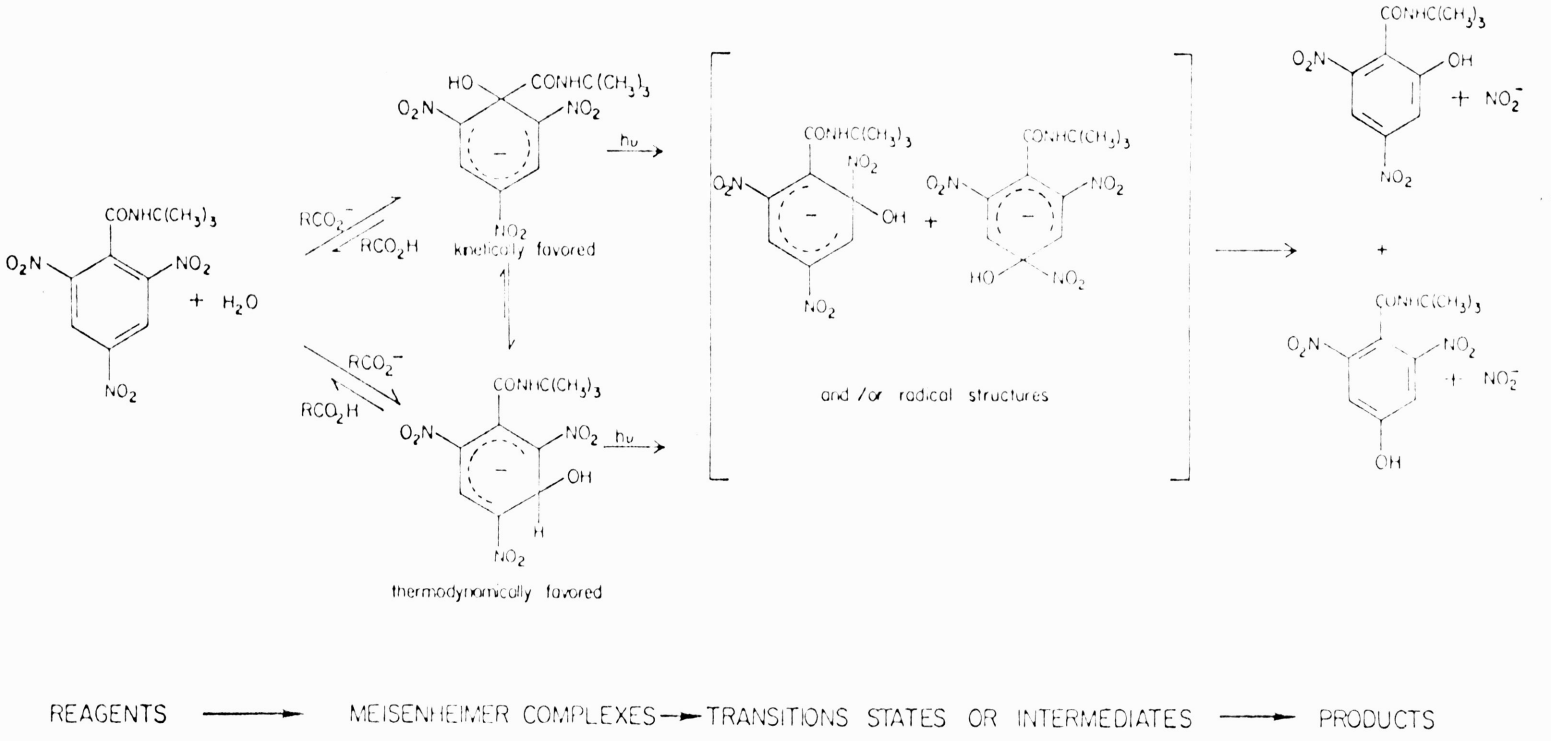


Figure 1. Reaction scheme for N-tert-butyl-2,4,6-trinitrobenzamide (NtBB) and sodium cholate (NaC).

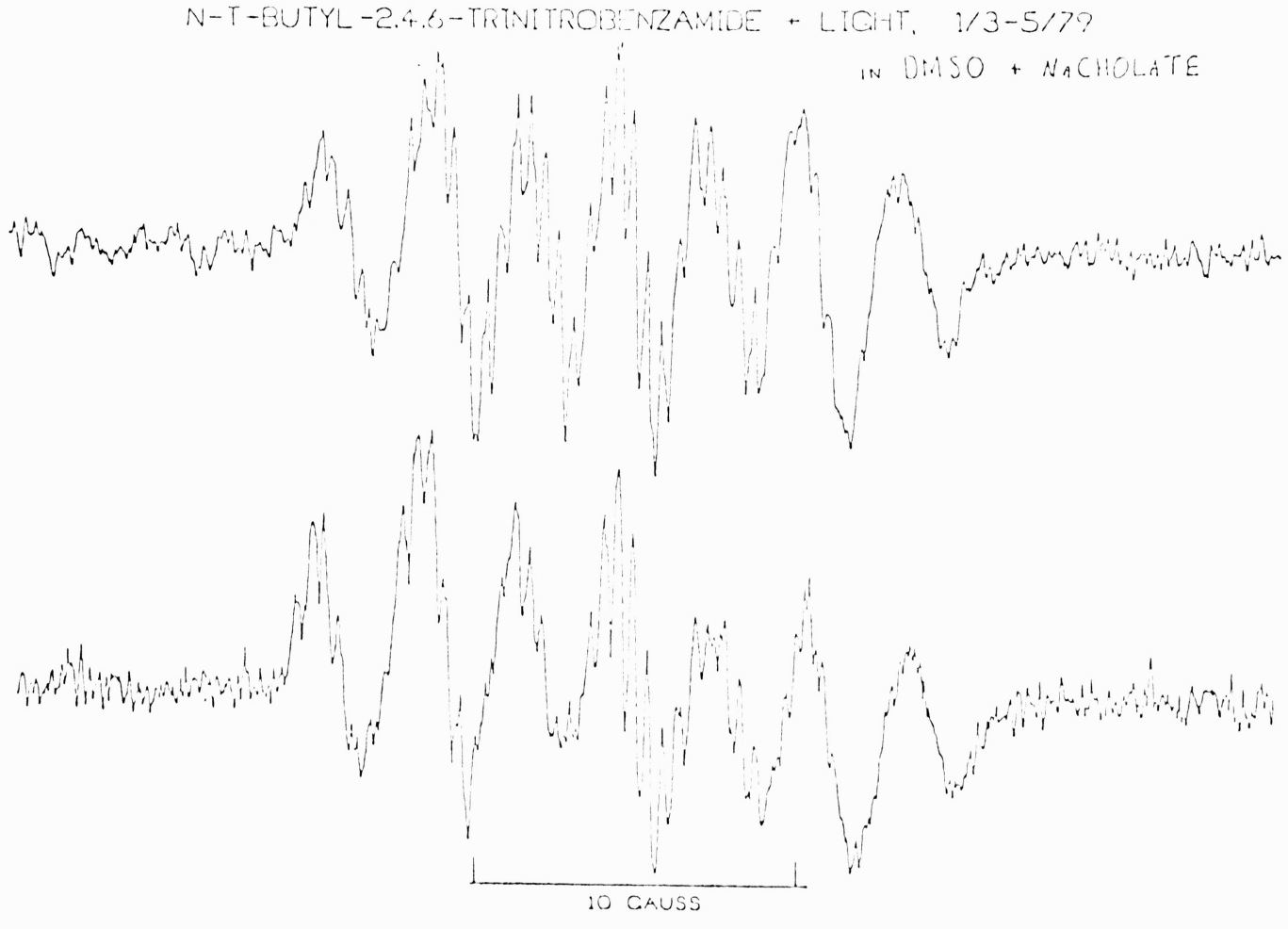
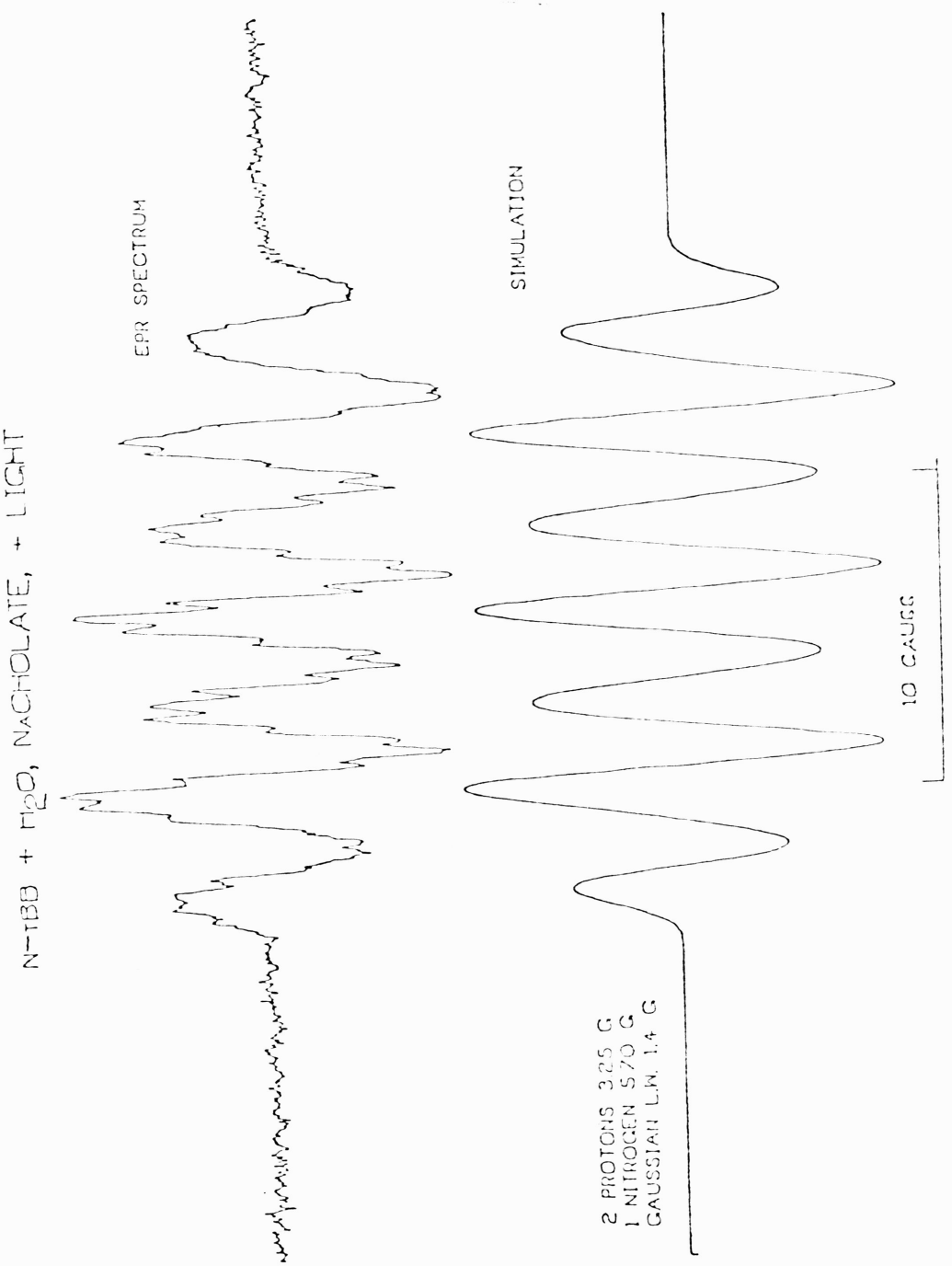


