Rapid Intermolecular Electron Transfer Specific to the Zwitterionic Form of *N*-(9-(10-Hydroxyanthryl))piperidine (HAP)

Robert W. Sweger and Anthony W. Czarnik*

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received April 18, 1990*

Abstract: The acid-catalyzed condensation of anthrone with excess piperidine affords both *N*-anthrylpiperidine (80–85%) and HAP (5–10%). The ^1H and ^{13}C NMR spectra of *N*-(9-anthryl)piperidine are unexceptional and consistent with the structure assignment. However, the NMR spectra of HAP in DMSO-d_6 reveal, except for impurities, only resonances for the aliphatic protons or carbons. Treatment of the DMSO-d_6 solution with either strong acid or base results in appearance of the expected aromatic protons or carbons, with integrations and/or chemical shifts as expected for the predicted ionic forms of HAP produced under these conditions. We have interpreted the unusual NMR behavior of HAP in DMSO-d_6 in terms of intermolecular electron transfer with an impurity of the corresponding O-centered radical, observable by ESR. Of the four ionization states available to 10-*N*-piperidinylanthranol, only the zwitterionic form exhibits electron transfer that is rapid and reversible. The results of NMR studies on the N-methylated derivative of HAP are consistent with this interpretation.

We have recently had the occasion to examine the chemistry of 9-(*N*,*N*-dialkylamino)anthracenes. In fact, a search of the literature revealed that no examples of 9-(*N*,*N*-dialkylamino)-anthracenes have been reported. The preparation of 9-amino-anthracene[1] and 9-methylaminoanthracene[2] have been described, as have those of 9,10-diamino-[3] and 9,10-bis(dimethylamino)-anthracene.[4] The existence of the above compounds makes the absence of 9-(*N*,*N*-dialkylamino)anthracenes particularly intriguing. We now report that 9-(*N*,*N*-dialkylamino)anthracenes can be prepared by the condensation of unhindered secondary amines with anthrone; however, both the desired anthracene derivative and the corresponding anthranol are obtained. The NMR behavior of the dialkylaminoanthranol was unexpected, and prompted us to investigate its origin.

Results

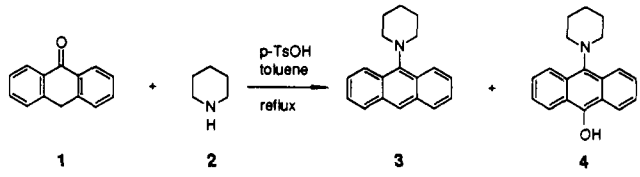
The acid-catalyzed condensation of anthrone (**1**) with excess piperidine (**2**) as shown in Scheme I affords both CH_2Cl_2 soluble (**3**, 80–85%) and insoluble (**4**, 5–10%) products. The ^1H and ^{13}C NMR spectra of *N*-(9-anthryl)piperidine (**3**) are consistent with the structure assignment. However, the NMR spectra of HAP (**4**) in DMSO-d_6 reveal, except for impurities, only resonances for the aliphatic protons (spectrum A of Figure 1) or carbons. Treatment of the DMSO-d_6 solution with either strong acid or base results in appearance of the expected aromatic protons or carbons, with integrations and/or chemical shifts as expected for the predicted ionic forms of **4** produced under these conditions.

Methylation of **4** under neutral conditions afforded the product of N-alkylation, anthranol **5** (Scheme II). O-Methylation of **5** could be accomplished upon pretreatment with base to afford methoxyanthracene **7**. The NMR spectra of both **4** and **5** were broadened under appropriate conditions in DMSO-d_6, while methoxyanthracene **7** gave unexceptional spectra under all conditions. Treatment of either **4** or **5** with excess BHT resulted in no change in the respective aromatic regions of either NMR spectrum. Conversely, titration of **4** with increasing concentrations of "TEMPO-H" (a highly active hydrogen atom donor) resulted in the gradual appearance of the aromatic signals (Figure 2).

Discussion and Conclusions

Structure Assignment of the CH_2Cl_2 Insoluble Product. Our initial attempts to prepare *N*-(9-anthryl)piperidine (**3**) by the condensation of anthrone (**1**) with piperidine (**2**) yielded a bright gold solid, obtained by selective precipitation from methylene chloride, in 5–10% yield. Characterization of the gold powder was attempted using ^1H NMR spectroscopy; however, the spectrum in DMSO-d_6 (spectrum A of Figure 1) does not show any anthracene peaks, but only piperidine-like aliphatic peaks at 1.4 ppm and 2.7 ppm. The aromatic region does contain peaks due to the presence of small amounts of contaminating anthraquinone and dianthraquinone, which could not be removed readily. The spectrum obtained is categorically not that of piperidine itself, as determined from a mixed NMR experiment; furthermore, piperidine is a colorless liquid, while the product is a gold powder. The ^{13}C NMR in DMSO-d_6 showed an identical behavior. None of the *p*-TsOH used as catalyst was observed in either spectrum.

Scheme I. Synthesis of *N*-(9-Anthryl)piperidine (**3**) and Its Autoxidation Product **4**



1 **2** **3** **4**

Line-broadening effects such as these are attributable to either electron or hydrogen atom transfer reactions, which can serve to distribute spin throughout a sample rapidly on the NMR time scale. In an effort to obtain an unbroadened spectrum, a few drops of trifluoroacetic acid (TFA) were added to the NMR sample and the spectrum was retaken. This produced a new, complete ^1H NMR spectrum corresponding to the TFA salt of HAP (spectrum B of Figure 1); note the shift of the piperidinyl protons. TFA added to the ^{13}C NMR sample likewise resulted in the emergence of sharp aromatic carbon resonances. That ^{13}C NMR spectrum further indicated the absence of a proton at C-10, as it appeared as a singlet in the off-resonance decoupled spectrum.

In our structural assignment for the CH_2Cl_2-insoluble product, the formation of a dimer (**8**) was initially considered. This structure fit the ^{13}C NMR data well and the ^1H NMR data reasonably well, but our inability to obtain mass spectral data on this sample made unambiguous assignment difficult. Precedence for the formation of such a dimer comes from the fact that anthranol undergoes an analogous reaction.[5] However, dimer formation was ruled out as a possibility because the series of methylation reactions shown in Scheme II could not be explained

(1) Meisenheimer, J. *Chem. Ber.* **1900**, *33*, 3547.
(2) Meyer, K. H.; Schlosser, H. *Ann.* **1920**, *420*, 113.
(3) Schiedt, B. *J. Prakt. Chem.* **1941**, *157*, 203.
(4) Chung, Y.-S.; Duerr, B.; McKelvey, T.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1989**, *54*, 1018.
(5) Majeski, E. J.; Stuart, J. D.; Ohnesorge, W. E. *J. Am. Chem. Soc.* **1968**, *90*, 633.

