

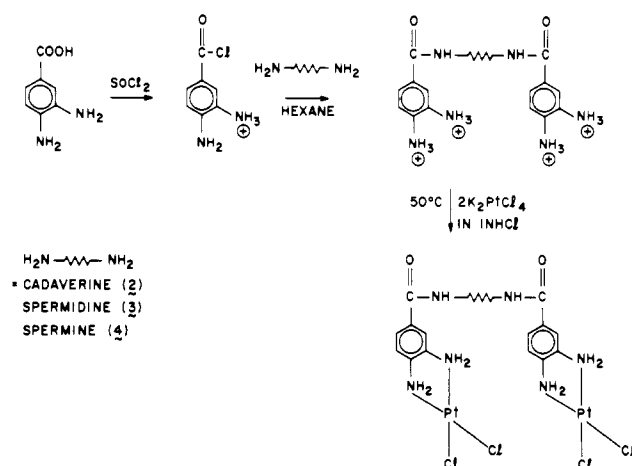
NMR spectra of the complexes were recorded in 1 M NaCl solution.

It has been established previously that *cis*-DDP is an effective anticancer agent while its trans analogue lacks activity.^{1,2} The optical binding studies on DDP-poly(dA-dT) complexes show significant differences between the two isomers, with the *cis* isomer stabilizing twice the number of base pairs (reaching of number of ~32 per bound Pt for the reaction conditions specified in this work) about its binding site compared to the trans isomer. Further, the transition midpoint for the opening of base pairs centered about bound Pt occurs at a much higher temperature for the *cis* isomer compared to the trans isomer, indicative of the formation of a more stable complex with the *cis* isomer.

It has been proposed that the covalent interaction between dichlorodiammineplatinum(II) and the nucleic acid involves nitrogen and/or oxygen atoms on the base pair edges though the exact nature of binding is still a subject of controversy.¹¹⁻¹⁴ The NMR studies suggest that the base pair overlaps in poly(dA-dT) are not significantly perturbed on formation of the DDP-(synthetic DNA) complexes. However, the selective change in one of the sugar H-1' chemical shifts on formation of the *cis*-DDP-poly(dA-dT) complex suggests that the covalent interaction does result in a perturbation in either the adenosine or thymidine glycosidic torsion angle.

Registry No. *cis*-DDP, 15663-27-1; *trans*-DDP, 14913-33-8; dA, 958-09-8; dT, 3416-05-5.

Scheme I



duced many new active antitumor agents, they generally involve monomeric platinum complexes. We report here the synthesis of a series of new bis(*cis*-dichloro(diamine)platinum(II)) complexes with a variable and flexible bridge.⁶ The design of these platinum complexes allows us to investigate the effect of the bridging chain length on their binding to DNA, particularly in light of the fact that their antitumor activity is related to their ability to interact with DNA. This is accomplished by a study of melting profiles of the reaction products of these bis(platinum) complexes with the synthetic DNA, poly(dA-dT).

Since *cis*-[Pt(diamine)Cl₂] where diamine = *o*-phenylenediamine was shown to be an active antitumor agent against ADJ/PC6 plasma cell tumor,^{5c} the compound with diamine = 3,4-diaminobenzoic acid (DAB) was chosen for the synthetic convenience of bridging two such units via two amide linkages with diamines such as cadaverine (H₂N(CH₂)₅NH₂), spermidine (H₂N(CH₂)₃NH(CH₂)₄NH₂), and spermine (H₂N(CH₂)₃NH(CH₂)₄NH(CH₂)₃NH₂). These diamines possess the following desirable characteristics: (1) they span roughly

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Contribution from Bell Laboratories,
Murray Hill, New Jersey 07974

Synthesis of Bis(*cis*-dichloro(diamine)platinum(II)) Complexes with Variable Bridges and Study of Their Binding with Poly(dA-dT) by Melting Profiles