Figure 2. Epr spectra of the radical(s) formed in DMSO by photolysis of NtBB and NaC.

Figure 3. Epr spectrum and its simulation of radical species formed from NtBB in NaC solution under photolytic conditions.


N-TBB + H2O, NaCholate, + LIGHT
EPR SPECTRUM
SIMULATION
10 GAUSS
2 PROTONS 3.25 G
1 NITROGEN 5.70 G
GAUSSIAN L.W. 1.4 G

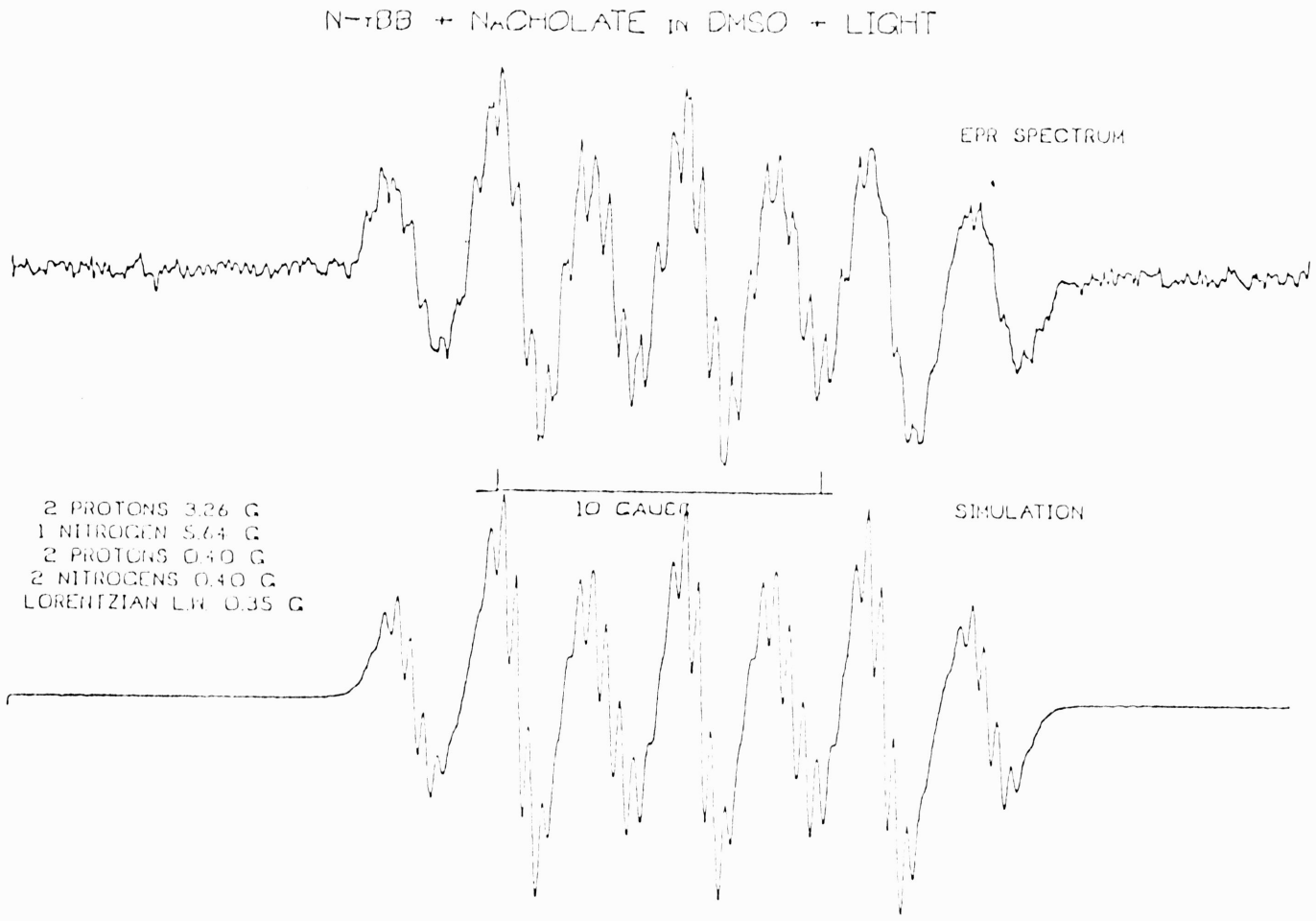


Figure 4. Epr spectrum and its simulation for the radical species formed in the photolytic reaction of NtBB and NaC in DMSO solution.

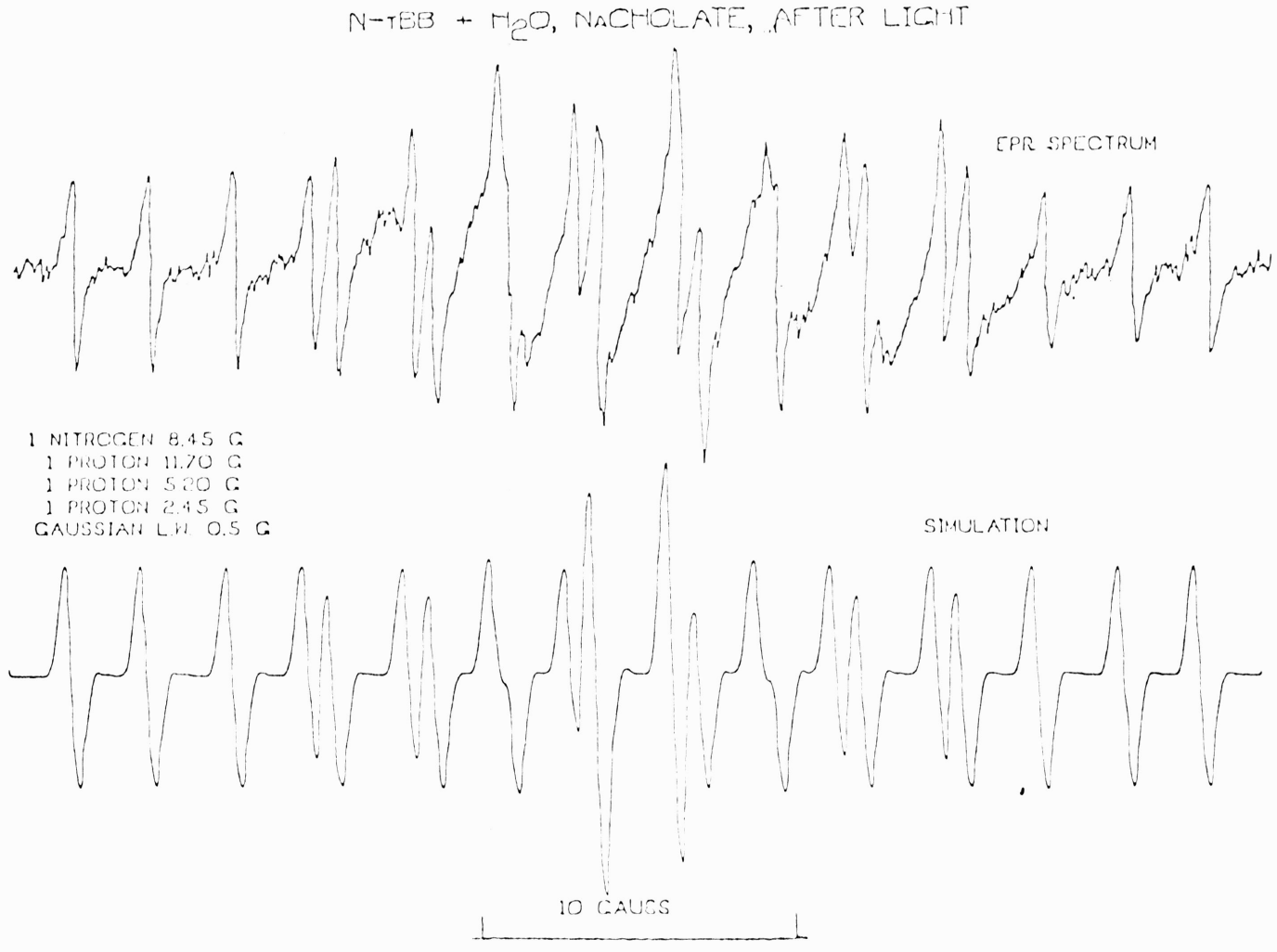
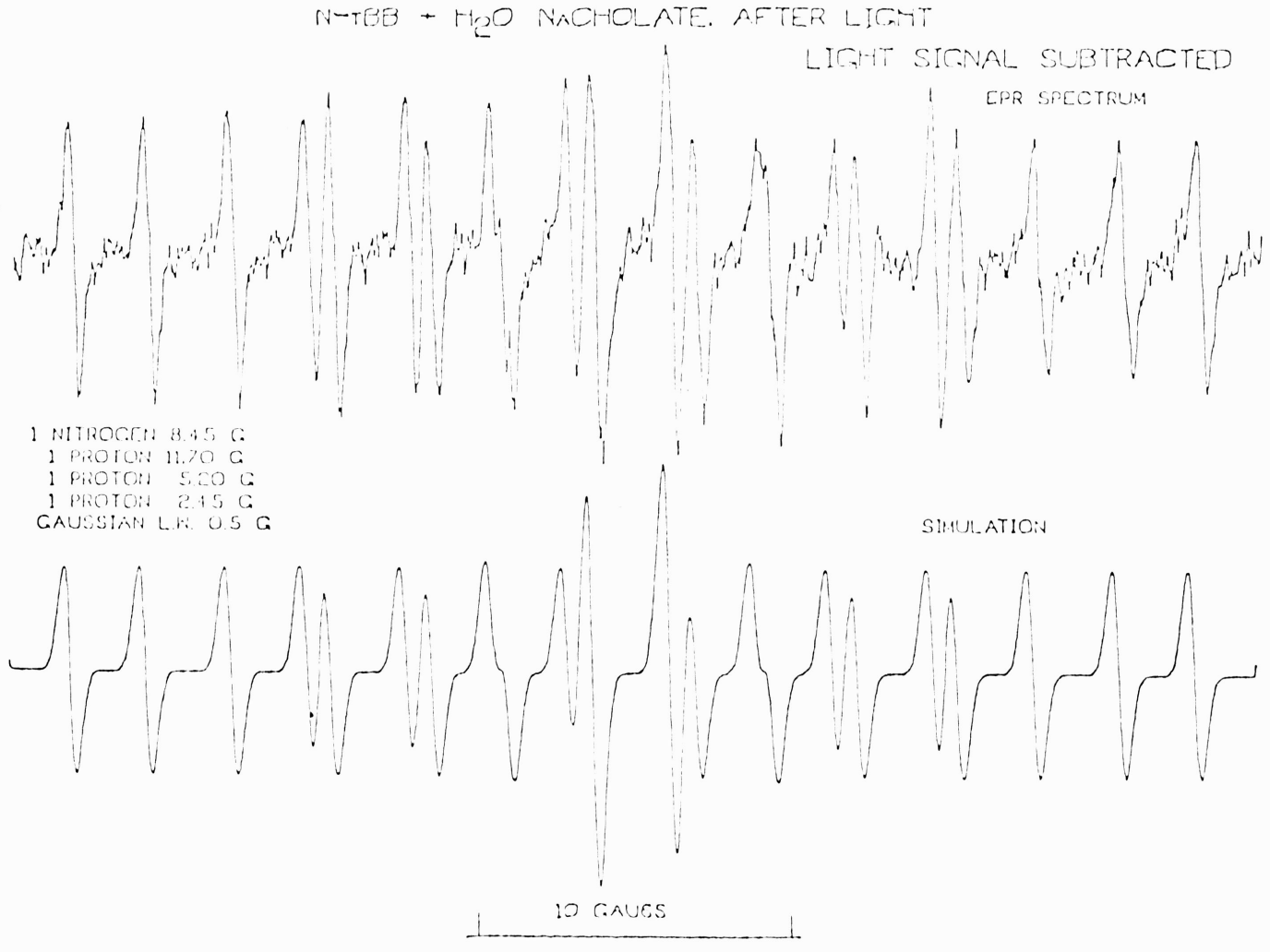


