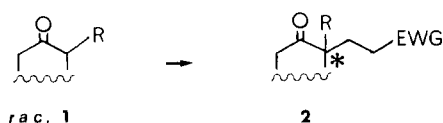
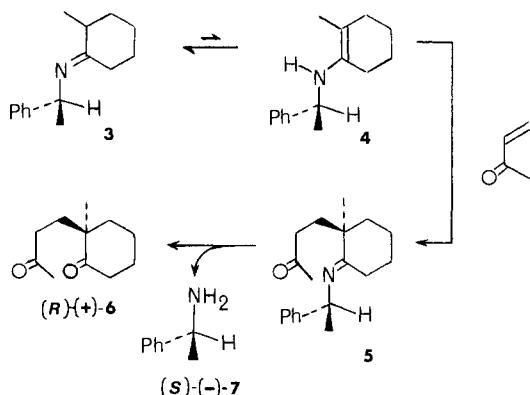


Scheme I



EWG = electron withdrawing group

Scheme II



88% yield, $[\alpha]_D^{20} +34.3^\circ$ (*c* 1.36, EtOH), 91% ee, and the starting amine 7, which was recovered, in an almost quantitative yield, without any loss of optical purity, merely by neutralization (NaOH) of the aqueous layers.

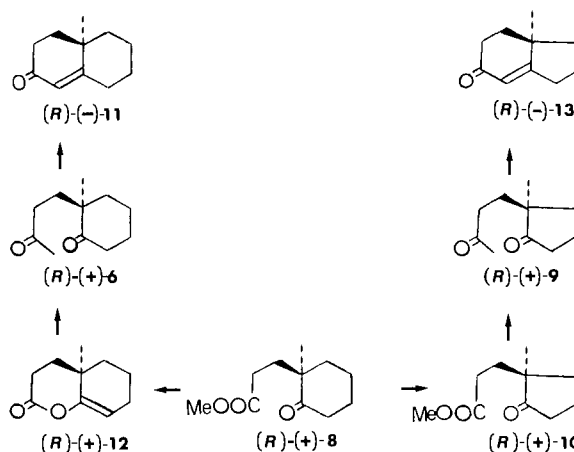
Clearly, as previously reported for alkylations of this type,⁶ the reactive nucleophilic species in this reaction is the secondary enamine 4, in tautomeric equilibrium^{6a,b} with the imine 3, which reacts with methyl vinyl ketone regioselectively⁷ and stereoselectively.

Similar results were observed under the same conditions using other cycloalkanone imines derived from amine 7 and various electron-deficient alkenes. In this manner (*R*)-(+)-keto ester 8 (from imine 3 and methyl acrylate), (*R*)-(+)-diketone 9, and (*R*)-(+)-keto ester 10 (from 2-methylcyclopentanone imine derivative by reaction with methyl vinyl ketone and methyl acrylate, respectively) were obtained.^{5,8}

The enantiomeric excesses of the new chiral compounds were established by ¹H NMR spectroscopy using a chiral LISR (for keto esters 8 and 10). Furthermore the configurational assignments and the enantiomeric excesses were both determined by the chemical correlations (for all new chiral compounds) depicted in Scheme III.

Base-induced cyclization⁹ of diketone 6 led to the known¹⁰ (*R*)-(-)-octalone⁵ 11. Keto ester 8 was correlated with the same octalone through the (*R*)-(+)-enol lactone^{5,11} 12, according to the well-known Belleau-Fujimoto sequence.¹² The same six-membered ring keto ester 8 was transformed¹³ into the five-membered

Scheme III



ring keto ester 10. Finally compound 10 was converted¹⁴ to diketone 9, which was cyclized¹⁵ into (*R*)-(-)-hydrindenone¹⁶ 13.

This new process involves the following important features: Use of an inexpensive auxiliary chiral amine (both enantiomers are commercially available), which is easily and quantitatively recycled. Very mild reaction conditions and very simple procedure allowing large-scale preparations. Exclusive alkylation at the more substituted carbon atom. Creation of quaternary carbon centers bearing functionalized side chains. Excellent chemical yields and high enantiomeric excesses.

With suitable substituents, the synthetic chiral compounds are well adapted for further diastereoselective reactions that can lead to the syntheses of important chiral biologically active compounds.