In-Bok Paek, P. A. Snyder-Robinson, and Boon-Keng Teo*

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Since Rosenberg's discovery of the anticancer activity of *cis*-dichlorodiammineplatinum(II) (DDP) (whereas the trans analogue is ineffective), there has been a considerable amount of work aimed at synthesizing new platinum compounds with more desirable properties.¹⁻⁵ While these studies have pro-

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10, 15, and 20 Å, respectively, in length when fully stretched and (2) they themselves bind with DNA via, presumably, electrostatic interactions.⁷

Experimental Section

The monomer *cis*-(Pt(DAB)Cl₂) (1) was prepared by reacting stoichiometric amount of 3,4-diaminobenzoic acid (DAB) with K₂PtCl₄ in 1 N HCl at 50 °C in the dark for 24 h.^{8a} The yellowish brown product exhibits ν_{CO} and (in addition to those attributable to the functional groups) $\nu_{\text{Pt-Cl}}$ bands at 1720 (vs) and 314 (m), 297 (sh) cm⁻¹, respectively, in addition to bands attributable to coordinated DAB. The doublet structure of $\nu_{\text{Pt-Cl}}$ is consistent with the *cis*-Pt-(amine)₂Cl₂ configuration. Anal. Calcd for C₇H₈N₂Cl₂PtO₂ (1): C, 20.11; H, 1.93; N, 6.70; Cl, 16.96. Found: C, 19.51; H, 2.17; N, 7.22; Cl, 17.55.

The bis(platinum) complexes [*cis*-PtCl₂(DABA)]₂(bridge) where DABA = 3,4-diaminobenzamide and bridge = cadaverine (2), spermidine-HCl (3), and spermine-2HCl (4) were prepared according to Scheme I via standard reactions. The brown products exhibit infrared bands (in cm⁻¹) at 1717 (vs) and 309 (m), 293 (sh) for 2, 1718 (vs) and 305 (sh), 291 (m) for 3, and 1715 (vs) and 313 (m), 298 (sh) for 4 which can be attributed to ν_{CO} and $\nu_{\text{Pt-Cl}}$, respectively. Each compound also exhibits infrared bands attributable to the coordinated DABA ligand and the protonated polyamine bridge. The frequencies and the doublet structure of the $\nu_{\text{Pt-Cl}}$ bands strongly suggest a *cis*-Pt(amine)₂Cl₂ configuration for compounds 1–4. Anal. Calcd for C₁₉H₂₆N₆Cl₄Pt₂O₂ (2): C, 25.29; H, 2.90; N, 9.31; Cl, 15.71. Found: C, 24.64; H, 2.47; N, 8.17; Cl, 14.32. Anal. Calcd for C₂₁H₃₂N₇Cl₃Pt₂O₂ (3): C, 25.68; H, 3.28; N, 9.98; Cl, 18.05. Found: C, 24.03; H, 2.22; N, 8.47; Cl, 15.12. Anal. Calcd for C₂₄H₄₀N₈Cl₂Pt₂O₂ (4): C, 26.80; H, 3.75; N, 10.42; Cl, 19.78. Found: C, 24.67; H, 2.45; N, 8.01; Cl, 15.01. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

We note that the analytical results are less accurate for complexes 3 and 4. One possibility is some side reactions involving the secondary amines in the bridge. However, we note that in the final step of the syntheses, the reactions of the ligand with K₂PtCl₄ were performed under acidic condition (pH < 1)^{8b} such that all the secondary amines of spermidine or spermine bridges are fully protonated as indicated in the formula. As for the second step of the reaction scheme, the ease of amide formation for the secondary amine(s) in spermidine and spermine are significantly lower than that for the primary amines. Furthermore, the observed elemental analyses are totally inconsistent with additional PtCl₂ or Pt(DABA)Cl₂ moieties attached to the spermidine or spermine bridge. Attempts to purify these compounds, however, were hampered by their low solubilities in inert solvents. Solvents such as Me₂SO will dissolve these compounds but also cause decomposition. Nevertheless, the spectroscopic and the analytical results presented here, as well as the fact that these compounds gradually dissolve upon reaction with poly(dA-dT), attest to their identity.