Figure 5. Epr spectrum and its simulation of the radical species in the photolysis of NtBB, H_2O, and NaC in DMSO 5 minutes after the light has been turned off.

Figure 6. Epr spectrum and its simulation of the radical species in the photolysis of NtBB, H_2O, and NaC in DMSO 5 minutes after the light has been turned off, with subtraction of the signals from the initially formed radical.


N-tBB + H_2O NaCHOLATE. AFTER LIGHT
LIGHT SIGNAL SUBTRACTED
EPR SPECTRUM
1 NITROGEN 8.45 G
1 PROTON 11.70 G
1 PROTON 5.20 G
1 PROTON 2.45 G
GAUSSIAN L.R. 0.5 G
SIMULATION
10 GAUSS

in the nucleophilic aromatic substitution of NtBB.[39] The photochemical behavior of this complex was investigated under conditions identical to those utilized for NtBB. The kinetics of both radical formation and decomposition were determined for NtBB (Figures 7-16) and its hydroxy-Meisenheimer complex. The role of water was also investigated (Figure 13) in the rate of radical formation and decay.

Two free radicals appear to be involved. These radicals may be involved in σ-complex formation - one which is formed very rapidly (Figures 14-16), and the second, more long-lived radical which consists of a 7-line pattern (Figures 2 & 3) which can be simulated using the following parameters: 2-protons, 3.25 gauss; 1 nitrogen, 5.70 gauss; and Gaussian line width, 1.4 gauss. These parameters similate the basic features of the spectra of Figure 3; however, a far better simulation of the spectra of the same solution was obtained using the following parameters; 2 protons, 3.26 gauss; 1 nitrogen, 5.64 gauss; 2 protons, 0.40 gauss; 2 nitrogens, 0.40 gauss; Lorentzian line width, 0.35 gauss, as illustrated in Figure 4. The latter simulation and the observed hyperfine structure may suggest the presence of more than one fairly stable free radical. It is probable that this is an aromatic free radical or an anion radical species; however, its structure has not yet been determined.

After light, this system decays, giving a relatively stable free radical consisting of 20-lines at low modulation amplitude (Figures 5 and 6). A simulation in agreement with the observed spectra has been obtained using values of: 1 nitrogen, 8.45 gauss; 1 proton, 11.70 gauss; 1 proton, 5.20 gauss; 1 proton, 2.45 gauss; Gaussian line width, 0.5 gauss

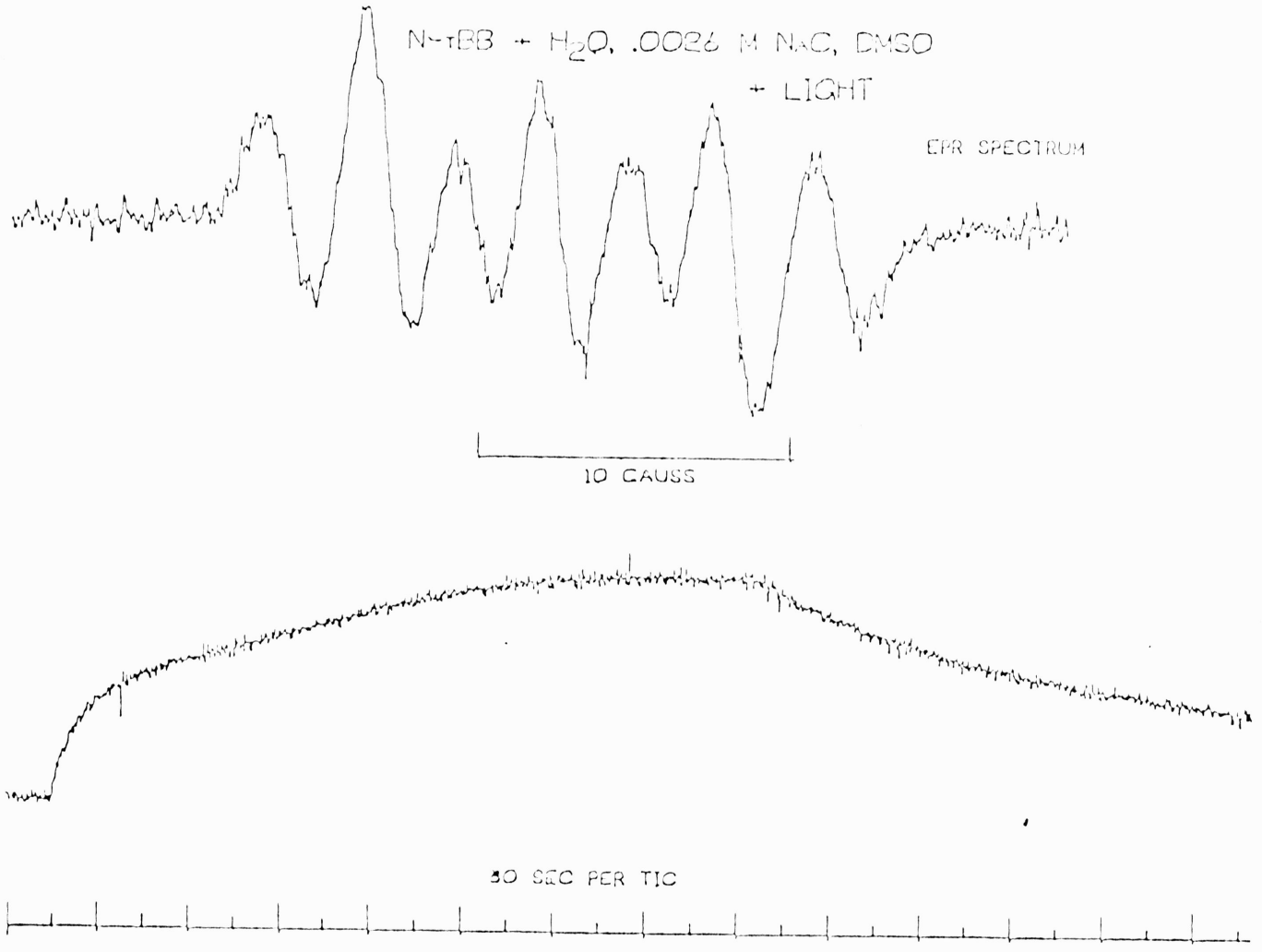


Figure 7. Epr spectrum and kinetics for the photolytic reaction of NtBB, H_2O (1.0 M), and NaC (0.0026 M) in oxygen-free DMSO solution.