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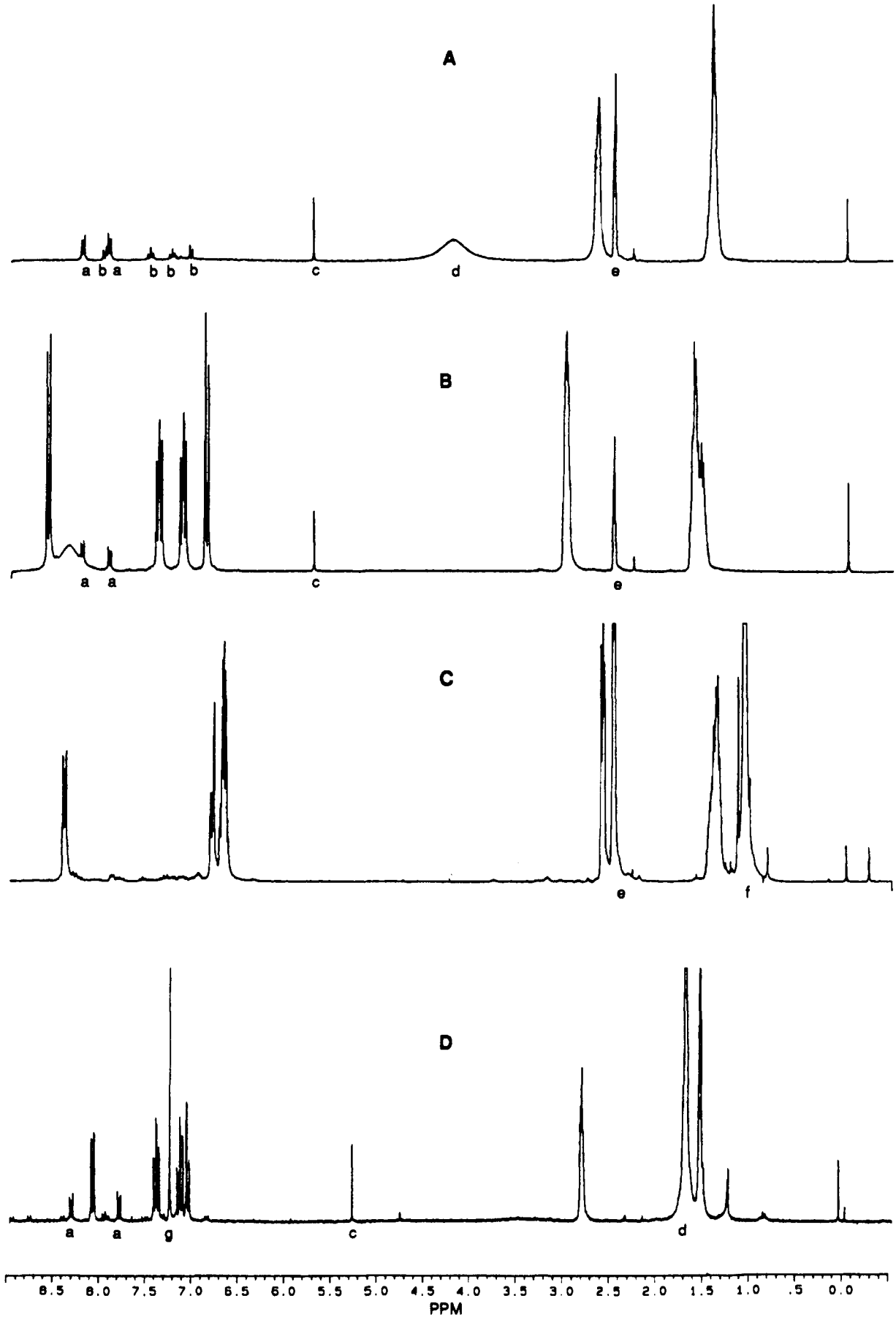
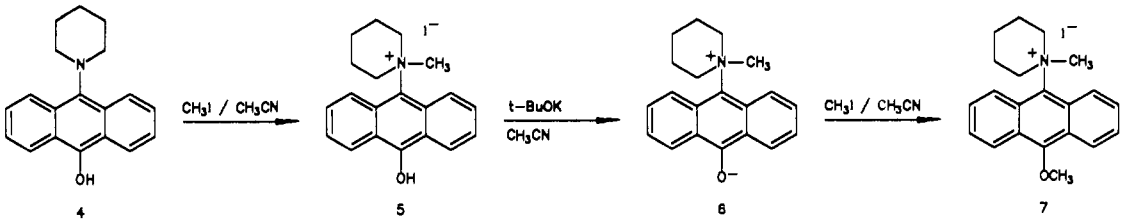


Figure 1. ^1H NMR spectra of HAP (36 mM) taken in (A) DMSO-d_6, (B) DMSO-d_6 with excess trifluoroacetic acid, (C) DMSO-d_6 with excess *t*-BuOK added, (D) $CDCl_3$. The following impurity peaks have been identified: (a) anthraquinone, (b) dianthraquinone, (c) CH_2Cl_2, (d) water, (e) DMSO-d_5, (f) $(CH_3)_3COK$, (g) $CHCl_3$.

Scheme II. Methylation Reactions of HAP (**4**)



if **8** was the starting material. The actual product is dialkylaminoanthranol derivative **4**, which is obtained by the autoxidation of dialkylaminoanthracene **3**. Both ^1H and ^{13}C NMR in DMSO/TFA are consistent with this assignment. Anthranol similarly undergoes autoxidation, yielding anthraquinone as product.[6]

The first methylation of **4** under neutral conditions occurs on nitrogen (**4** → **5**), locking the piperidine ring into a conformation in which the protons do not equilibrate between equatorial and axial positions. Chemical shift data suggest that the equatorial N–C–H protons are held over the aromatic ring and appear as a downfield triplet at 3.30 ppm; the corresponding axial protons appear at 3.00 ppm. Evidence supporting the N-methylation assignment was obtained from NOE experiments, which showed magnetization transfer between the piperidinyl protons at 3.30 ppm and the methyl singlet at 3.04 ppm. Methylated derivative **5** must be a strained molecule; however, the isostructural 9-*tert*-butylanthracene can be synthesized.[7]

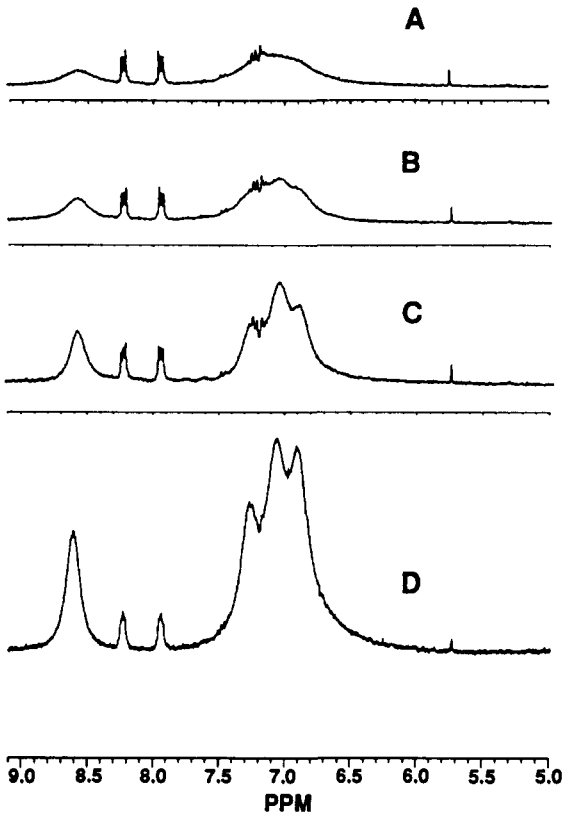


Figure 2. ^1H NMR spectra of HAP (36 mM) taken in DMSO-d_6 with (A) 3.6 mM TEMPOH, (B) 18 mM TEMPOH, (C) 54 mM TEMPOH, (D) 144 mM TEMPOH. Anthraquinone, dianthraquinone, and CH_2Cl_2 impurities are identified as for Figure 1.