The binding of these bis(platinum) complexes to poly(dA-dT) was studied by optical melting profiles. Reactions of 1–4 with 3 mM (phosphate concentration) poly(dA-dT) were performed in 5 mM cacodylate buffer at pH 7 at room temperature for 1–3 days. (Reaction times of 1–3 days did not affect the melting profiles to any significant extent. Furthermore, reactions were performed in three separate stages with duplicate runs, and controls agree within experiment error.)

In each case, BP/M (base pair to metal) ratios of 4, 8, 16, and 32 were investigated. At the end of the reaction, the solution was diluted by 20-fold for the melting curve (A_{260}) measurements. During the course of the reaction, the platinum compound gradually dissolves as they react with poly(dA-dT) to give a clear light brown solution. For BP/M = 4, the solutions sometimes turned turbid. In these cases, the solutions were filtered. However, the melting curves were virtually identical before and after filtration.

Poly(dA-dT) as lyophilized sodium salt was purchased from Collaborative Research (Lot 714-57A) and has the following characteristics: λ_{max} = 263 nm at pH = 7.0; OD/mg = 19.2 at 260 nm; S_{20} = 9.5; T_m = 65 °C. It was dialyzed in our laboratory against 5 mM cacodylate buffer for 24 h during which the buffer was changed twice. The polynucleotide concentration was based on an extinction coefficient of ϵ_{260} = 6.7×10^3 in phosphates.

The melting profiles (as ΔA_{260}) were recorded with the use of a Gilford 2400-2 spectrophotometer equipped with a thermoprogrammer, Model 2527, a reference compensator, and a special cuvette assembly which uses a thermoelectric device to pump heat into or out of the sample. A free poly(dA-dT) sample was run as a control. The samples (in 10-mm quartz cells) were heated at a constant rate of 1 °C/min from 25 to 80 °C. At the end of each run, the samples were cooled down to 25 °C and subjected to additional heating cycles which are distinctly different from the first cycle.

Results and Discussion

We have studied the optical melting behavior of the reaction products of poly(dA-dT) with *cis*-(Pt(DAB)Cl₂) (1) and bis[*cis*-(PtCl₂(DABA)]₂(bridge) (where bridge = cadaverine (2), spermidine-HCl (3), and spermine-2HCl (4), DAB = 3,4-diaminobenzoic acid, and DABA = 3,4-diaminobenzamide) in order to explore the characteristics and specificity (if any) of the interaction of these platinum complexes with DNA. Poly(dA-dT) was chosen for two reasons. First, the helix to coil transition of free poly(dA-dT) occurs at favorably low temperatures. In 5 mM cacodylate buffer, poly(dA-dT) melts at 37 °C. Second, the diamines show preferential binding for A-T-rich over G-C-rich DNA.⁷

Figure 1A shows the melting profiles for the reaction products of 1–4 (hereafter referred to as I–IV, respectively) with poly(dA-dT) for BP/M ratio of 32 whereas Figure 1B depicts the melting curves for III with BP/M ratios of 4, 8, 16, and 32. Several important features are obvious from these results. First, both the mono- and bis(platinum) complexes exhibit biphasic structures in their double helix to single strand transitions. Second, the low-temperature phase melts at about the same (or somewhat lower) temperature as (than) free poly(dA-dT) (~37 °C), whereas the high-temperature phase melts at considerably higher temperature, indicating a region of a high degree of helical stabilization. Since the extent of the high-temperature phase correlates directly with the metal content (vide infra), we assign the low-temperature phase to the "platinum-free" region and the high-temperature phase to the "platinum-bound" (or stabilized) region. Third, though the melting of poly(dA-dT) is completely reversible, we found no renaturation for the high-temperature phase. A direct consequence is that the second and subsequent heating cycles are different from the first one. These observations are similar to that observed by Harder⁹ and Canuel et al.¹⁰ for the reaction product of *cis*-Pt(NH₃)₂Cl₂ with poly(dA-dT). For example, Harder⁹ observed a biphasic melting curve of roughly equal ΔA_{260} for BP/M = 10 with melting temperatures of 35 and 42 °C for poly(dA-dT) incubated with *cis*-DDP for 16 h at 21 °C in 5 mM NaClO₄. The high-temperature transition, which is not renaturable, is considerably broader than the low-temperature transition. At BP/M = 2, a broad transition occurs with T_m of ca. 46 °C. As the drug level increases, the absorbance change, ΔA_{260} , decreases significantly.⁹ Finally, the "platinum-bound" region extends over increasing number of base pairs with increasing BP/M ratio (i.e., decreasing drug content; cf. Figure 1B), indicating a larger degree of "effective" influence at low drug levels, until it reaches a plateau. Similar