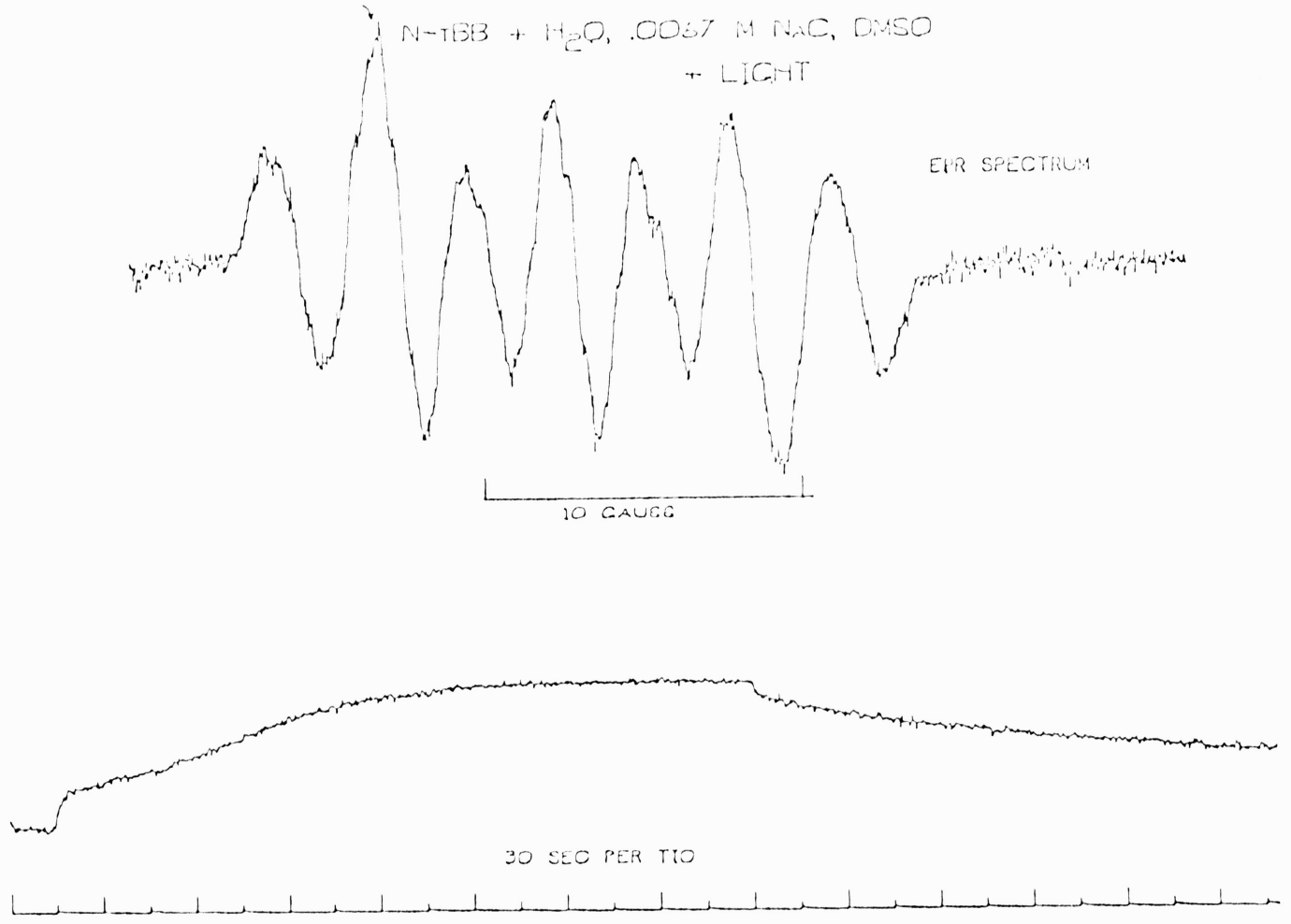


Figure 8. Epr spectrum and kinetics for the photolytic reaction of NtBB, H_2O (1.0 M), and NaC (0.0067 M) in oxygen-free DMSO solution.

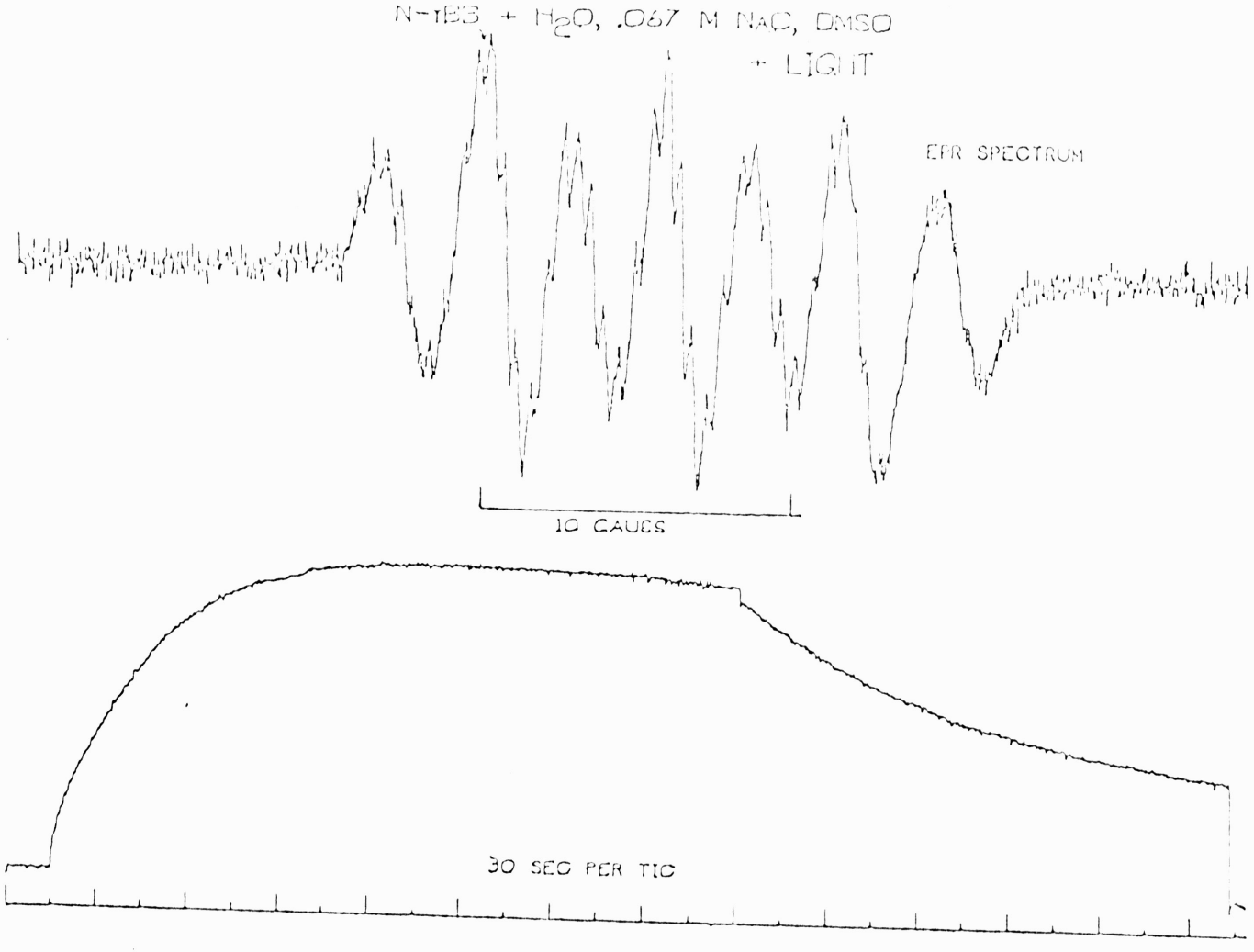


Figure 9. Epr spectrum and kinetics for the photolytic reaction of NtBB, H_2O (1.0 M), and NaC (0.067 M) in oxygen-free DMSO solution.

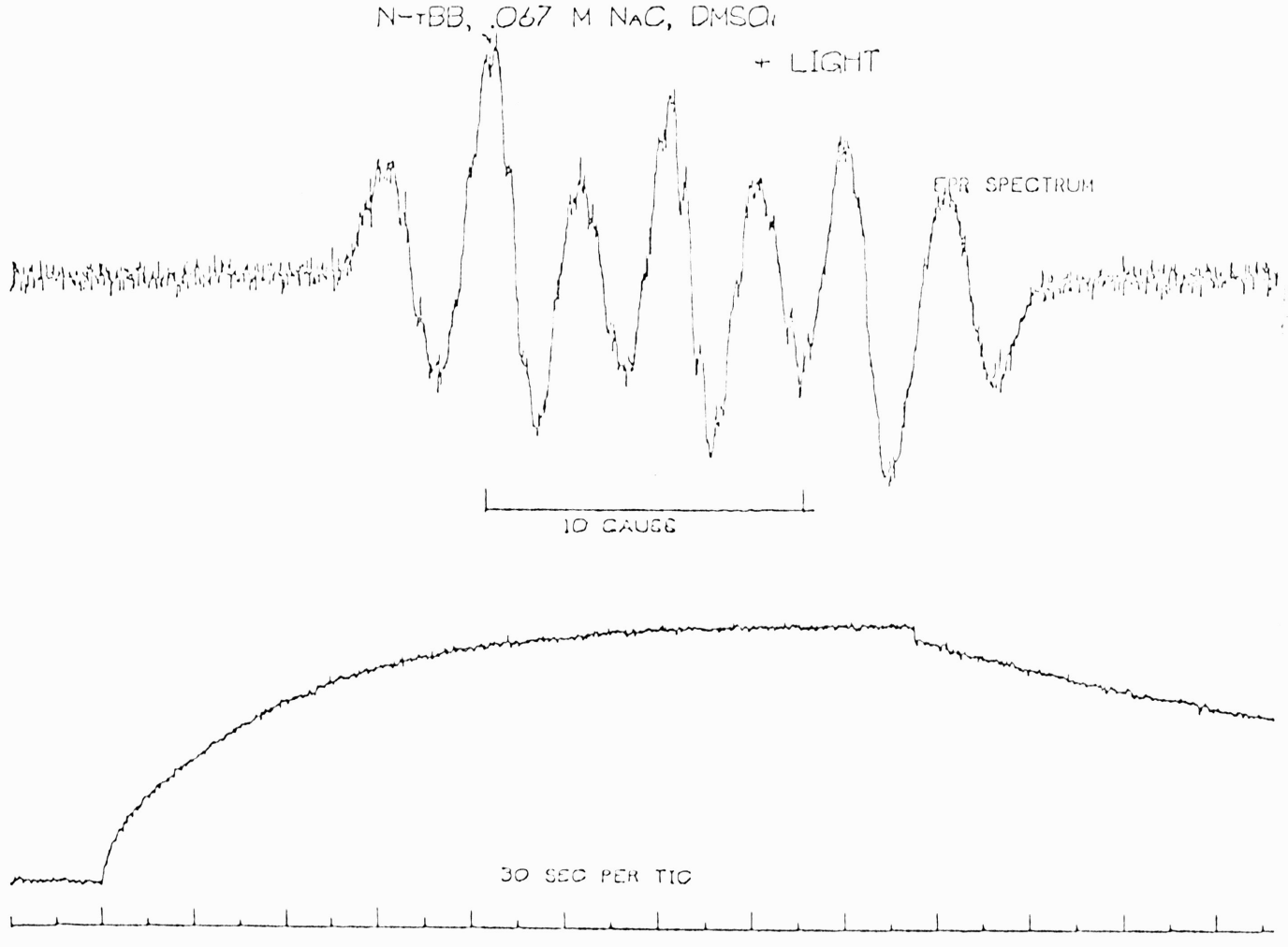


Figure 10. Epr spectrum and kinetics for the photolytic reaction of NtBB and NaC (0.067 M) in oxygen-free DMSO solution.