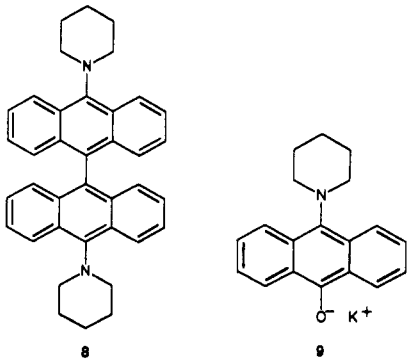


Figure 3. The hypothetical bianthryl form of *N*-anthrylpiperidine (**8**) and the structure of potassium 10-*N*-piperidinylanthranolate (**9**).

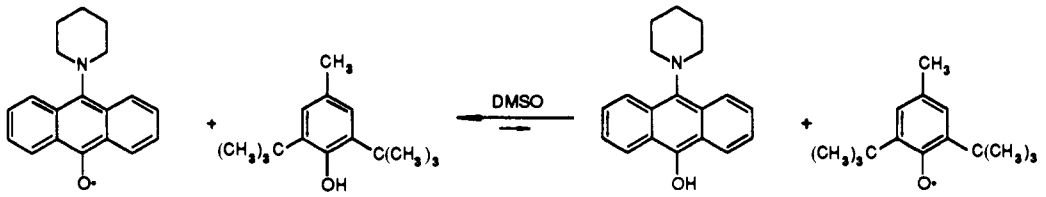
Compound **5** in DMSO shows characteristic UV peaks at 374, 408, and 428 nm. Upon addition of strong base, either *t*-BuOK or *n*-BuLi, a broad UV absorption band centered at 524 nm appears assigned to oxyanion **6**. Addition of a weaker base, triethylamine, produces a broad UV absorption band centered at 518 nm; however, this band is less intense than that caused by addition of strong base. Similarly, *N*-(10-hydroxyanthryl)-piperidine (**4**) in DMSO yields a UV spectrum with characteristic peaks at 374, 406, 428, and 514 nm. Addition of *t*-BuOK to the solution of **4** enhances the long-wavelength absorption band due to complete formation of oxyanion **9**; the solution changes from brown-orange to red-violet. Addition of triethylamine to a DMSO solution of **4** also enhances the long-wavelength band; incomplete O-deprotonation causes this band to be less intense than the band generated by addition of stronger base. The assignments of oxyanion structures **6** and **9** are supported by the fact that addition of strong base to a DMSO solution of anthranol itself results in formation of a similar broad UV absorption centered at 502 nm; this anthranolate decomposed to anthraquinone upon prolonged exposure to the atmosphere. The UV absorption band due to the oxyanion generated from anthranol by triethylamine is also much less intense than the absorption band generated by addition of *t*-BuOK.

The second methylation shown in Scheme II occurs on oxygen (**5** → **7**). Structural proof for the formation of **7** is provided by ^1H NMR; the second methyl group appears at 4.3 ppm, corresponding exactly to the chemical shift for the methoxy groups of 9,10-dimethoxyanthracene.[8] Apparently the methylpiperidinium substituent has little effect on the chemical shift of the methoxy group in **7**; analogously, the methoxy chemical shift of various para-substituted anisoles does not vary significantly from that of anisole itself.[9]

A Mechanistic Proposal for the Observed Aromatic Line Broadening. With the structure assignment complete for HAP (**4**) as a product of the condensation reaction between anthrone and piperidine, the intriguing question remained: What has caused the anthracene portions of the NMR spectra to disappear? General line broadening of the NMR spectra due to radical impurities can be eliminated as a possibility owing to the fact that the alkyl peaks of the piperidine unit are present and sharp. The answer begins to take shape when one notes the analogy to fredericamycin A (**10**, Figure 4) whose similar NMR behavior has been examined in detail.[10] In that study the authors conclude

(6) *The Chemistry of the Quinoid Compounds*; Patai, S., Ed.; Wiley: New York, 1974; pp 132–134.
(7) Parish, R. C.; Stock, L. M. *J. Org. Chem.* **1966**, *31*, 4265.
(8) Meek, J.; Monroe, P.; Boubolis, C. *J. Org. Chem.* **1963**, *28*, 2572.
(9) Concluded by inspection of various representative spectra in: *The Aldrich Library of NMR Spectra*; Pouchert, C. J., Ed.; Aldrich Chemical Co.: Milwaukee, WI, 1983.
(10) Hilton, B. D.; Misra, R.; Zweier, J. L. *Biochemistry* **1986**, *25*, 5533.

Scheme III. Equilibrium Established by Addition of BHT (**17**) to a DMSO Solution Containing Both **4** and a Small Amount of **14**



14 **17** **4** **18**

that fredericamycin A exists in a reversible equilibrium between reduced and oxidized forms. The reduced form is red in solution and has sharp ^1H and ^{13}C NMR peaks for the entire molecule. Fredericamycin A reacts with oxygen; this oxidized form is a free radical as shown by EPR studies, is blue in solution, and yields NMR spectra in which only the quinoid portions of the molecule are broadened beyond detection. Upon addition of trifluoroacetic acid, the solution becomes red, and both ^1H and ^{13}C NMR peaks are sharp for the entire molecule.

In order to explain the extreme line broadening seen for the anthracene portion of **4**, we turn to the cubic reaction scheme shown in Figure 5. We suggest that the partitioning between various ionic states (i.e., **4**, **9**, **11**, **12**) is solvent dependent, and that only the electron transfer reaction between **11** and **15** is fast in both directions on the NMR time frame. If a small[11] fraction of **4** were present in the radical form (i.e., **14**), it should be detectable by EPR. Indeed, the solid sample of **4** shows a signal at 3460 to 3469 G; the absence of hyperfine coupling indicates that the spin is not localized on nitrogen. In dialkylaminoanthranol **4**, as in fredericamycin A, some mechanism for rapid intermolecular exchange of the radical must exist to allow a small percentage of radical species to cause complete quenching of the aromatic NMR signal. Spectrum A of Figure 1 is that of 36 mM HAP (**4**) in DMSO-d_6. This spectrum shows quenched anthracene peaks due to a rapid exchange process. Addition of TFA to **4** in DMSO (spectrum B) causes the anthracene ^1H NMR peaks to appear with correct integrations. Anthranol **4** is present in this acidic medium as ammonium salt **12**;[12] this species apparently is no longer capable of rapid intermolecular exchange as the anthracene peaks are sharp. If instead of adding acid to **4** in DMSO one adds strong base (*t*-BuOK), oxyanion **9** is obtained. The ^1H NMR of **9** (spectrum C) also shows anthracene peaks. Thus, one can obtain a full spectrum of HAP in DMSO-d_6 by adding either strong acid or strong base, so either acid or base must stop the rapid spin exchange. The final "upper" corner of the cube in Figure 5 is sampled by dissolving **4** in a solvent that is less polar than DMSO, such as chloroform. The ^1H NMR of **4** in $CDCl_3$ (spectrum D of Figure 1) demonstrates sharp anthracene peaks without addition of acid or base. Apparently, only one edge of the "cube" allows for rapid, reversible electron exchange. We postulate that the zwitterion form **11** is required to facilitate the rapid exchange that causes line broadening. While **9** is a strong reductant, **14** is a poor oxidant. Likewise, **16** is a strong oxidant while **12** is a poor reductant. Only the **11**/**15** couple possesses the right potential difference for rapid electron transfer. All of the same effects seen in the ^1H NMR spectra have been observed in the corresponding ^{13}C NMR spectra.

