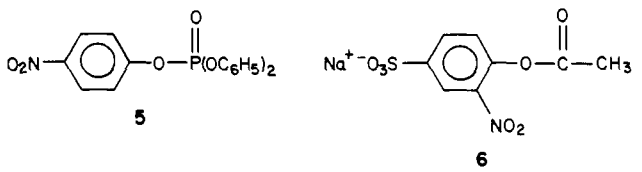

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formation). Varying the ratio of **2** to **6** from 10/1 to 1/1 to 1/2 to 1/5 led to two important observations: (1) Substrate is completely hydrolyzed even when present in excess over the catalyst. (2) The second-order rate constant k_{OH} is identical for all four runs (600 M^{-1} s^{-1}). These results can only be explained by a rate-determining acylation of the surfactant followed by rapid deacylation and regeneration of the original catalytic species.

Since the CH_2CHO unit can be attached easily to any molecule bearing an amino group (e.g., an aminocyclodextrin), the prospects seem good for creating additional biomimetic catalysts.

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Chiral Discrimination in the Covalent Binding of Bis(phenanthroline)dichlororuthenium(II) to B-DNA

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Recently there has been increased attention focused on the binding of metal complexes to nucleic acids and nucleic acid constituents.[1] This interest stems in large part from the successful application of cis-dichlorodiammineplatinum(II) (*cis*-DDP) as an antitumor drug.[2] Our laboratory has utilized chiral transition-metal complexes in designing specific probes for nucleic acid structure. The tris(phenanthroline) complexes of zinc(II)[3] and ruthenium(II)[4] display enantiomeric selectivity in binding to DNA by intercalation. Because of their high specificity in noncovalent binding to right- or left-handed DNAs, enantiomers of tris(4,7-diphenylphenanthroline)ruthenium(II) and -cobalt(III) provide respectively spectroscopic probes[5] and cleaving agents[6] that are DNA conformation-specific. We became interested in developing a covalent analogue of this series in order to incorporate some stereospecificity into new drug design. We report here that bis(1,10-phenanthroline)dichlororuthenium(II) ($(phen)_2RuCl_2$) binds covalently to the DNA duplex and exhibits striking enantiomeric selectivity different from that seen on intercalation.

In buffer containing 10% ethanol, 50 mM $NaNO_3$, 5 mM Tris at pH 7.1, *rac*-$Ru(phen)_2Cl_2$[7] (50 μM) was incubated either at ambient temperatures or 37 °C for variable amounts of time with calf thymus DNA[8] (500 μM nucleotide). Following incubation, NaCl and 95% ethanol were added to quench the reaction and precipitate the DNA, with unbound ruthenium remaining in solution. After centrifugation, the supernatant was assayed spectrometrically, compared to controls lacking ruthenium or DNA, and levels of bound and free metal complex were determined. This experiment measures only covalent binding to the DNA. We repeated the procedure using the coordinatively saturated tris(phenanthroline)ruthenium cation, $Ru(phen)_3^{2+}$, which binds by intercalation;[4] under these assay conditions no binding to DNA was observed.[9] A plot of the extent of coordination to DNA by the $(phen)_2Ru^{2+}$ cation as a function of time is shown in Figure 1. A maximum binding ratio of 0.045, or one $(phen)_2Ru^{2+}$ moiety for every 11 base pairs, is obtained at about 3.5 h. This dependence on time is consistent with kinetics of ligand substitution in ruthenium(II) complexes.[10]

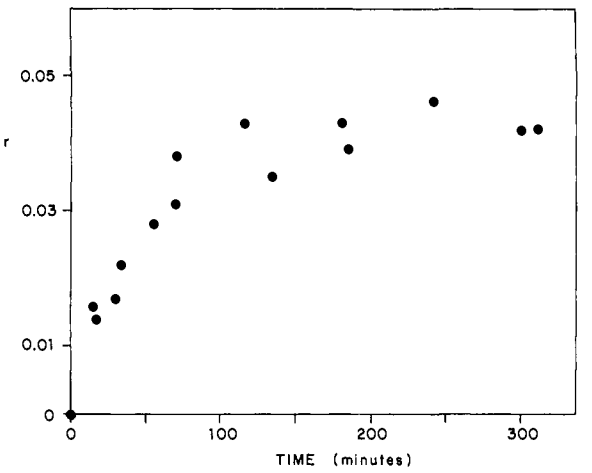

Figure 1. Plot of $(phen)_2RuCl_2$ binding to calf thymus DNA as a function of time; r is the ratio of bound ruthenium to nucleotide concentrations.

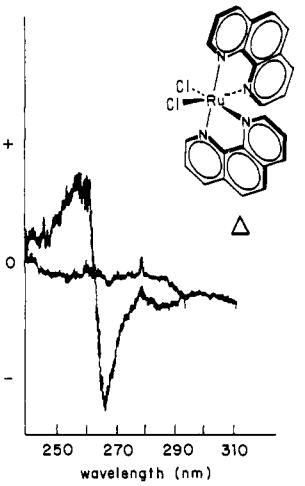

Figure 2. Circular dichromism of the supernatant after ethanol precipitation of the ruthenium complex bound to B-DNA. Binding to B-DNA is stereoselective and leads to enrichment of the supernatant in the unbound Δ isomer (inset).