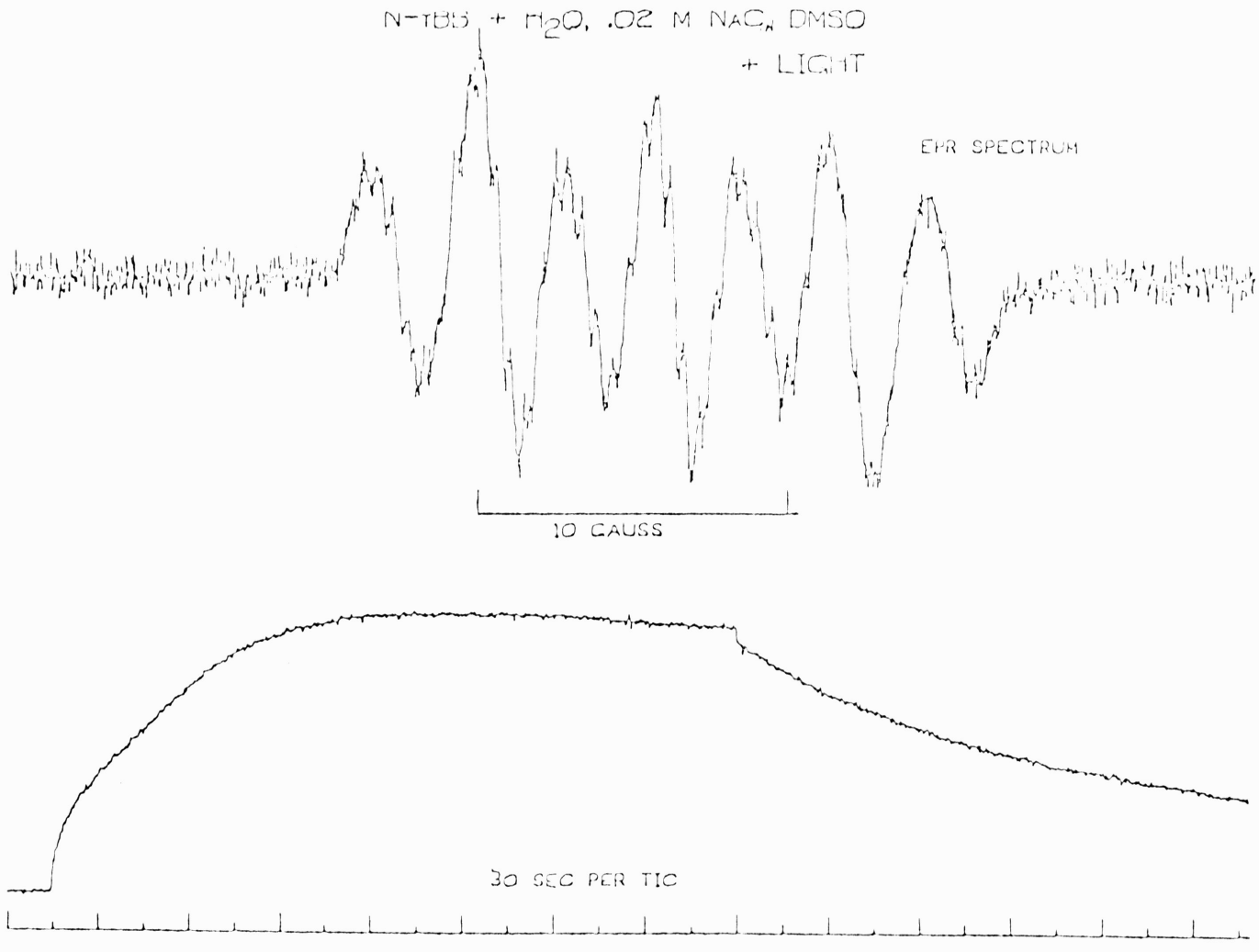


Figure 11. Epr spectrum and kinetics for the photolytic reaction of NtBB, H_2O (1.0 M), and NaC (0.02 M) in oxygen-free DMSO solution.

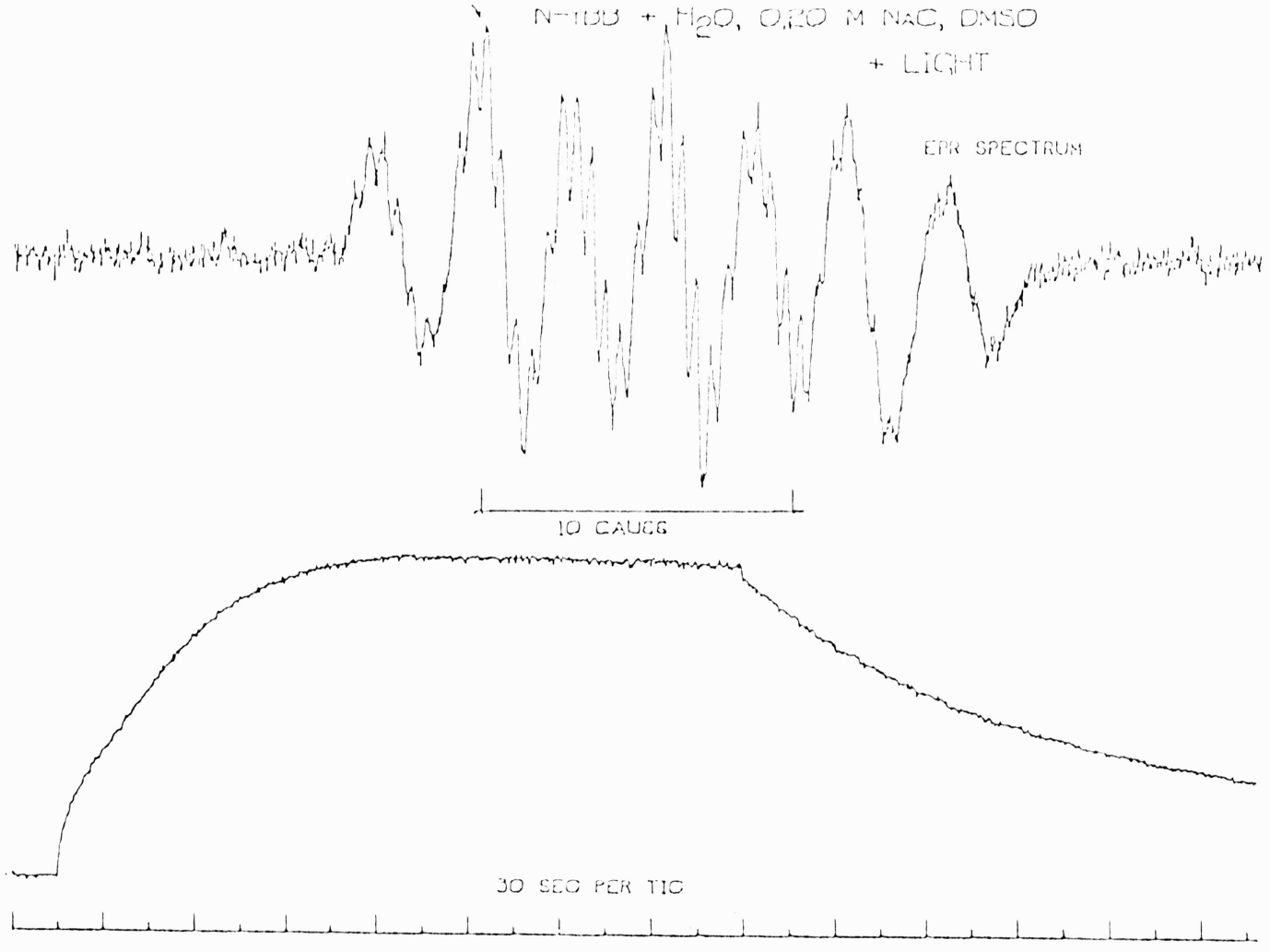


Figure 12. Epr spectrum and kinetics for the photolytic reaction of NtBB, H_2O (1.0 M), and NaC (0.20 M) in oxygen-free DMSO solution.