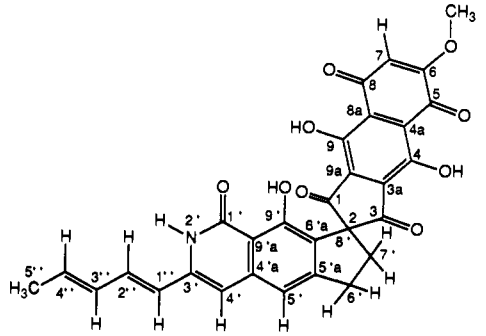


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Figure 4. The structure of fredericamycin A.

An alternate hypothesis, that addition of acid or base destroys the radical impurity, was eliminated using the following series of NMR experiments. (1) To a DMSO-d_6 solution of **4**/**14** was added one equiv of trifluoroacetic acid, which led to correctly integrating aromatic resonances. (2) One equivalent of *t*-BuOK was added to the same solution, which resulted in almost complete rebroadening of the aromatic region. (3) Addition of excess *t*-BuOK to the same solution afforded the same spectrum observed previously in DMSO/*t*-BuOK solution (spectrum C of Figure 1). Clearly, the line-broadening species is not destroyed on the addition of acid.

Adding credence to the claim that zwitterion **11** is the species undergoing rapid electron exchange are the ^1H NMR spectra of the methylated derivatives **5** and **7**. Monomethylated derivative **5** is isoelectronic with **12**, and similarly gives a yellow-green solution in DMSO. Compound **5** shows an unbroadened ^1H NMR spectrum in both the anthracene and piperidine regions. However, addition of either *t*-BuOK or triethylamine to the DMSO solution of **5** generates oxyanion **6**, and the ^1H NMR now demonstrates extensive broadening in the anthracene region; the pathway facilitating intermolecular exchange has been opened by formation of a zwitterionic structure. (It is important to note that base addition cannot remove the nitrogen charge, thus reinforcing the conclusion that zwitterion formation is the key to rapid, reversible exchange.) Furthermore, reacidifying the NMR solution by addition of trifluoroacetic acid once again gives an unbroadened ^1H NMR spectrum because the rapid intermolecular exchange pathway has been removed. As anticipated, dimethylated adduct **7** does not exhibit any broadening of its ^1H NMR spectra under any of the aforementioned conditions.

We have carried out one experiment that appears to be inconsistent with our electron exchange model. Addition of *t*-BuOK to a $CDCl_3$ solution of **5** leads to phenoxide ion formation as indicated by its UV spectrum. However, the ^1H NMR of this solution is not broadened. To date, we have not satisfactorily explained this finding; reaction of the base with the solvent is one possibility.

Quenching of the Radical by Addition of Active Hydrogen Atom Donors. In an effort to learn about the nature of the radical species that results in broadening, an active hydrogen atom donor (2,6-di-*tert*-butyl-4-methylphenol; **17**, BHT) was added to the **4**/**14** solution in DMSO-d_6 (Scheme III). The resulting ^1H NMR still showed anthracene peaks broadened beyond detection even with an 8-fold molar excess of added BHT, suggesting that radical **14** is a much less active hydrogen atom acceptor than is the BHT radical (**18**).

Another attempt at removing species **14** from solution was made using 1-hydroxy-2,2,6,6-tetramethylpiperidine (**19**),[13] abbreviated

(11) The fraction of **4** present in the radical form must be small, or NMR spectra B, C, and D in Figure 1 would not show correct relative integrations for aromatic versus aliphatic regions.

(12) Note the shifts of the piperidinyl N-CH_2 and N-CH_2CH_2 peaks on addition of acid. Retention of the anthracene chromophore argues against protonation on carbon.

(13) Root, K. S.; Hill, C. L.; Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 5405.

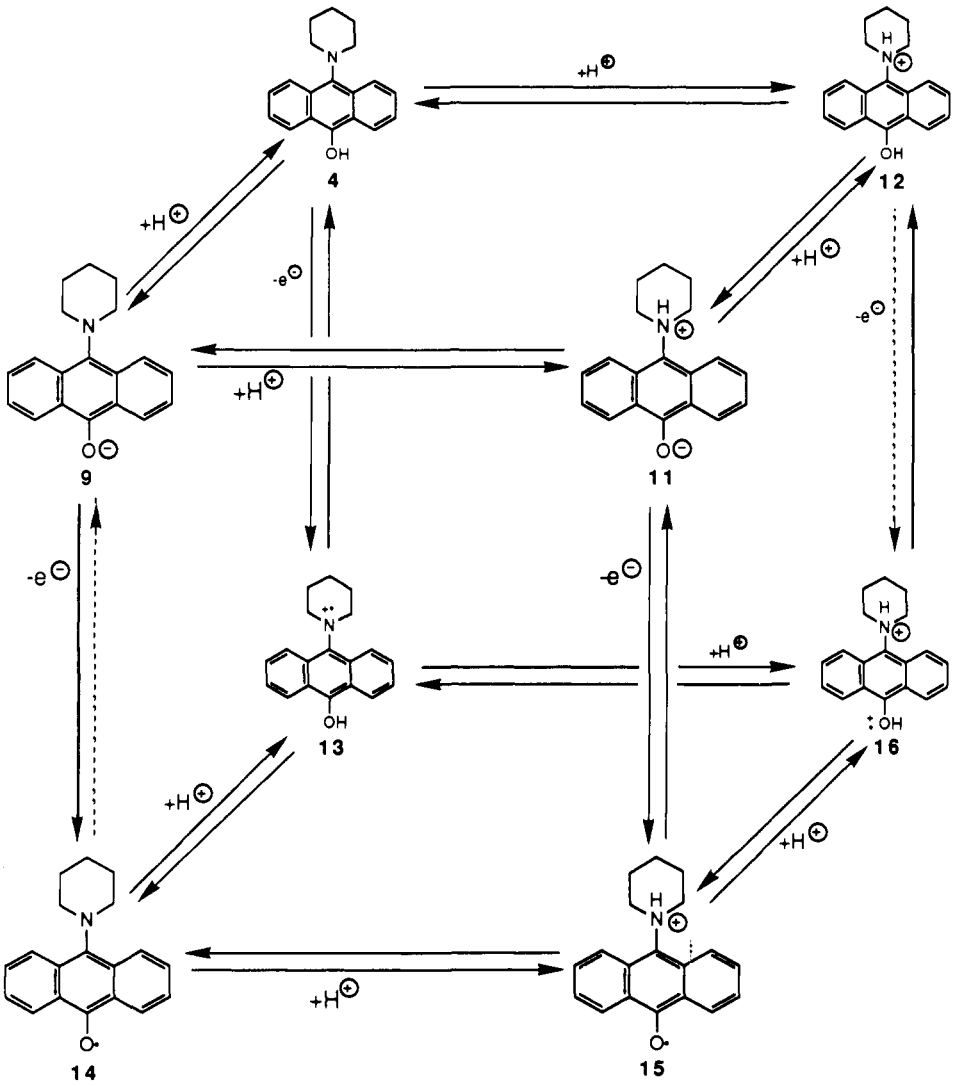
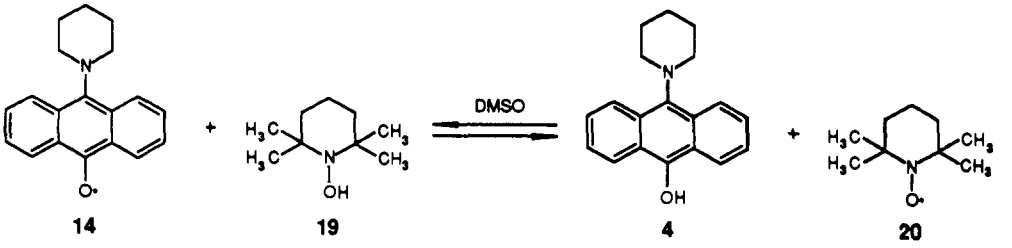
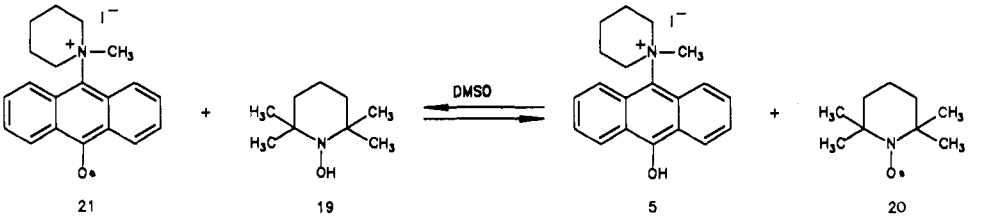