(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) Barton, J. K.; Lippard, S. J. *Met Ions Biol.* **1980**, *1*, 31. (c) Marzilli, L. G.; Kistenmacher, T. J.; Eichhorn, G. L. *Met. Ions Biol.* **1980**, *1*, 179. (d) Martin, R. B.; Mariam, Y. H. *Met. Ions Biol. Syst.* **1979**, *8*, 57. (e) Marzilli, L. G. *Prog. Inorg. Chem.* **1977**, *23*, 255. (f) Hodgson, D. J. *Prog. Inorg. Chem.* **1977**, *23*, 211.

(2) (a) Rosenberg, B.; Van Camp, L.; Trosko, J. E.; Mansour, V. H. *Nature (London)* **1969**, *222*, 385. (b) Rosenberg, B.; Van Camp, L. *Cancer Res.* **1970**, *30*, 1979. (c) For a review, see: Hill, J. M.; Loeb, E.; MacLellan, A.; Hill, N. V.; Khan, A.; King, J. J. *Cancer Treat. Rep.*, **1975**, *59*, 647. (d) Lippard, S. J. *Acc. Chem. Res.* **1978**, *11*, 211. (e) Hacker, M. P., Doyle, E. B., Krakoff, I. H., Eds. "Platinum Coordination Complexes in Cancer Chemotherapy"; Martinus Nijhoff: Boston, 1984.

(3) Barton, J. K.; Dannenberg, J. J.; Raphael, A. L. *J. Am. Chem. Soc.* **1982**, *104*, 4967.

(4) Barton, J. K.; Danishefsky, A. T.; Goldberg, J. M. *J. Am. Chem. Soc.* **1984**, *106*, 2172.

(5) Barton, J. K.; Basile, L. A.; Danishefsky, A.; Alexandrescu, A. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 1961.

(6) Barton, J. K.; Raphael, A. L. *J. Am. Chem. Soc.* **1984**, *106*, 2466.

(7) The preparation of this compound was analogous to the synthesis of *cis*-bis(2,2'-bipyridine)ruthenium(II) dichloride by: Sullivan, B. P.; Salmon, D. J.; Meyer, T. J. *Inorg. Chem.* **1978**, *17*, 3334. Spectroscopic data in EtOH were as follows: ϵ 1.08 × 10^4 M^{-1} cm^{-1} at 496 nm, ϵ 7.25 × 10^4 M^{-1} cm^{-1} at 267 nm. In aqueous solution the complex may be considered a mixture of hydrolyzed species.

(8) Supplied by Sigma and purified by phenol extraction as in: Barton, J. K.; Lippard, S. J. *Biochemistry* **1979**, *12*, 2661.

(9) Subsequent precipitation of the resuspended $(phen)_2Ru^{2+}$-DNA pellet released no free ruthenium. This observation is also consistent with covalent binding.

(10) Isied, S. S.; Taube, H. *Inorg. Chem.* **1976**, *15*, 3070.

0002-7863/85/1507-0708$01.50/0

Significant enantiomeric discrimination accompanies this covalent binding. The circular dichroism of the supernatant, the unbound fraction, is shown in Figure 2. Optically enriched $Ru(phen)_2Cl_2$ solutions have not been obtained previously by using more conventional methods.[11] The magnitude of the rotation in the ultraviolet region is approximately 5 times larger than that seen earlier for $(phen)_3Ru^{2+}$ solutions at comparable levels of intercalative binding. Hence the degree of chiral selectivity for this covalent adduct appears substantially greater than for $(phen)_3Ru^{2+}$.[12] The absolute configuration may be assigned by derivatization to the tris(phenanthroline)ruthenium(II) species.[14] Consistent with simple exciton theory, we assign the CD in the ultraviolet region given in Figure 2 as that for the Δ isomer. In contrast to earlier observations concerning $(phen)_3Ru^{2+}$ binding to DNA, here it is Λ-$(phen)_2Ru^{2+}$ that binds preferentially to the B-DNA helix.

The enantiomeric discrimination of the bis(phenanthroline)-ruthenium complex in binding to B-DNA must differ from the tris(phenanthroline) cation not only in degree but also in the structural basis for the stereoselectivity. Ruthenium(II) complexes have a high affinity for the heterocyclic bases of DNA.[16] A likely site of metalation would be the N-7 of guanine, which is readily accessible in the major groove. Initial intercalation is probable; immediate hypochromic changes in the ruthenium charge transfer band accompany the addition of DNA. However, additional spectroscopic changes become evident on a time scale that correlates to the covalent binding given in Figure 1. Model building shows that from an initially intercalated position the Λ isomer is well oriented for covalent binding to base positions above and below. The Δ isomer cannot be similarly aligned for covalent binding, since the other nonstacked phenanthroline ligand is considerably crowded by the right-handed helical column (base and sugar phosphate groups). A bifunctional coordination oriented by initial intercalation could account for the high stereoselectivity we observe. It is interesting that for intercalation by $(phen)_3Ru^{2+}$ the Δ isomer, which has the same helical screw sense as the right-handed B-DNA, is preferred, while here metalation of base positions seems to require the Λ configuration, that is a structure *complementary* to the B-DNA helix.