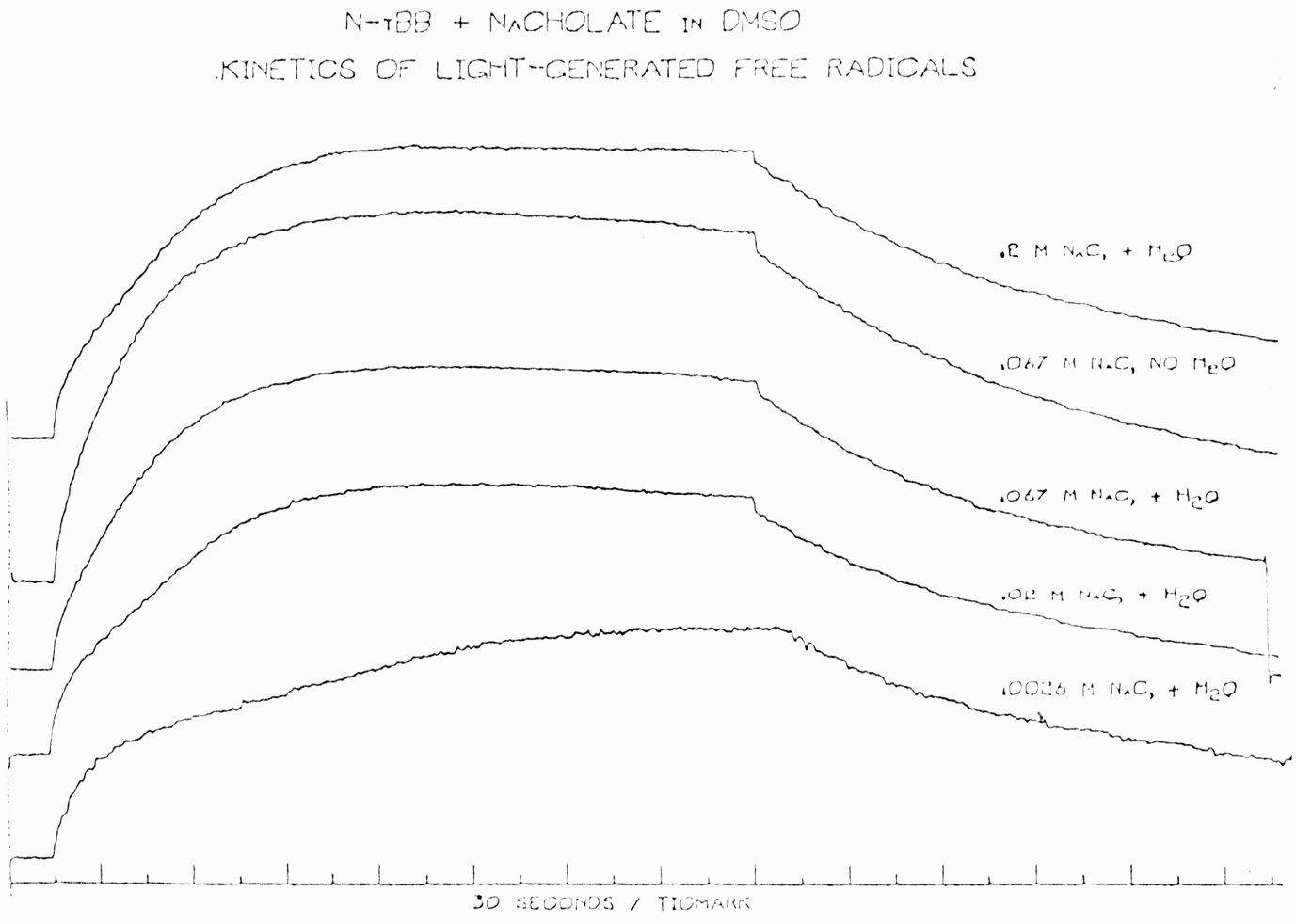


Figure 13. Kinetics of the light-generated free radicals in the reaction of NtBB and NaC in DMSO in the presence and absence of water.

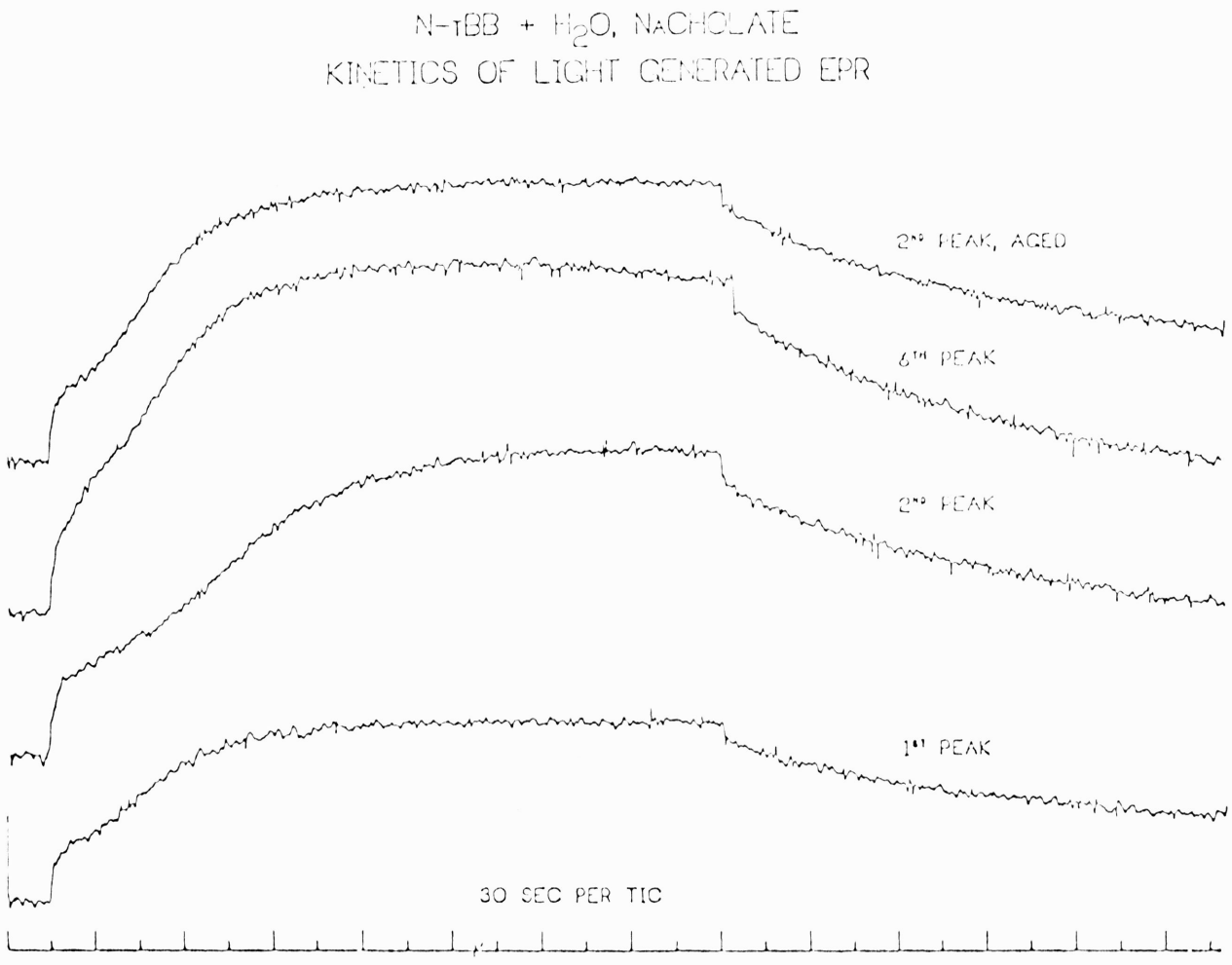


Figure 14. Kinetics of the light-generated epr spectra for the different peaks in NtBB, H_2O (1.0 M) and NaC (0.0067 M) in DMSO solution in the presence and absence of light.

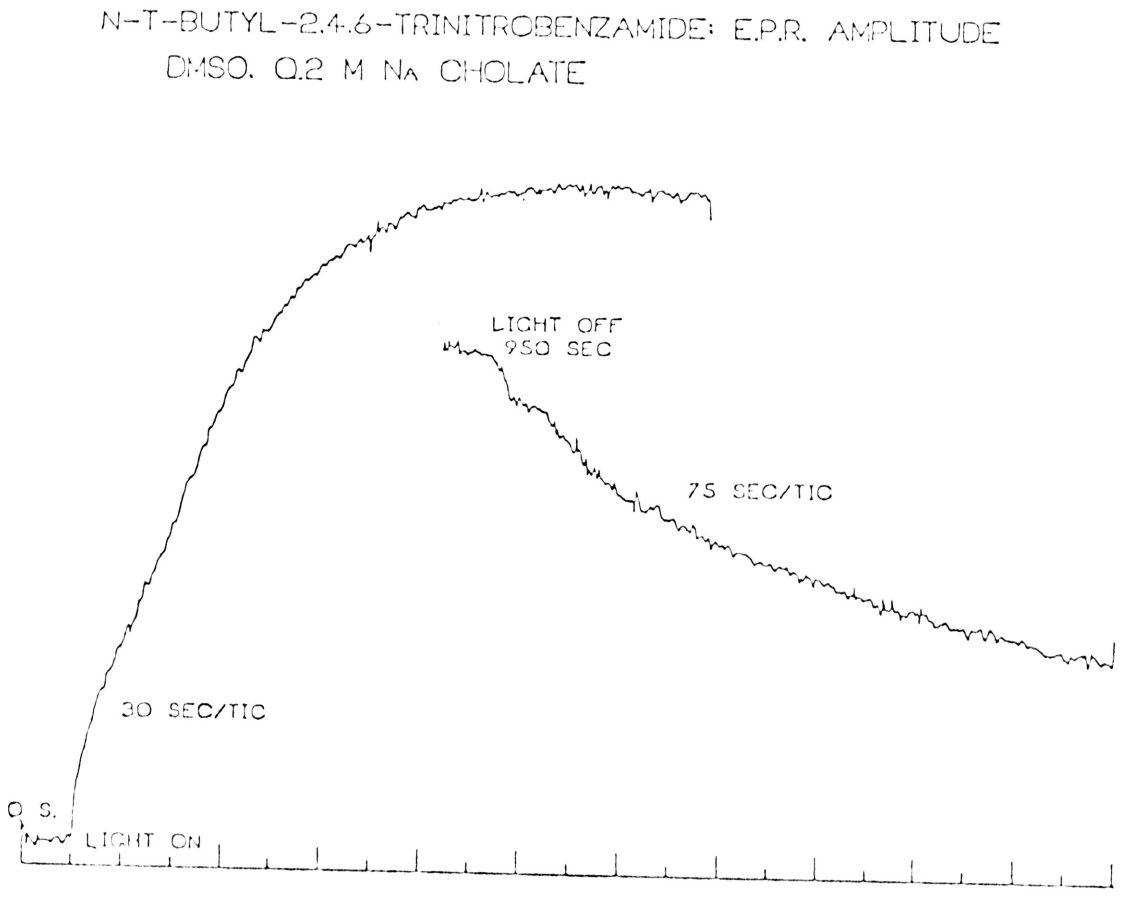


Figure 15. Kinetics of the photolytic reaction of NtBB and 0.20 M NaC in DMSO solution containing 1.0 M H_2O.