(13) (1) Ring oxidation into diacid: CrO₃, AcOH, 75 °C, 15 h. (2) seven-membered ring anhydride formation: Ac₂O, reflux, 4 h. (3) ring contraction: 220 °C, 25 torr, neat, 15 min.

(14) (1) NaOH, then H₃O⁺; (2) 3 equiv LDA and then excess LiMe.

(15) NaOH 5%, MeOH, reflux, 16 h, 80% yield.

(16) The hydrindenone 13, $[\alpha]_D^{20} -108^\circ$ (*c* 3.50, EtOH), 90% ee, has not been reported previously in the literature in its optically active form.

Synthesis, Structure, and Antitumor Properties of Platinum Complexes of Vitamin C

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The widespread success of cisplatin, *cis*-[Pt(NH₃)₂Cl₂], in the clinical treatment of testicular and ovarian cancers has stimulated research in the area of metal-based anticancer drugs and spurred the search for compounds with improved therapeutic properties.¹ One new group of promising antitumor agents, which has shown good activity in a variety of preclinical antitumor screens, are the *cis*-diamineplatinum complexes of vitamin C. These complexes represent the first transition-metal ascorbates to yield to complete structural characterization.

A series of stable complexes of the form *cis*-[Pt(RNH₂)₂(ascorbate)] has been isolated and structurally characterized. The ascorbate ligand in these compounds is bound to platinum in a

(5) Purified by "flash" chromatography on silica, homogeneous by TLC and giving satisfactory IR and ¹H NMR spectra.

(6) (a) Pfau, M.; Ribière, C. *J. Chem. Soc., Chem. Commun.* 1970, 66-67. (b) Pfau, M.; Ribière, C. *Bull. Soc. Chim. Fr.* 1971, 2584-2590. (c) Pfau, M.; Ribière, C. *Bull. Soc. Chim. Fr.* 1976, 776-780. (d) Pfau, M.; Ughetto-Monfrin, J. *Tetrahedron* 1979, 35, 1899-1904. (e) Pfau, M.; Ughetto-Monfrin, J.; Joulain, D. *Bull. Soc. Chim. Fr.* 1979, 627-632.

(7) As previously reported, the alkylation takes place exclusively at the more substituted carbon atom, see ref 6d and p 3411 of: Hickmott, P. W. *Tetrahedron* 1982, 38, 3363-3446.

(8) 8: 81% yield, $[\alpha]_D^{20} +33.8^\circ$ (*c* 2.95, EtOH), 90% ee. 9: 83% yield, $[\alpha]_D^{20} +26.7^\circ$ (*c* 1.50, EtOH), 89% ee. 10: 79% yield, $[\alpha]_D^{20} +35.7^\circ$ (*c* 1.68, EtOH), 90% ee.

(9) MeONa 5% in MeOH, 35 °C, 1 h, 94% yield.

(10) Following specific rotation was reported for pure (*R*)-(-)-octalone 11: $[\alpha]_D^{24} -207^\circ$ (*c* 1, EtOH). Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* 1982, 104, 4021-4023.

(11) Compound 12, mp 33°C, $[\alpha]_D^{20} +157^\circ$ (*c* 2.46, EtOH), 90% ee, was obtained from keto ester 8 through the corresponding keto acid, $[\alpha]_D^{20} +30.0^\circ$ (*c* 4.77, EtOH), 90% ee.

(12) Weill-Raynal, J. *Synthesis* 1969, 49-56.

(1) (a) Lippard, S. J., Ed. "Platinum, Gold and Other Metal Chemotherapeutic Agents"; American Chemical Society: Washington, DC, 1983; ACS Symp. Ser. No. 209. (b) Hacker, M. P., Doyle, E. B., Krakoff, I. H., Eds. "Platinum Coordination Complexes in Cancer Chemotherapy"; Martinus-Nijhoff: Boston, 1984.