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(8) (a) In neutral medium, a green compound with similar infrared spectrum and identical formula was obtained which presumably corresponds to the Magnus-type salt [Pt(DAB)]₂²⁺[PtCl₄]²⁻. (b) In this context, we observe that Pt(spermine)⁴⁺Cl₄⁻ was prepared from Pt(NH₃)₂Cl₂ and spermine under alkaline condition (pH > 10) (See: Tsou, K. C.; Yip, K. F.; Lo, K. W.; Ahmad, S. J. *Clin. Hematol. Oncol.* **1977**, *7*, 322).

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(10) It should be noted that though each platinum probably binds to one or two base pairs, its influence actually extends over many more base pairs. See, for example: Canuel, L. L.; Teo, B. K.; Patel, D. J. *Inorg. Chem.*, preceding paper in this issue.

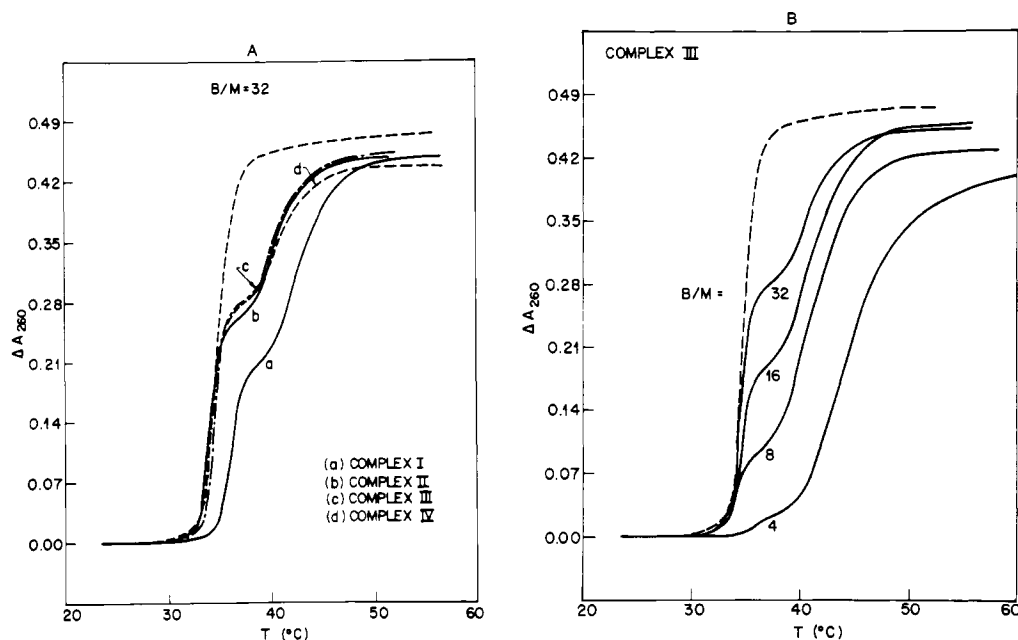


Figure 1. Melting profiles (absorbance change at 260 nm vs. temperature) of (A) complexes I–IV formed by reacting poly(dA–dT) with 1–4 at BP/M = 32 and (B) complex III formed by reacting poly(dA–dT) with 3 at BP/M = 4, 8, 16, and 32. The dashed curve is the melting profile for free poly(dA–dT) as a control.