Figure 5. A reaction scheme showing the various single proton or electron equilibria available to a sample of **4** containing an impurity of **14**.

Scheme IV. Equilibrium Established by Addition of TEMPOH (**19**) to a DMSO Solution Containing Both **4** and a Small Amount of **14**



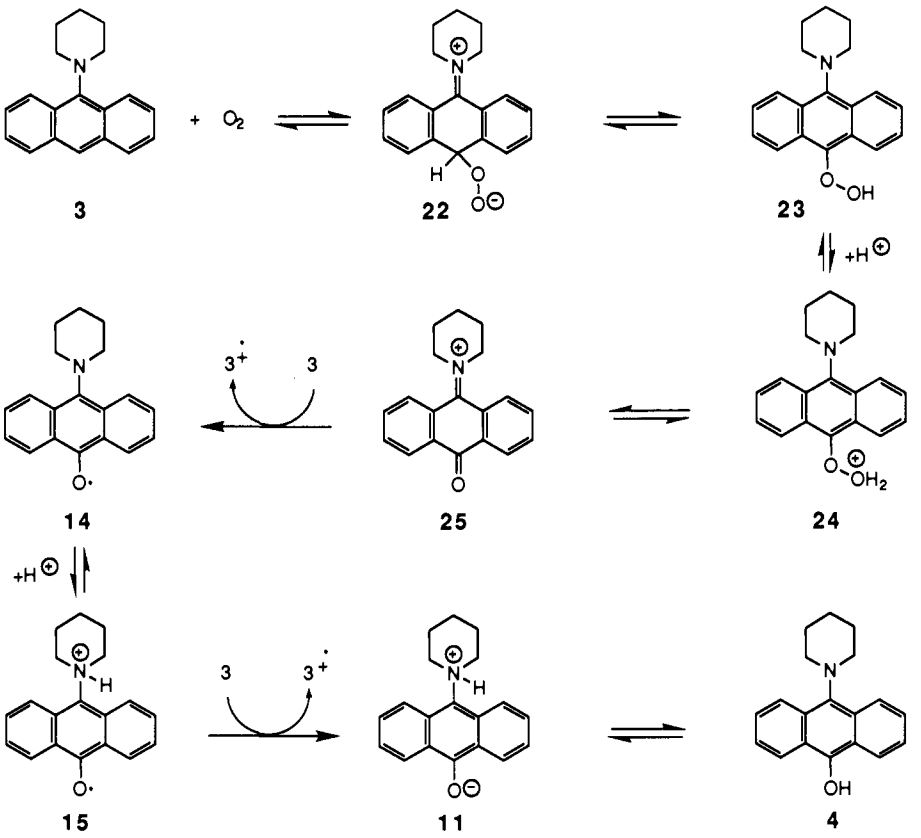
Scheme V. Equilibrium Established by Addition of TEMPOH (**19**) to a DMSO Solution Containing Both **6** and a Small Amount of **21**



TEMPOH (Scheme IV). TEMPOH is an even more active hydrogen atom donor than is BHT, the product being the highly stable radical 2,2,6,6-tetramethylpiperidine-*N*-oxyl (**20**, TEMPO). The NMR integration results indicate that only a small percentage of **4** can be present as **14**, so initially only 0.1 equiv of **19** was added to the solution of **4**/**14**. As shown in spectrum A of Figure 2, the anthracene peaks were no longer broadened beyond detection. Addition of more TEMPOH, to 0.5, 1.5, and 4.0 equiv, resulted in continuous sharpening of the aromatic resonances.

Addition of 2.5 equiv of TEMPOH to monomethyl salt **5** had no effect on the ^{1}H NMR as anticipated; however, when *t*-BuOK is added subsequently, the anthracene peaks are completely

Scheme VI. A Reaction Pathway Rationalizing the Autoxidation of *N*-(9-Anthryl)piperidine (**3**) to HAP (**4**)



broadened. This result suggests similarly high stabilities of radicals **21** and **20**.

Generation of the Radical by Addition of Hydrogen Atom Acceptors. In our hands, several preparations of HAP (**4**) yielded a gold powder whose ^{1}H NMR spectrum in DMSO-d_6 showed sharp, clear anthracene peaks. The UV spectrum of the ^{1}H NMR sample contained a broad peak centered at 516 nm, characteristic of the anthranolate group; therefore, zwitterion **11** forms in DMSO-d_6 solution, but still the anthracene ^{1}H NMR peaks are sharp and clear. We suggest that these preparations have yielded dialkylaminoanthranol **4** without contamination by radical **14**. In support of this conclusion, we observed that, upon addition of TEMPO (1.0 equiv) to the above ^{1}H NMR sample, the anthracene peaks were broadened beyond detection. The TEMPO accepted a hydrogen atom from **4** to form TEMPOH and **14**. In DMSO-d_6, **4** is in equilibrium with zwitterion **11**, facilitating rapid intermolecular electron exchange; the anthracene ^{1}H NMR peaks are thus broadened beyond detection.

Proposed Pathway for Autoxidation. Having rationalized the unusual NMR behavior of HAP, we turned toward developing a rational pathway for the formation of **4**. The autoxidation of *N*-(9-anthryl)piperidine (**3**) to form **4** is proposed to occur by autoxidation as shown in Scheme VI. In an effort to obtain evidence in support of this pathway, the preparation of **4** was performed with added anthraquinone (0.25 equiv). If anthraquinone and piperidine react to form intermediate **25**, then by adding anthraquinone the yield of **4** should increase. The preparation of **4** spiked with 0.25 equiv of anthraquinone indeed resulted in an increased yield of **4** (27% compared to 10% without added anthraquinone). The preparation of **4** was repeated with 1.0 equiv of anthraquinone added, and the yield of **4** increased to 62%. These results lend support for the formation of **25** as an intermediate in the preparation of **4**. In addition, the mechanism provides a reasonable pathway for the formation of radical impurity **14**.

The direct autoxidation is also indicated by reactions using preformed and isolated **3**. A solid sample of *N*-(9-anthryl)-piperidine (containing 75% **3** and 25% **4** as shown by ^{1}H NMR) was transformed upon standing for 2 days at room temperature to HAP (45%), anthraquinone (50%), and dianthraquinone (5%). A color change from bright orange to dark orange-brown accompanied this solid-state reaction.