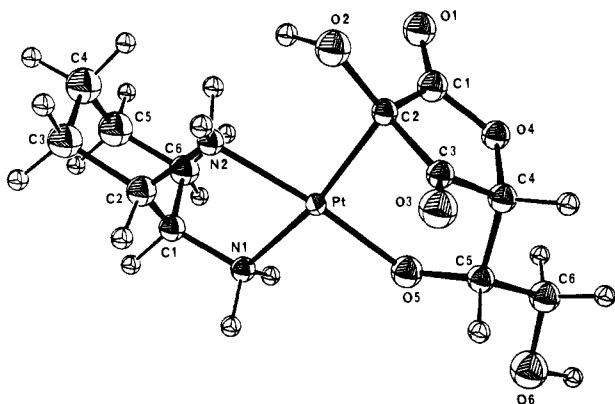
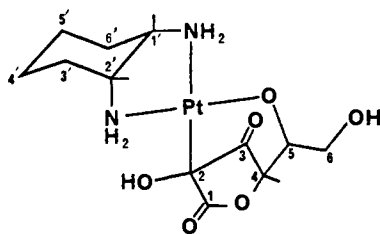


Figure 1. ORTEP illustration of the structure of the $[\text{Pt}(\text{cis-dach})(\text{ascorbate})]$ chelate (**1**), showing the 40% probability thermal ellipsoids for all non-hydrogen atoms.

unique fashion: X-ray crystallographic studies of the *cis*-1,2-diaminocyclohexane (*cis*-dach) analogue show that the ascorbate ligand is coordinated to the metal through the C2 carbon atom and a deprotonated hydroxyl group (O5). NMR studies show



that C2–O5 binding of the ascorbate dianion is a common feature of this series of platinum complexes. While a number of structural models have been proposed previously for bidentate binding of ascorbate to transition metals,² these models involve only oxygen binding sites. As shown in this study, the C2 carbon atom of ascorbic acid also serves as a binding site for transition metals, and this mode of coordination should be considered in existing and future studies of metal–ascorbate interactions.

The *cis*-diamineplatinum ascorbate chelates are prepared from the corresponding diaminediaqua complexes, *cis*- $[\text{Pt}(\text{RNH}_2)_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$, by reaction with sodium ascorbate in aqueous solution under nitrogen.³ The amine ligands can be monodentate, for example ammonia or alkylamine, or bidentate as in the case of ethylenediamine or dach. The resulting *cis*- $[\text{Pt}(\text{RNH}_2)_2(\text{ascorbate})]$ complexes are very stable in aqueous or alcoholic solutions and, as found in the case of $[\text{Pt}(\text{cis-dach})(\text{ascorbate})]$, can be obtained in yields of up to 75%.

When the initial diaminediaqua complex is prepared from a mixture of *cis*- and *trans*-dach isomers, as many as 10 products of the ascorbate reaction can be resolved by using reverse-phase HPLC techniques. This number can be reduced greatly by using the individual dach isomers.⁴ When the *cis*-dach isomer, $[\text{Pt}(\text{cis-dach})(\text{H}_2\text{O})_2](\text{NO}_3)_2$, was used in the reaction, only three major platinum-containing products were detected by HPLC. These were isolated and purified using preparative HPLC and fractional crystallization techniques, and the antitumor activity of each evaluated *in vivo* using the sarcoma ascites (S180a) tumor model.³

The first platinum-containing component was structurally characterized by NMR spectroscopy and single-crystal X-ray diffraction techniques.⁵ An ORTEP illustration of this compound,

$[\text{Pt}(\text{cis-dach})(\text{ascorbate})]\cdot 3\text{H}_2\text{O}$ (**1**),⁶ is presented in Figure 1. As shown in this view of the molecule, the dianionic ascorbate ligand is bound to platinum through the C2 carbon and the deprotonated hydroxyl group, O5. While the bond lengths and angles within both the platinum coordination sphere and the *cis*-dach ring are normal,⁷ the geometry of the ascorbate ligand is, as expected, quite different from that of either ascorbic acid or its monoanionic salts.⁸ The C–C and C–O bond lengths within the five-membered ring indicate that the ligand can be viewed as a carbon-bound α -hydroxy- β -diketonate. Indeed, the geometry within the C1 to C3 region of the ascorbate ligand is similar to that found in the carbon-bound acetylacetonate ligand in $\text{K}[\text{Pt}(\text{acac})_2\text{Cl}]$.⁹ While this type of bonding has been observed in a number of platinum complexes of acac, this is the first example of metal binding to the C2 carbon of ascorbic acid. Metal coordination through the ascorbate O5 oxygen also is unique. This binding site has not been considered to be important in existing reports on transition-metal complexes of ascorbic acid.¹⁰