behavior was observed for the binding of *cis*-DDP with poly(dA–dT).¹⁰

A detailed comparison of the melting behavior of I with those of II–IV revealed that the monomer 1 "binds" more base pairs than the bis(platinum) complexes 2–4 for a given BP/M ratio. Furthermore, though the number of base pairs "bound" by the dimers 2–4 are qualitatively similar (cf. Figure 1A), there are subtle and significant differences reflecting differences in their mode of binding. A somewhat more quantitative measure of the effect imposed by these platinum complexes on the melting of poly(dA–dT) can be obtained by considering the number of base pairs "affected" by each platinum. It can be seen from Table I that, in all cases, the ratio of the free to the "bound" regions as measured by the relative changes in ΔA_{260} decreases progressively with decreasing BP/M ratio while the transition temperature for the "bound" region increases since more platinum tends to affect more base pairs. If we define α and β as the numbers of "bound" base pairs per metal atom (at the same BP/M ratio) in the monomer complex I and the bis(platinum) complexes II–IV, respectively, (as shown in Figure 2a) and assume that α or β can be estimated by $b(\text{BP}/M)$ where b is the fraction of ΔA_{260} due to the platinum "bound" region, we find that β is considerably less than α for BP/M ≥ 8 (cf. Table I). This is taken as a strong indication that the "bound" regions in the bis(platinum) complexes II–IV can overlap, giving rise to $\beta = 1/2(\alpha + S)$ for $S < \alpha$ where α and β correspond to the same BP/M ratio and S is the number of base pairs span by the bis(platinum) complexes¹¹ (cf. Figure 2a). In cases where such overlap vanishes (at long bridge length or low BP/M ratio), $\beta = \alpha$ for $S \geq \alpha$, which is equivalent to independent platinum. From our experimental data, we can estimate the S value for each bis(platinum) complex as listed in Table I. It is surprising to observe that, with the exception of II, S is fairly constant with respect to BP/M within each complex. The average is 7.1 (13), 6.4 (15), and 4.9 (13) for 2, 3, and 4, respectively. Another significant result which is evident from Table I is that the S value is not linearly proportional to the bridge length

Table I. Melting Data of the Complexes Formed by Reacting the Monomer (1)^a and the Bis(platinum) Complexes (2–4)^a with Poly(dA–dT) in 5 mM Cacodylate Buffer (pH 7) at Room Temperature

complex ^a	BP/M ^b	b^c	$(\alpha, \beta)^d$	S^e
I	4	0.94 (8)	3.8 (3)	
	8	0.82 (8)	6.6 (7)	
	16	0.75 (6)	12.0 (10)	
	32	0.55 (4)	17.6 (14)	
II	4	0.81 (5)	3.2 (2)	f
	8	0.73 (5)	5.8 (4)	5.0 (8)
	16	0.62 (3)	9.9 (4)	7.8 (10)
	32	0.41 (3)	13.1 (11)	8.6 (22)
III	4	0.92 (4)	3.7 (2)	f
	8	0.77 (5)	6.2 (4)	5.8 (8)
	16	0.58 (4)	9.3 (7)	6.6 (14)
	32	0.38 (3)	12.2 (11)	6.8 (22)
IV	4	0.90 (4)	3.6 (2)	f
	8	0.69 (4)	5.5 (3)	4.4 (7)
	16	0.53 (4)	8.5 (6)	5.0 (11)
	32	0.36 (5)	11.5 (16)	5.4 (20)