Analogies to the NMR Behavior of Fredericamycin A. Our results show many similarities to those obtained previously with fredericamycin A.[10] In both cases a portion of the NMR, both ^{1}H and ^{13}C, shows resonances that are broadened to the point that they cannot be observed. The severe broadening effect is caused by the presence of a phenoxy radical. Intermolecular exchange of the unpaired electron from the radical facilitates complete broadening in only one fragment of either **4** or fredericamycin A (**10**). The major difference between the two compounds is the mechanism responsible for the extreme line broadening. Fredericamycin A has been shown to form a stabilized free radical upon exposure to oxygen, and addition of trifluoroacetic acid reduces the radical, removing its presence from solution. Our results suggest that the radical form (**15**) is often present in some small amount in our samples of HAP; **15** is a required intermediate in our proposed mechanism. The cause of the NMR broadening is formation of a zwitterion that opens a rapid pathway for intermolecular exchange of the unpaired electron. Radical **14** is not converted to a nonradical species upon addition of acid as has been suggested to occur in fredericamycin A.

Synthesis of *N*-Anthrylpiperidine. Finally, it should be noted that our original target compound, *N*-(9-anthryl)piperidine (**3**), has been prepared. If the reaction mixture from the condensation of anthrone with piperidine is filtered prior to concentration and selective precipitation, the desired 9-(*N*,*N*-dialkylamino)anthracene **3** is obtained. A mixed NMR experiment demonstrates that this product is not the semistable hydrogen-bonded complex that forms between piperidine and anthranol.[14] Interestingly, compound **3** has been obtained in good yield under aerobic (81% yield) as well as anaerobic (88% yield) conditions. The chemistry of **3** and other 9-(*N*,*N*-dialkylamino)anthracenes and 10-(*N*,*N*-dialkylamino)-anthranols is currently under study.

(14) Anthranol forms semistable hydrogen-bonded complexes with amines, such as with triethylamine: Baba, H.; Takemura, T. *Tetrahedron* **1968**, *24*, 4779.

Summary

The condensation of anthrone (**1**) with piperidine (**2**) affords both the expected aminoanthracene (**3**) and its autoxidation product, **4**. The NMR spectra of **4** in DMSO-d_6 are broadened in the aromatic region, often to the point that the aromatic resonances do not appear at all. Such broadening is well-precedented to occur by either electron or hydrogen atom transfer; ESR indicates the presence of an oxyradical that is most reasonably **14**. This radical must be present in <5 mol %, because addition of TFA to the DMSO solution affords aromatic resonances of correct integration. Because broadening is not observed in DMSO/TFA, DMSO/*t*-BuOK, or $CHCl_3$, and because the UV of **4** in DMSO indicates the presence of an anthranolate species that must be **11**, we conclude that electron transfer involving **4** must be rapid on the NMR time scale only for its zwitterionic form, species **11**. Consecutive acid/base additions indicate that the line-broadening species is not simply destroyed upon the addition of acid. The *N*-methyl derivative of **11**, which has a cationic nitrogen that is not neutralized with base, confirms this general picture; only its zwitterion form demonstrates line broadening. As this zwitterion is incapable of hydrogen atom transfer, the electron transfer mechanism for spin transfer must be operative.

Experimental Section

General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, BC. FT-NMR spectra were obtained at 11.75 T (500 MHz) or 7.0 T (300 MHz). We thank Mr. Richard Weisenberger and Dr. C. E. Cottrell for their assistance in obtaining high-field NMR spectra, respectively, at The Ohio State University Instrumentation Center, and Mr. Carl Engelman for other NMR assistance. We were unable to obtain parent molecular ions for any of the 9-(*N*,*N*-dialkylamino)anthracene or 9-(*N*,*N*-dialkylamino)anthranols in this series using either EI or FAB desorption techniques. As shown in Figure 1, the NMR spectra often contain varying minor amounts of the following impurities: anthraquinone, dianthraquinone, dichloromethane, and water. UV spectra were obtained on a Hewlett-Packard 8451A diode array spectrophotometer. Anhydrous *p*-toluenesulfonic acid was obtained by azeotropic removal of water (approximately 100 mL of benzene per 10 g of *p*-tosic acid) using a Dean-Stark trap; benzene was subsequently removed by evaporation in vacuo at approximately 50 °C. Degassed toluene was obtained by bubbling dry argon through anhydrous toluene (99%+), purchased from the Aldrich Chemical Co., Milwaukee, WI, for 1 h while under reduced pressure. Piperidine, purchased from Aldrich, was degassed in the same manner. All syntheses were performed under an argon atmosphere and in reduced light.

***N*-(9-(10-Hydroxyanthryl))piperidine (HAP; 4).** Anthrone (4.0 g, 21 mmol) and anhydrous *p*-toluenesulfonic acid (200 mg) were placed in anhydrous toluene (20 mL) with stirring. Upon addition of piperidine (8.3 mL, 84 mmol), the mixture changed from cream-yellow to orange-red. The mixture was heated to reflux, causing complete dissolution. Refluxing was continued for 20 h; then the system was cooled to room temperature and concentrated to dryness in vacuo to give a bright orange solid. The solid was suspended in methylene chloride (125 mL), and the resulting orange suspension was stirred for 10 h. Filtration under argon gave a gold solid that was washed with methylene chloride (3 × 30 mL) to afford anthranol **4** (containing ca. 10% anthraquinone) as a gold powder (639 mg, 11%): mp 178–183 °C; UV ($(CH_3)_2SO$) 374 nm (5421), 406 nm (7413), 428 nm (5364), 514 nm (405); ^1H NMR ($(CD_3)_2SO$) δ 1.45 (s, 6, $(CH_2)_3$), 2.70 (s, 4, CH_2NCH_2), 6.2–9.0 (these aromatic peaks have been present in only a few preparations of **4**; br s, 8, ArH); ^{13}C NMR ($(CD_3)_2SO$) δ 24.4 (t), 25.9 (t), 46.3 (t).

Anal. Calcd for $C_{19}H_{19}NO + 0.1C_{14}H_8O_2$: C, 82.17; H, 6.69; N, 4.70. Found: C, 80.59;[15] H, 6.85; N, 4.75.

Addition of a slight excess of trifluoroacetic acid to a DMSO solution of **4** afforded the following spectral characteristics: UV ($(CH_3)_2SO$) 374 nm (5300), 408 nm (6900), 428 nm (5700); ^1H NMR ($(CD_3)_2SO$) δ 1.52–1.67 (m, 6, $(CH_2)_3$), 2.95–3.03 (m, 4, CH_2NCH_2), 6.88 (d, 2, Ar H), 7.13, (t, 2, Ar H), 7.38 (t, 2, Ar H), 8.39 (d, 2, Ar H); ^{13}C NMR ($(CD_3)_2SO$) δ 21.7 (t), 22.3 (t), 43.9 (t), 120.2 (s), 123.1 (s), 123.2 (d), 123.6 (d), 126.1 (d), 126.2 (d), 132.1 (s), 149.5 (s).

Addition of excess *t*-BuOK (2.5 equiv) to a DMSO solution of **4** afforded the following spectral characteristics: UV ($(CH_3)_2SO$) 410 nm (13 800), 526 nm (5000); ^1H NMR ($(CD_3)_2SO$) δ 1.10 (s, 23, $(CH_3)_3C$), 1.33–1.49 (m, 6, $(CH_2)_3$), 2.60 (t, 4, CH_2NCH_2), 6.64–6.83 (m, 4, Ar H), 6.81 (m, 2, Ar H), 8.41 (m, 2, Ar H).