The second component of the “ $\text{Pt}(\text{cis-dach})(\text{ascorbate})$ ” reaction was identified, by NMR spectroscopy, as a second isomeric form of compound **1**. In this case the ascorbate ligand is bound (also through C2 and O5) to the platinum in an opposite orientation relative to the *cis*-dach ring. Since the *cis*-dach ligand is asymmetric with respect to the axis that bisects the N1–Pt–N2 angle, two isomers are produced when the platinum binds to the rectus face of the ascorbate ligand.¹¹ This isomer, $[\text{Pt}(\text{cis-dach})(\text{ascorbate})]\cdot 3\text{H}_2\text{O}$ (**2**),⁶ is less soluble in water than **1**, and as a result, these components are readily separated by recrystallization techniques.

The third component of the reaction has been identified tentatively as a bis(ascorbate) complex, $[\text{Pt}(\text{cis-dach})(\text{ascorbate})_2]\cdot 2\text{H}_2\text{O}$ (**3**), on the basis of elemental analysis data.¹² This component is somewhat less stable in aqueous solution than the C2–O5 chelates and after a few hours converts into ascorbic acid and the chelates **1** and **2**. The ¹⁹⁵Pt NMR spectrum of **3** contains two signals with chemical shifts that are similar to those found for compounds **1** and **2**, suggesting that **3** contains one carbon-bound and one oxygen-bound ligand. The presence of two Pt resonances suggests that the bis(ascorbate) complex also exists in two isomeric forms. While it appears that the bis(ascorbate) complex contains one carbon- and one oxygen-bound ascorbate ligand, the precise position of binding sites on the ascorbate ligands in **3** remains to be determined. Further studies of these materials, which are highly active in the S180a tumor screen, are in progress.

When the “ $\text{Pt}(\text{trans-dach})(\text{ascorbate})$ ” preparation was carried out with either of the resolved, dach enantiomers *trans*-(*R,R*)-dach or *trans*-(*S,S*)-dach, the product contained two major platinum-containing components. These were shown to be similar to those obtained from the “ $\text{Pt}(\text{cis-dach})(\text{ascorbate})$ ” reaction, i.e., the $[\text{Pt}(\text{trans-dach})(\text{ascorbate})]$ chelate, and the bis(ascorbate) complex $[\text{Pt}(\text{trans-dach})(\text{ascorbate})_2]$. Only one form of the ascorbate chelate is observed with each of the *trans*-dach enan-

(5) Compound **1** crystallizes in the monoclinic space group $P2_1$ with the following cell parameters: $a = 6.425(1) \text{ \AA}$, $b = 20.542(2) \text{ \AA}$, $c = 6.662(1) \text{ \AA}$, $\beta = 104.90(1)^\circ$, $V = 849.7 \text{ \AA}^3$, $Z = 2$. The structure was solved by using standard Patterson and Fourier methods using 1633 unique reflections ($2\theta < 50^\circ$) collected on a Nonius CAD-4F diffractometer using $\text{Mo K}\alpha$ radiation. Refinement of the absorption corrected data, with all atoms (except H) assigned anisotropic thermal parameters, has converged at $R_F = 0.020$ and $R_{wF} = 0.027$. Full details will be reported at a later date.

(6) Anal. ($\text{PtC}_{12}\text{H}_{26}\text{N}_2\text{O}_9$) Pt, C, H, N.

(7) (a) Lock, C. J. L.; Pilon, P. *Acta Crystallogr., Sect. B* **1981**, *B37*, 45. (b) Bruck, M. A.; Bau, R.; Noji, M.; Inagaki, K.; Kidani, Y. *Inorg. Chim. Acta* **1984**, *92*, 279.

(8) Hvostef, J., in ref 2, pp 37–57.

(9) Mason, R.; Robertson, G. B.; Pauling, P. L. *J. Chem. Soc. A* **1969**, 1004.

(10) (a) Kriss, E. E. *Russ. J. Inorg. Chem. (Engl. Transl.)* **1978**, *23*, 1004.

(b) Pelizzetti, E.; Mentasti, E.; Prumauro, E. *Inorg. Chem.* **1978**, *17*, 1181.

(c) Nordenskiöld, L.; Lowalewski, J.; Benetis, N. *Inorg. Chim. Acta* **1981**, *56*, L21.

(d) Jameson, R. F.; Blackburn, N. J. *J. Inorg. Nucl. Chem.* **1975**, *37*, 809.