^a Complexes I–IV refer to the reaction products of poly(dA–dT) with *cis*-(Pt(DAB)Cl₂) (1) and bis[*cis*-(PtCl₂(DABA)₂](bridge) where bridge = cadaverine (2), spermidine (3), and spermine (4), respectively. Abbreviations: DAB = 3,4-diaminobenzoic acid; DABA = 3,4-diaminobenzamide. The numbers in parentheses refer to error estimates of the last significant figure. ^b Base pair to metal ratio. ^c Fractional increase in ΔA_{260} of the high-temperature phase (vs. total ΔA_{260}) in the melting profiles. ^d α and β refer to the effective number of bound or affected base pairs as estimated by $b(\text{BP}/M)$ for complexes I and II–IV, respectively. ^e Base pair span as estimated^{10,11} by $S = 2\beta - \alpha$ where α and β correspond to the same BP/M ratio. ^f For $\beta \approx \alpha$, S cannot be calculated.

which increases from 2 (cadaverine) to 3 (spermidine) to 4 (spermine). We believe that these phenomena can be attributed to the fact that the NH_2^+ group(s) on the bridges of 3 and 4 can bind electrostatically with the phosphates of the helix backbone, resulting in the "coiling" of the bridge around the double helix and/or providing anchoring position(s) on the duplex. It is interesting to note that this rationale is consistent with the observation that the S value decreases with increasing number of NH_2^+ groups in the bridge (0, 1, and 2 for the dimers 2, 3, and 4, respectively). And finally, the somewhat

(11) In reality, for even α , $\beta = 1/2(\alpha + S)$ for $S < \alpha$ and $\beta = \alpha$ for $S \geq \alpha$, whereas for odd α , $\beta = 1/2(\alpha + S - 1)$ for $S < \alpha + 1$ and $\beta = \alpha$ for $S \geq \alpha + 1$. This uncertainty may cause error of ± 1 in the S values.

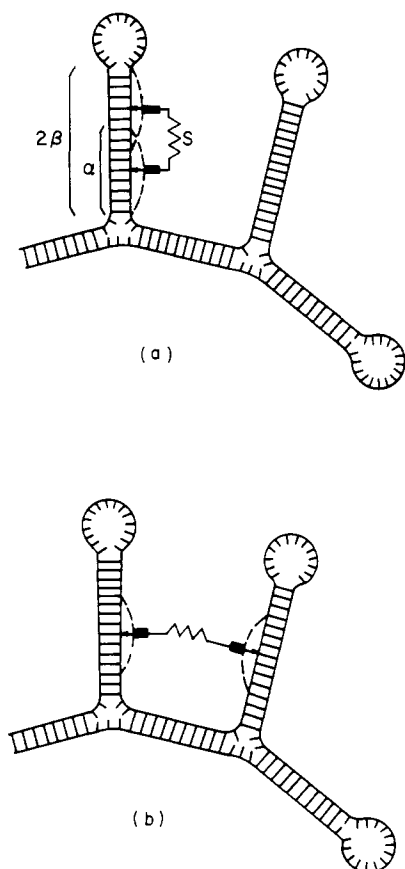


Figure 2. Schematic representations of possible modes of binding of the bis(platinum) complexes with poly(dA-dT). Here α and β are the numbers of base pairs stabilized per platinum and S is the base pair span. In (a) both platinum bind the same stem and the two α regions overlap whereas in (b) the bis(platinum) complex bridges two adjacent hair-pin stems.

increasing S values for **2** as the BP/M ratio increases may indicate that **2** binds the polynucleotide *via additional pathways* which are different from the presumed chelation on the same stem of the double helix (cf. Figure 2a). Since it is known that poly(dA-dT) forms hair-pin loops, one possibility is that **2**, which lacks the anchoring NH_2^+ groups, may bridge across two hair-pin loops (cf. Figure 2b) such that, at high BP/M ratios, each platinum can cover relatively more base pairs on different hair-pin stems thereby giving rise to higher β and hence larger S values.

Acknowledgment. We thank L. Canuel and D. Patel at Bell Laboratories for valuable consultations.

Registry No. 1, 56815-80-6; 2, 78656-89-0; 3, 78656-90-3; 4, 78656-91-4; K_2PtCl_4 , 10025-99-7.