Condensation with Added Anthraquinone. The given experimental procedure for the preparation of **4** was repeated with 0.25 equiv of anthraquinone added simultaneously with the anthrone in the initial reaction mixture, which afforded a gold powder (1.068 g, 37%) that by ^1H NMR contained 78% of **4** and 22% anthraquinone: ^1H NMR ($(CD_3)_2SO$) δ 1.44 (s, 6, $(CH_2)_3$), 2.69 (m, 4, CH_2NCH_2), 6.96 (d, 2, Ar H), 7.12 (t, 2, Ar H), 7.31 (d, 2, Ar H), 7.99 (m, anthraquinone), 8.18 (m, anthraquinone), 8.60 (d, 2, Ar H).

The given experimental procedure for the preparation of **4** was repeated with 1.0 equiv of anthraquinone added which afforded a gold powder (2.457 g, 84%) that by ^1H NMR contained 62% of **4** and 38% anthraquinone: ^1H NMR ($(CD_3)_2SO$) δ 1.46 (s, 6, $(CH_2)_3$), 2.69 (m, 4, CH_2NCH_2), 6.20–9.00 (br, s, 8, Ar H), 7.99 (m, anthraquinone), 8.19 (m, anthraquinone).

***N*-(9-(10-Hydroxyanthryl))-*N*-methylpiperidine, Iodide Salt (5).** Compound **4** (500 mg, 1.8 mmol) was added to a stirred solution of methyl iodide (5.0 mL, 80 mmol) in anhydrous acetonitrile (25 mL). The resulting solution was stirred at room temperature for 40 h during which time the color changed from orange to yellow-tan. The mixture was evaporated to dryness in vacuo to afford a tan powder (**5**; 510 mg, 74%): mp 183–190 °C; UV ($(CH_3)_2SO$) 374 nm (5400), 408 nm (7000), 428 nm (6100); ^1H NMR ($(CD_3)_2SO$) δ 1.45–1.67 (m, 4, equatorial $CH_2CH_2NCH_2CH_2$ and $CH_2CH_2CH_2N$), 1.76 (br s, 2, axial $CH_2CH_2NCH_2CH_2$), 3.00 (m, 2, axial CH_2NCH_2), 3.04 (s, 3, NCH_3), 3.32 (m, 2, equatorial CH_2NCH_2), 6.87 (d, 2, Ar H), 7.14 (q, 2, Ar H), 7.39 (q, 2, Ar H), 8.58 (d, 2, Ar H), 10.46 (s, 1, OH); ^{13}C NMR ($(CD_3)_2SO$) δ 19.48 (t), 22.14 (t), 43.72 (t), 50.86 (q), 119.96 (s), 122.85 (s), 122.94 (d), 123.48 (d), 125.93 (d), 125.98 (d), 131.85 (s), 149.20 (s). An unknown impurity, not observable in the ^1H NMR spectrum, demonstrated peaks at 20.45 (t), 20.70 (t), 21.51 (t), 22.61 (t), 42.69 (q), 53.72 (t), 61.52 (t).

Anal. Calcd for $C_{20}H_{22}NOI$: C, 57.29; H, 5.29; N, 3.34; I, 30.27. Found: C, 57.24; H, 5.62; N, 3.65; I, 30.49.

Addition of an excess of *t*-BuOK to a DMSO-d_6 solution of **5** gave the following spectral data: UV ($(CH_3)_2SO$) 410 nm (25 400), 524 nm (7500); ^1H NMR ($(CD_3)_2SO$) δ 1.10 (s, $(CH_3)_3C$), 1.34–1.52 (m, 4, equatorial $CH_2CH_2NCH_2CH_2$ and $CH_2CH_2CH_2N$), 1.74 (br s, axial $CH_2CH_2NCH_2CH_2$), 2.61 (t, 2, axial CH_2NCH_2), 3.03 (s, 3, NCH_3), 3.26 (t, 2, equatorial CH_2NCH_2).

Addition of excess triethylamine to a DMSO-d_6 solution of **5** gave the following NMR data: ^1H NMR ($(CD_3)_2SO$) δ 0.97 (t, $(CH_3CH_2)_3N$), 1.49–1.61 (m, 4, equatorial $CH_2CH_2NCH_2CH_2$ and $CH_2CH_2CH_2N$), 1.76 (br s, 2, axial $CH_2CH_2NCH_2CH_2$), 2.57 (q, $(CH_3CH_2)_3N$), 2.98 (t, 2, axial CH_2NCH_2), 3.05 (s, 3, NCH_3), 3.31 (t, 2, equatorial CH_2NCH_2), 6.65–7.80 (br m, 6, ArH), 8.30–8.90 (br s, 2, ArH).

***N*-(9-(10-Methoxyanthryl))-*N*-methylpiperidine, Iodide Salt (7).** Compound **5** (50 mg, 0.124 mmol) was added to anhydrous acetonitrile (10 mL) with stirring, and then potassium *tert*-butoxide (270 mg, 2.4 mmol) and methyl iodide (0.30 mL, 4.8 mmol) were added. Stirring for 24 h produced a white precipitate (KI) that was filtered and discarded. The clear yellow filtrate was concentrated in vacuo to yield a cream-yellow solid that was triturated with chloroform (75 mL). Filtration and concentration of the chloroform phase gave an orange-brown semisolid. Recrystallization from chloroform (10 mL) produced colorless crystals as a non-UV-absorbing impurity, which was again removed by filtration. The clear brown filtrate was concentrated in vacuo and coevaporated several times with chloroform to give a tan powder (**7**; 25 mg, 48%): mp 175–195 °C dec.; UV ($(CH_3)_2SO$) 366 nm (2250), 386 nm (3863), 408 nm (4429); ^1H NMR ($(CD_3)_2SO$) δ 1.46–1.56 (m, 2, equatorial $CH_2CH_2NCH_2CH_2$), 1.75 (br d, 2, axial $CH_2CH_2NCH_2CH_2$), 1.95 (s, 1, axial $CH_2CH_2CH_2N$), 2.07 (s, 1, equatorial $CH_2CH_2CH_2N$), 2.84 (s, 2, axial CH_2NCH_2), 3.03 (s, 3, NCH_3), 3.29 (t, 2, equatorial CH_2NCH_2), 4.26 (s, 3, OCH_3), 6.92 (d, 2, Ar H), 7.23 (t, 2, Ar H), 7.53 (t, 2, Ar H), 8.42 (d, 2, Ar H); ^{13}C NMR ($(CD_3)_2SO$) δ 19.55, 20.54, 50.91, 61.62, 63.55, 122.51, 123.87, 125.53, 126.40, 126.49, 127.91, 131.86, 152.46.

Additions of TEMPOH to a Sample of HAP (4) with Broadened Anthracene Peaks in DMSO-d_6. Addition of 0.1 equiv of TEMPOH[13] (3.0 mg, 0.2 mmol) to a solution of **4** (50 mg, 0.18 mmol) in DMSO-d_6 (5 mL) afforded the following spectral characteristics: ^1H NMR ($(CD_3)_2SO$) δ 1.00 (s, 3.1, $(CH_2)_3$ of TEMPOH), 1.38 (s, 1.5, CH_2NCH_2 of TEMPOH), 1.44 (s, 6, $(CH_2)_3$), 2.67 (d, 4, CH_2NCH_2), 6.40–7.60 [br s, 3.3 (expected: 6), ArH], 8.35–9.00 [br s, 0.9 (expected: 2), Ar H].