(e) Gupta, R. N.; Sen, B. K. *Ibid.* **1975**, *37*, 1548.

(f) Siddiqui, J. S.; Srivastava, S. C. *Indian J. Chem., Sect. A* **1983**, *22A*, 353.

(11) Chelate formation can be viewed as a stereoselective process, since ring closure through C2 and O5 is not possible when platinum binds to the opposite diastereotopic face of the ascorbate ligand.

(12) Anal. ($\text{PtC}_{18}\text{H}_{32}\text{N}_2\text{O}_{14}$) Pt, C, H, N.

(2) Martell, A. E. In “Ascorbic Acid: Chemistry, Metabolism, and Uses”; Sieb, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, DC, 1982; Adv. Chem. Ser. No. 200, pp 153–178.

(3) Amundsen, A. R.; Stern, E. W. U.S. Pat. 4457926, 1984.

(4) Kidani, Y.; Inagaki, K. U.S. Pat. 4169846, 1979.

tiomers since the "Pt(*trans*-dach)" moiety possesses pseudo-twofold rotational symmetry. Both of the ascorbate chelates [Pt(*trans*-(*R,R*)-dach)(ascorbate)]·3H₂O (**4**)⁶ and [Pt(*trans*-(*S,S*)-dach)(ascorbate)]·2H₂O (**5**)¹³ have been isolated as pure components and shown to be structurally analogous to the crystallographically characterized [Pt(*cis*-dach)(ascorbate)] analogue **1** by using NMR spectroscopy. While the individual diastereomeric forms of the bis(ascorbate) component [Pt(*trans*-dach)(ascorbate)₂]·2H₂O (**6**) have yet to be isolated, chemical analysis of the mixed *R,R* and *S,S* forms of **6**¹² is in agreement with the proposed chemical formulation.

These novel complexes of vitamin C are the first carbon-bound analogues of *cis*-diamineplatinum(II) to display good antitumor activity in vivo. We are presently examining a number of related compounds to determine structure-activity relationships among complexes in this potentially broad class of new antitumor agents.

Supplementary Material Available: Listings of bond lengths and angles (Table S1) and atomic positional and thermal parameters (Table S2) for compound **1**, and ¹⁹⁵Pt and ¹³C NMR data (Tables S3 and S4) for compounds **1-5** (4 pages). Ordering information is given on any current masthead page.

(13) Anal. (PtC₁₂H₂₄N₂O₈) Pt, C, H, N.

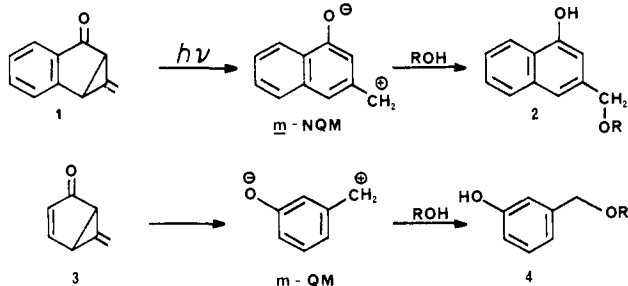
Picosecond Absorption Studies on *m*-Naphthoquinomethane. Singlet-Triplet Intersystem Crossing

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We report the use of picosecond flash photolysis to investigate the chemical dynamics of *m*-naphthoquinomethane (*m*-NQM), a member of the meta quinonoid series of non-Kekulé molecules.² That this species has a triplet ground state is suggested by a semiempirical molecular orbital calculation³ and is confirmed experimentally^{2a} by electron paramagnetic resonance (EPR) spectroscopic studies of immobilized samples at 77 K. In chemical reactions, *m*-NQM and its close relative *m*-quinomethane (*m*-QM) behave as dipolar intermediates and readily add nucleophiles such as amines, electron-rich olefins, and alcohols.^{2a} The alcoholyses give high yields of phenolic ethers **2** and **4**. Although the evidence⁴



favors singlet *m*-NQM and *m*-QM, respectively, as the *first*-

(1) (a) University of Colorado. (b) Yale University.
(2) (a) Rule, M.; Matlin, A.; Seeger, D.; Hilinski, E.; Dougherty, D.; Berson, J. *Tetrahedron* **1982**, *38*, 787 and references cited therein. (b) Platz, M. In "Diradicals"; Borden, W., Ed.; Academic Press: New York, 1982; and references cited therein.
(3) Lahti, P.; Rossi, A.; Berson, J. A., manuscript in preparation.
(4) (a) Matlin, A.; Inglin, T.; Berson, J. *J. Am. Chem. Soc.* **1982**, *104*, 4954. (b) Inglin, T. Ph.D. Thesis, Yale University, New Haven, CT, 1984.