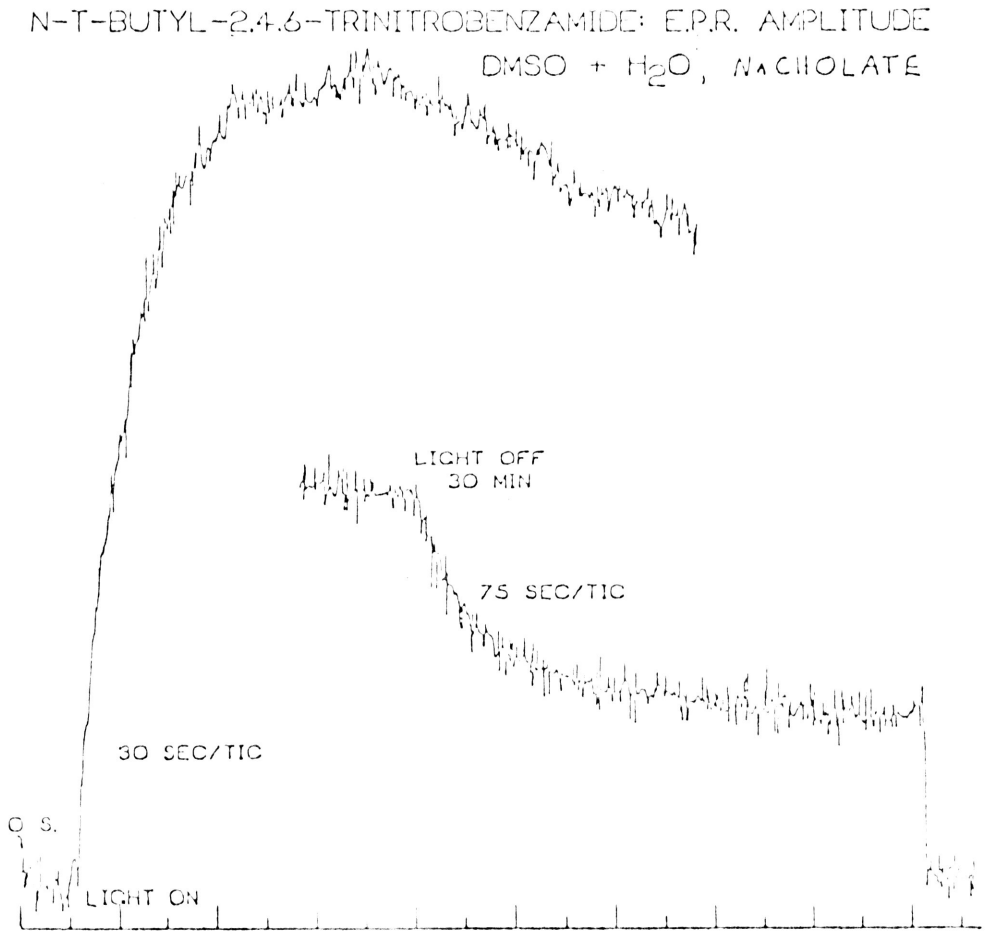


Figure 16. Kinetics of the photolytic reaction of NtBB, H_2O (1.0 M) and NaC in DMSO solution.

after decay involving another possible free radical species to one with 20 lines. Notably, this spectrum is identical to that found upon photolysis of the intermediate OH-Meisenheimer complex of NtBB in the absence of NaC (Figures17 and 18). This can be simulated using parameters identical to those for Figure 5. In the presence of NaC, the epr spectra of the complex appear to be more complex (Figures 18 and 19). They are not identical to either the 7- or the 20-line spectra. These spectra warrant further investigation.

Rates were followed on different peaks to assess the rates of formation and decay (Figure 14), and it is apparent from the rates of decay that at least two free radicals species are involved. The rate also appears to be affected by the concentration of H_2O in the system (Figure 13).

The role of free radicals in nucleophilic aromatic substitution has been a subject of controversy for many years. Russian work has been recently reviewed by Shein on deactivated substitution.[33] Bunnett has reviewed the reaction by activated aromatic systems in the presence of strong bases.[34] It is probable that the same types of free radical species are involved in the substitution of activated and deactivated aromatic compounds. Additionally, light dependence has been qualitatively observed using nmr spectroscopy. The presence of free radicals in the nucleophilic aromatic substitution has been inferred since ca. 1970 from observed line-broadening in ^1H nmr spectra of in situ generated σ-complexes. Free radicals in these cases could be involved either in complex formation or in its decomposition. The concentration of free radicals has, however, been determined (based on Fremy's salt) to be approximately 10^{-4} to 10^{-5} M; consequently, it is apparent that

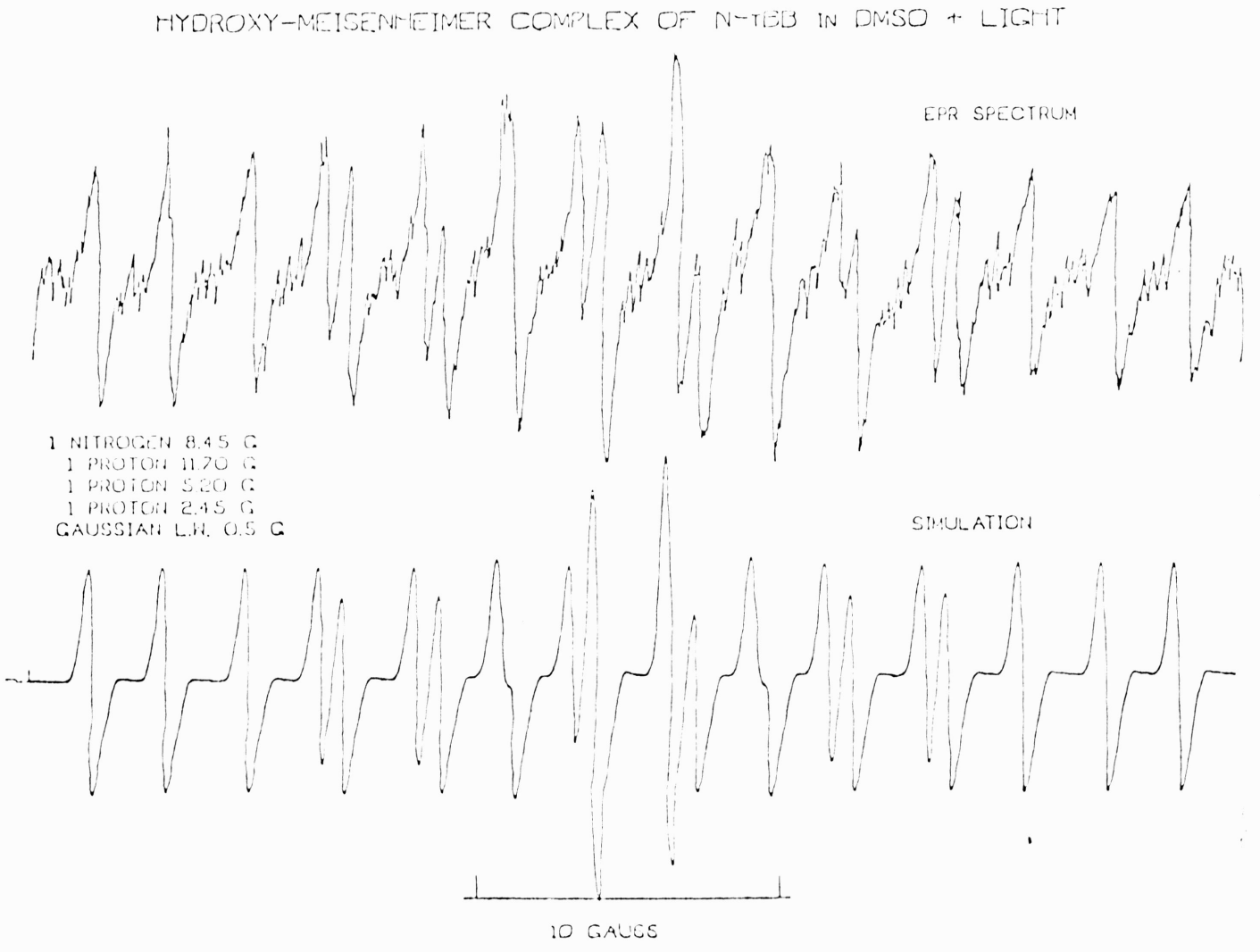


Figure 17. Epr spectrum from the OH-Meisenheimer complex of NtBB under photolytic conditions in DMSO (upper) and its simulation (lower).