Addition of 0.5 equiv of TEMPOH (11 mg, 0.07 mmol) to a solution of **4** (40 mg, 0.14 mmol) in DMSO-d_6 (4 mL) afforded the following spectral characteristics: ^1H NMR ($(CD_3)_2SO$) δ 1.00 (s, 7.8, $(CH_2)_3$ of

(15) Although this analysis is not within 0.4% of the theoretical as required by current convention, all other characterizations of this sample were consistent with the structure assignment.

TEMPOH), 1.39 (s, 3.9, CH_2NCH_2 of TEMPOH), 1.44 (s, 6, $(CH_2)_3$), 2.67 (s, 4, CH_2NCH_2), 6.50-7.70 [br m, 4.2 (expected: 6), Ar H], 8.30-9.00 [br s, 1.3 (expected: 2), Ar H].

Addition of 1.5 equiv of TEMPOH (26 mg, 0.16 mmol) to a solution of **4** (30 mg, 0.11 mmol) in DMSO-d_6 (3 mL) afforded the following spectral characteristics: ^{1}H NMR ($(CD_3)_2SO$) δ 1.00 (s, 16.8, $(CH_2)_3$ of TEMPOH), 1.38 (s, 8.4, CH_2NCH_2 of TEMPOH), 1.44 (s, 6, $(CH_2)_3$), 2.67 (s, 4, CH_2NCH_2), 6.40-7.60 [br m, 4.6 (expected: 6), Ar H], 8.30-8.85 [br s, 1.1 (expected: 2), Ar H].

Addition of 4.0 equiv of TEMPOH (23 mg, 0.14 mmol) to a solution of **4** (10 mg, 0.036 mmol) in DMSO-d_6 (1 mL) afforded the following spectral characteristics: ^{1}H NMR ($(CD_3)_2SO$) δ 1.01 (s, 57, $(CH_2)_3$ of TEMPOH), 1.39 (s, 29, CH_2NCH_2 of TEMPOH), 1.45 (s, 6, $(CH_2)_3$), 2.69 (s, 4, CH_2NCH_2), 6.30-7.60 (br m, 6, Ar H), 8.30-8.95 (br s, 2, Ar H).

***N*-(9-Anthryl)piperidine (3). Anaerobic Conditions.** Anthrone (4.0 g, 21 mmol) and anhydrous *p*-toluenesulfonic acid (200 mg) were sealed under an argon atmosphere by a series of evacuation with a vacuum line, then filling with argon. Degassed toluene (20 mL) was added via syringe with stirring, giving a cream-yellow mixture. Degassed piperidine (8.3 mL, 84 mmol) was added via syringe producing a dark orange-red mixture. The solution was refluxed for 40 h, then cooled to room temperature, giving an orange precipitate. The precipitate was filtered in a drybox and washed with degassed toluene (10 mL) to yield an orange powder (**3**; 4.83 g, 88%): 164-169 °C; UV ($(CH_3)_2SO$) 328 nm (3550), 370 nm (1940), 396 nm (2050); ^{1}H NMR ($(CD_3)_2SO$) δ 1.45 (s, 6, $(CH_2)_3CH_2N$), 2.70 (d, 4, CH_2NCH_2), 7.27 (t, 2, Ar H), 7.40 (t, 2, Ar H), 7.71 (s, 1, Ar H), 7.85 (d, 2, Ar H), 8.48 (d, 2, Ar H); ^{13}C NMR ($(CD_3)_2SO$) δ 23.9 (t), 25.2 (t), 45.7 (t), 110.8 (d), 121.3 (d), 124.1 (d), 125.3 (d), 127.4 (d), 133.0 (2 overlapping singlets), 156.2 (s).

Anal. Calcd for $C_{19}H_{19}N\cdot H_2O$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.64; H, 7.45; N, 4.53.[15]

Aerobic Conditions. Anthrone (2.0 g, 10.5 mmol) and anhydrous *p*-toluenesulfonic acid (100 mg) were added to anhydrous toluene (10 mL) with stirring. No precautions were taken to exclude atmospheric oxygen. Upon addition of piperidine (4.2 mL, 42 mmol) the mixture changed from cream-yellow to orange-red. The mixture was heated to reflux, resulting in complete dissolution. Refluxing was continued for 22 h; then the solution was cooled to room temperature giving an orange precipitate in a dark red solution. Filtration and washing with toluene (15 mL) gave an orange powder (**3**; 2.32 g, 81%), identical by ^{1}H NMR with the material produced under anaerobic conditions.

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Novel Inclusion of Bis(2-pyridylcarbinolato)copper(II) by Cyclodextrins

Hiroshi Yokoi,*,† Minoru Satoh,‡ and Masamoto Iwaizumi‡

Contribution from the Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan, and Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Sendai 980, Japan. *Received May 21, 1990*

Abstract: Formation of the inclusion complexes of bis(2-pyridylcarbinolato)copper(II) with cyclodextrins (CDs) has been studied extensively by electron spin resonance (ESR) and circular dichroism measurements. It has been found that the copper(II) complex forms a 1:1 inclusion complex with α-CD but a more stable 2:1 complex with γ-CD. The stability constants of these inclusion complexes have also been estimated by an ESR method. The 2:1 inclusion complex showed a triplet-state ESR spectrum characteristic of copper(II) dimers. A dimeric structure has been proposed based on computer simulation of the ESR spectrum. This inclusion system may be a new model for multifactorial biological systems for molecular recognition and for mimicking active transport or concentration of substances.

Cyclodextrins (CDs) are cyclic oligosaccharides with internal cavities capable of forming inclusion complexes with small organic and organometallic compounds in aqueous solutions.[1-5] They have been studied extensively as models for enzyme active sites with the intention of mimicking enzyme activity and understanding the mechanism of molecular recognition.[1-4] However, there are very few reports about the inclusion of small and ordinary metal complexes by CDs. The purpose of this paper is to report a novel inclusion phenomenon of bis(2-pyridylcarbinolato)copper(II) by CDs. The inclusion mode described here appears to be unique and suggestive in considering the mechanisms of molecular recognition and active transport or concentration of substances in biological systems.

Experimental Section

Materials. The α-CD, β-CD, γ-CD, and D-trehalose and 2-pyridylcarbinol were obtained from Nakarai and Aldrich, respectively, and were used as received. Bis(2-pyridylcarbinolato)copper(II) was prepared as a tetrahydrate by the following method. $CuCl_2\cdot 2H_2O$ (25 mmol) and 2-pyridylcarbinol (50 mmol) were dissolved in water (100 mL), the solution was adjusted to pH ~9, and the desired product was precipitated. The crude product was recrystallized from water at pH ~9. Anal. Calcd for $C_{12}H_{12}N_2O_2Cu\cdot 4H_2O$: C, 40.99; H, 5.73; N, 7.96. Found: C, 41.08; H, 5.66; N, 7.75.

Measurements. A JEOL JES-FE2XG ESR spectrometer (X-band) was used to measure ESR spectra of frozen aqueous solutions at 77 K; a Takeda Riken TR-5501 frequency counter and an ECHO Electronics EFM-2000 NMR field meter were used in measurements of the microwave frequency and magnetic fields, respectively. A computer simulation of the dimer ESR spectra of the above copper(II) complex was carried out at the Computer Center of Tohoku University with a program based on the point-dipole approximation.[6,7] Visible and UV spectra and cir-

†Shizuoka University.
‡Tohoku University.

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