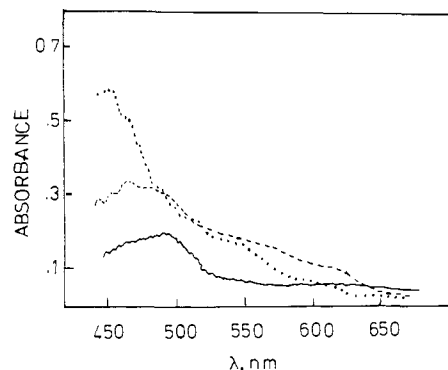


Figure 1. Spectra observed 25 ps after 355-nm excitation of **1** in cyclohexane (—), benzene (---), and acetonitrile (.....).

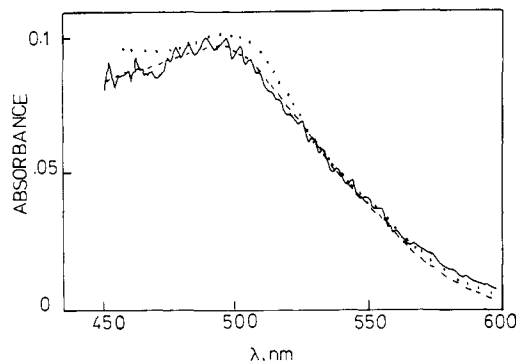


Figure 2. Spectra observed 9 ns after 355-nm excitation of **1** in cyclohexane (—), benzene (---), and acetonitrile (.....). The spectra have been redrawn to scale.

formed intermediates in the photolysis or pyrolysis of the precursors **1** and **3**, the spin state of the reactive form has not been clearly established.

The experimental procedure for obtaining absorption spectra of transient intermediates with a time resolution of 25 ps has been previously described in detail.⁵ Photolysis was performed at 355 nm on room temperature $\sim 5 \times 10^{-3}$ M solutions of **1** ($OD \geq 1.5$). The photolyzed solutions were frequently changed (<3000 laser shots) to prevent the buildup of photoproducts.

Photolysis of **1** in several different solvents produces a transient intermediate (A) within the laser pulse. Although the overall shape of the spectrum does not vary greatly, the maximum of A (Figure 1) changes dramatically with the polarity of the solvent: 490 (cyclohexane), 470 (benzene), <450 nm (CH₃CN). The transient A decays on the picosecond time scale to a new species (B), which is stable onto the nanosecond timescale. The absorption spectrum of B (Figure 2) at 9 ns shows $\lambda_{max} = 500$ nm and is insensitive to solvent polarity in the observable region. Importantly, the same species is produced in all three solvents. The insensitivity of the absorption spectrum of B at 9 ns suggests that A has largely disappeared.

The reaction of A \rightarrow B in the three solvents follows first-order kinetics as monitored by absorption spectroscopy at several wavelengths >525 nm. Measurements between 25 ps and 9 ns give $1/k = 250 \pm 100$ ps (cyclohexane), 750 ± 350 ps (benzene), and 2.74 ± 1.1 ns (CH₃CN). Pseudo-first-order reaction between **1** and A to give B requires implausibly large concentration and/or reaction rate for A and in any case is ruled out by the insensitivity of the observed rate constant to variation in the initial concentration of **1**.

Disappearance of A in benzene in the presence of a large excess of methanol follows pseudo-first-order kinetics. A plot of k_{obsd} vs. [CH₃OH] is linear ($r = 0.997$) with an intercept $k_1 = 8.5 \times 10^8$ s⁻¹ and a slope corresponding to a second-order rate constant $k_2 = 3.6 \times 10^8$ s⁻¹ M⁻¹. In pure methanol, neither the A nor B signal appears. The kinetic data may be expressed as $k_{obsd} = k_1$

(5) Simon, J.; Peters, K. *J. Am. Chem. Soc.* **1983**, *105*, 4875.