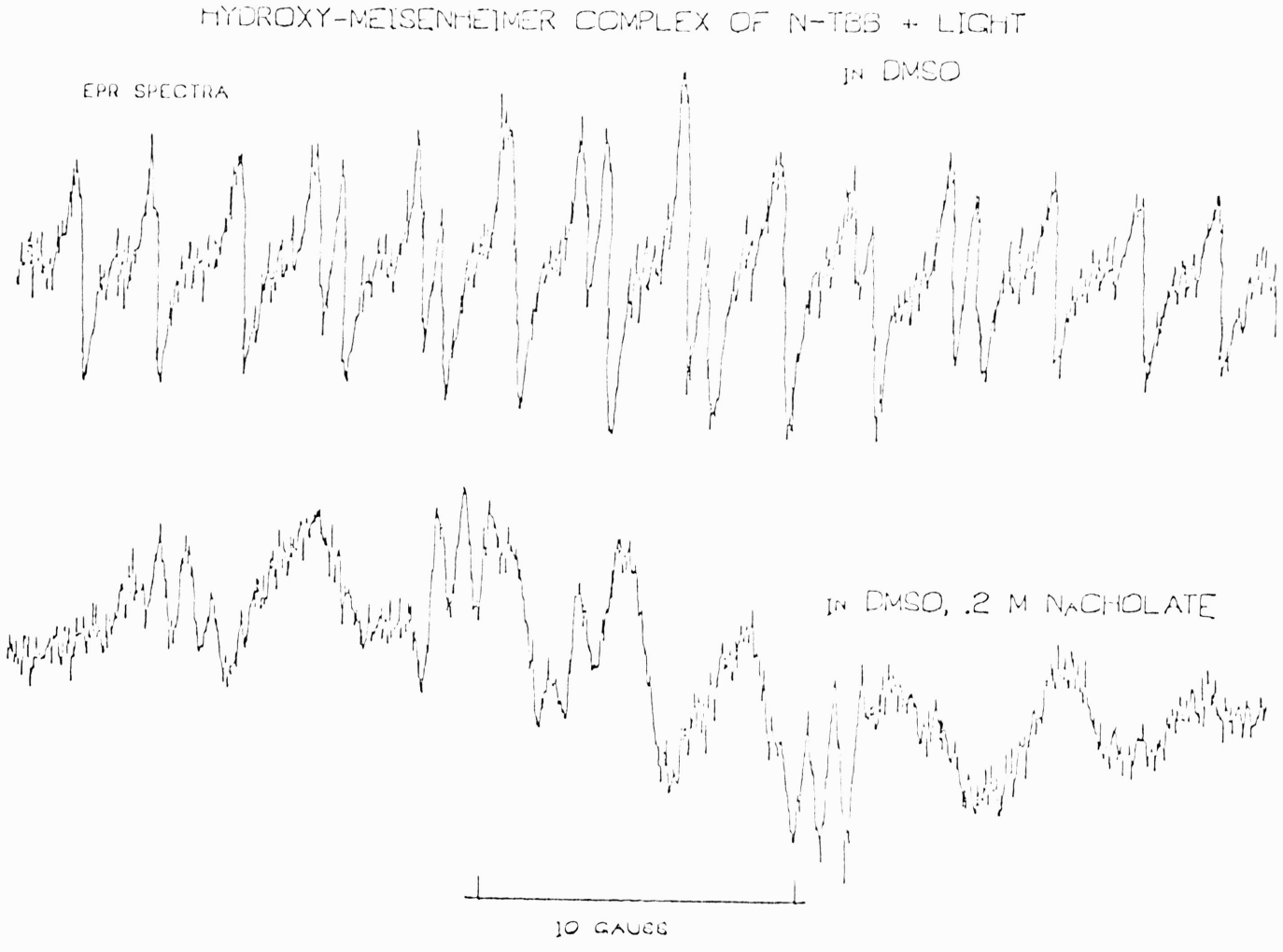


Figure 18. Epr spectra from the OH-Meisenheimer complex of NtBB under photolytic conditions in DMSO (upper) and in the presence of 0.20 M NaC in DMSO (lower).

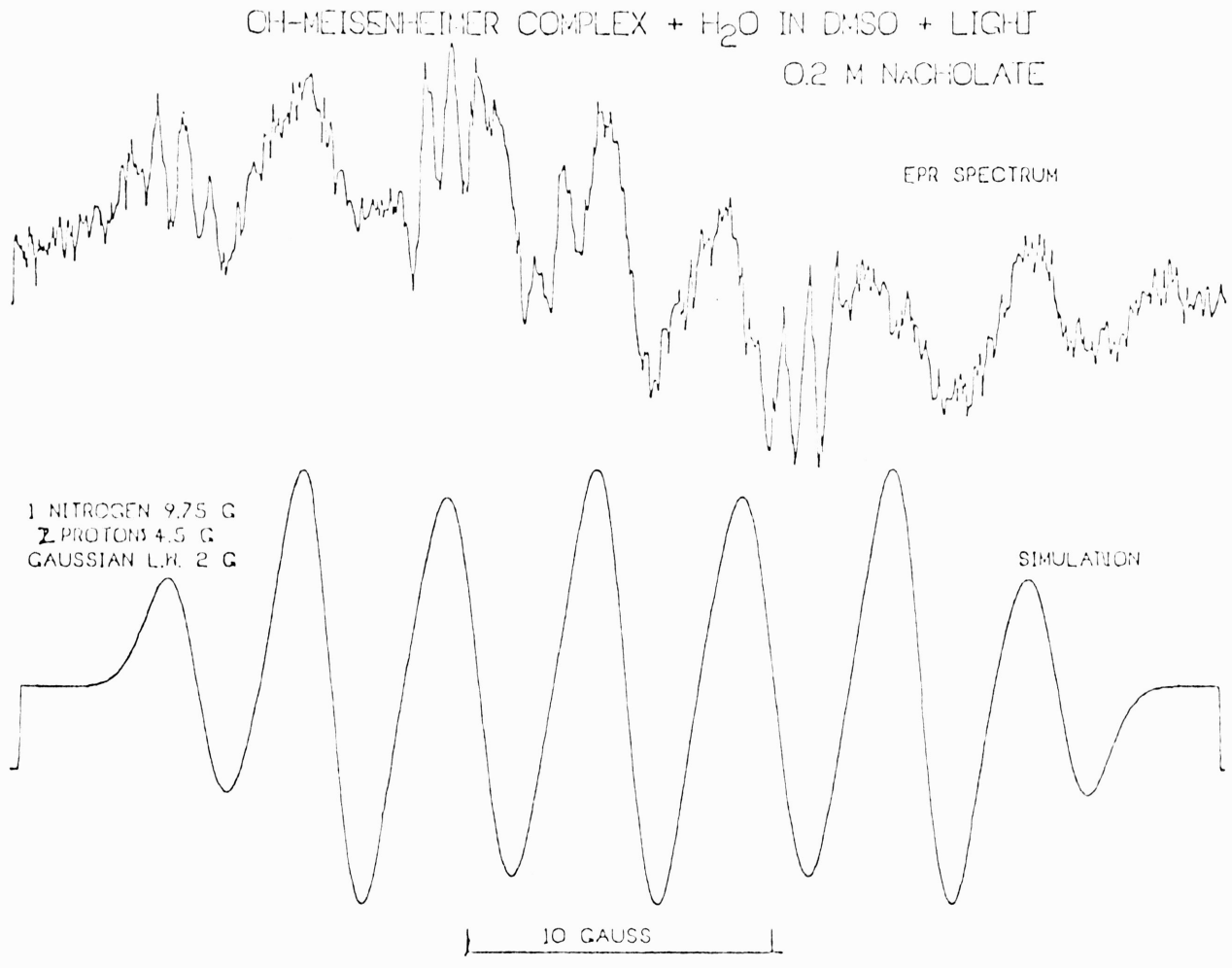


Figure 19. Epr spectrum from the OH-Meisenheimer complex of NtBB under photolytic conditions in NaC (0.20 M), H_2O (1.0 M), DMSO solution (upper) and its simulation (lower).

they play an important role in product formation in the presence of light. They may or may not be on the reaction coordinate for ionic nucleophilic aromatic substitution and/or may be involved in competing reactions both in the presence and absence of light.

Using NtBB, identical products are formed in the presence and absence of light; however, the reaction meahanism in the presence and absence of light may well differ.

CONCLUSION

The role of free radicals in the nucleophilic aromatic substitution of NtBB by NaC may serve well to elucidate that of free radicals in other nucleophilic aromatic substitutions. These results are conceptually compatible with mechanisms postulated for nucleophilic substitution of activated compounds in the presence of strong bases,[34] but are incompatible with the reaction scheme discussed by Shein[33] for the role of free radicals in nucleophilic substitution of deactivated aromatic compounds. It is apparent that further investigation is necessary to determine whether free radicals lie on the reaction coordinate. Spin traps and competitive kinetics "in the dark" would be extremely effective in providing information on the role of free radicals in the presence and the absence of light.

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APPENDIX

Bile salts are one of the most important groups of surfactants present in man. The effects of surfactants include interaction with biological membranes and modification of membrane permeability, interaction with drugs, interaction with the dosage form of a drug, and interaction with the organism by influencing absorption across membranes.

In man, there are six major bile salts[40] - the taurine and glycine conjugates of deoxycholic acid, chenodeoxycholic acid, and cholic acid, all present as the sodium and potassium salts. Bile also contains small amounts of the salts of lithocholic acid. Bile salts are produced in the liver as a result of cholesterol metabolism. The bile salts are then stored in the gall bladder, readily available for digestion. As previously mentioned, bile salts are conjugated in the liver prior to storage in the gall bladder. This conjugation is physiologically important in view of the solubility of the unconjugated bile salts. At the relatively low pH found in the upper small intestine, the unconjugated bile salts would be insoluble. This does not mean that all bile salts and acids in the intestine are conjugated. After excretion, the conjugated acids are subject to cleavage through microbial degradation. This same degradation by the intestinal flora has been implicated in the etiology of colon and breast cancer via aromatization. All the bile salts comprise a group of compounds which basically differ only in the position and number of hydroxyl groups on the steroid nucleus.

Bile salts play a primary role in the digestion and absorption of fats and the fat-soluble vitamins A, D, E, and K. They are responsible

for the emulsification of a variety of water-insoluble compounds, e.g., long chain triglycerides, and for stimulating the hydrolytic activity of pancreatic lipase. Bile salts are amphiphilic molecules; however, unlike most amphiphilic molecules, bile salts have a rigid carbon backbone with a cis A/B ring juncture (5β-hydrogen)which is responsible for the characteristic crescent shape of the molecule. In the intestine there are two lipids that are largely solubilized by the bile salt micelles - monoglycerides and fatty acids. The shape of the bile salt micelles in aqueous solution has been postulated to be a cylinder containing from 4 to 10 or 15 monomeric units, with the hydrophobic face of the steroid nucleus in the interior and the hydroxyl and acid groups oriented toward the bulk solvent. In nonpolar solvents a variety of surfactants form reversed or inverted micelles which, in general, are structurally the inverse of the so-called "normal" micelles. Bile salts, however, are only slightly soluble in non-polar solvents.