Contribution from the Department of Chemistry,
University of Minnesota, Duluth, Minnesota 55812

Photosubstitution Reactivity of Carbon Disulfide Complexes of Zerovalent Iron

Claude C. Frazier,* Ronald F. Kline, and David D. Barck

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Transition-metal $\eta^2\text{-CS}_2$ complexes have received considerable attention in recent years.¹ Much of this interest derives

Table I. Wavelength Dependence for Quantum Efficiency of $\text{Fe}(\eta^2\text{-CS}_2)(\text{CO})_2(\text{PR}_3)_2$ to $\text{Fe}(\text{CO})_3(\text{PR}_3)_2$ Conversion^a

starting complex	$10^2\Phi$		
	430 nm	366 nm	313 nm
$\text{Fe}(\eta^2\text{-CS}_2)(\text{CO})_2[\text{P}(\text{OMe})_3]_2$	2.7	6.4	8.4
$\text{Fe}(\eta^2\text{-CS}_2)(\text{CO})_2[\text{PEt}_3]_2$	3.4	5.7	8.8

^a 0.03 M metal complex in CO-saturated toluene. Quantum yields are $\pm 10\%$.

from the synthetic utility of carbon disulfide complexes in preparing thiocarbonyl compounds, dithiolene iron complexes, and carbon disulfide-bridged binuclear species.²⁻⁴ Reports of the dynamic behavior of the $\eta^2\text{-CS}_2$ ligand in mononuclear complexes, the fluxional nature of some CS_2 -bridged molecules, and the superior π -acceptor strength of the $\eta^2\text{-CS}_2$ ligand indicate a concomitant interest in the coordinative bonding of the carbon disulfide ligand.^{4a,5,6} While understanding of the thermal chemistry and solution dynamics of carbon disulfide compounds has progressed, there has not been a parallel development of the photochemistry of transition-metal carbon disulfide complexes. In this context, we wish to report the first photochemical study of this interesting class of compounds.

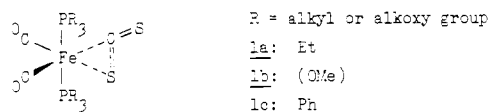
Experimental Section

The $\text{Fe}(\eta^2\text{-CS}_2)(\text{CO})_2(\text{PR}_3)_2$ complexes were prepared by the published method.^{1c} PEt_3 and $\text{P}(\text{OMe})_3$ were obtained from Strem Chemicals, Inc., and used without further purification. Solvents were purchased from commercial sources and were bubbled with nitrogen before use. Air-sensitive compounds and solutions were handled under nitrogen with the use of Schlenk equipment in conjunction with a vacuum inert-gas manifold.

The photolysis apparatus consisted of a 450-W Hanovia mercury lamp with λ_{irr} isolated with appropriate glass filters and filter solutions. Irradiations were performed in Schlenk tubes. Light intensities were measured by ferrioxalate actinometry. Product yields on irradiation were monitored by infrared spectroscopy using a Beckman IR 12 spectrophotometer. UV-vis solution spectra were obtained with a Beckman ACTA II spectrophotometer.

Results and Discussion

The iron(0) complexes $\text{Fe}(\eta^2\text{-CS}_2)(\text{CO})_2(\text{PR}_3)_2$ ($\text{R} = \text{alkyl}$ or alkoxy) (**1**) are among the best characterized of the $\eta^2\text{-}$



1

carbon disulfide transition-metal complexes. They are relatively easy to prepare, and most members of the $\text{Fe}(\eta^2\text{-CS}_2)(\text{CO})_2(\text{PR}_3)_2$ series are stable in deoxygenated solvents. The axial phosphines of **1** are labile with the less basic and/or sterically hindered phosphines being readily replaced with good nucleophiles.^{1c,d} In contrast to the ease of phosphine replacement, displacement of η^2 -coordinated carbon disulfide with phosphines or carbon monoxide is generally not observed

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