The stereoselective covalent binding of $Ru(phen)_2Cl_2$ to DNA could have significant biological consequences. The neutral $Ru(phen)_2Cl_2$ may be considered an octahedral analogue for *cis*-$Pt(NH_3)_2Cl_2$.[17] Recent reports of antitumor activities and toxicities of various ruthenium complexes,[1,18] the possible similarities between $Ru(phen)_2Cl_2$ and *cis*-DDP in interactions with DNA, and the striking stereoselectivity that we observe all suggest a potential chemotherapeutic application of chiral bis(amine)-ruthenium(II) complexes.

Acknowledgment. We thank A. Danishefsky for helpful discussions and E. Kanter for technical assistance. We are grateful to the National Institutes of Health (GM33309) for their financial support. J.K.B. is a Research Fellow of the Alfred P. Sloan Foundation.

(11) Some solvent dependence in the rate of racemization has been observed, but the racemization appears most sensitively to depend upon the presence of light (Danishefsky, A., unpublished results). The half-life for racemization in room light in our buffer is ~1 h. Our observations support those of: Arces Sagues, J. A.; Gillard, R. D.; Smalley, D. H.; Williams, P. A. *Inorg. Chim. Acta* **1980**, *43*, 211. Vagg, R.; Williams, P. A. *Inorg. Chim. Acta* **1981**, *51*, 61.

(12) On the basis of exciton theory,[13] we would expect the rotational strength of pure enantiomers of $Ru(phen)_2Cl_2$ in the vicinity of the ligand absorption to be one-half that of $Ru(phen)_3Cl_2$.

(13) Bosnich, B. *Acc. Chem. Res.* **1968**, *2*, 266.

(14) Optically enriched $(phen)_2RuCl_2$ solutions were refluxed in 70% ethanol for 2 h in the dark with stoichiometric phenanthroline. The reaction yielded optically active $(phen)_3Ru^{2+}$, for which the absolute configuration is known.[15] The sign and position of the ultraviolet CD for $(phen)_2Ru^{2+}$ is identical with that for $(phen)_3Ru^{2+}$.

(15) McCaffrey, A. J.; Mason, S. F.; Norman, B. J. *J. Chem. Soc. A* **1969**, 1428.

(16) (a) Clarke, M. J.; Taube, H. *J. Am. Chem. Soc.* **1974**, *96*, 5413. (b) Clarke, M. J. *Inorg. Chem.* **1977**, *16*, 738. (c) Clarke, M. J.; Buchbunder, M. *Inorg. Chim. Acta* **1978**, *27*, L87. (d) Clarke, M. J. *Inorg. Chem.* **1980**, *19*, 1103. (e) Graves, B. J.; Hodgson, D. J. *J. Am. Chem. Soc.* **1974**, *101*, 5608.

(17) The bite size for *cis*-DDP is 3.35 Å and for bis(diimine)dichloro-ruthenium(II) complexes is 3.49 Å. See, respectively: Milburn, G. H. W.; Truter, M. R. *J. Chem. Soc. A* **1966**, 1609. Pank, V.; Klaus, J.; von Veuton, K.; Feigel, M.; Bruder, H.; tom Dieck, H. *Transition Met. Chem. (Weinheim, Ger.)* **1981**, *6*, 185.

(18) (a) Clarke, M. J. *Met. Ions Biol. Syst.* **1980** *11*, 231. (b) Giraldi, T.; Sawa, G.; Berloli, G.; Mestroni, G.; Zassinovich, G. *Cancer Res.* **1977**, *37*, 2662. (c) Yasbin, R. E.; Matthews, C. R.; Clarke, M. J. *Chem.-Biol. Interact.* **1983**, *45*, 1. Tsuruo, T.; Iida, H.; Tsukagoshi, S.; Sakurai, Y. *Jpn. J. Cancer Res.* **1980** *7*, 151.

Conversion of a Cationic Alkene Hydride Complex of Tungsten into a Complex Containing a Terminal Alkylidene Ligand

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The formation of bridging alkylidene ligands from alkene ligands has been reported recently in three binuclear transition-metal complexes,[1] and isomerization of terminal alkylidene ligands to alkenes by a 1,2-hydride shift is well established, particularly for electrophilic transition-metal complexes,[2] but there have been no examples to date of the formation of a terminal alkylidene ligand from an alkene. This is a potentially important process which could be involved in the activation of metathesis catalysts,[3] and we now wish to report the first example of such a reaction by a route that apparently involves alkene insertion into a cis tungsten–hydride bond.

Treatment of the alkene complex $[W(\eta\text{-}C_5H_5)_2(C_2H_4)H]PF_6$[4] (**1**-$PF_6$) with I_2 in polar organic solvents such as acetone, acetonitrile, or tetrahydrofuran (THF) results in formation of the ethylidene complex $[W(\eta\text{-}C_5H_5)_2(CHCH_3)I]^+$ ($\mathbf{2}^+$) (eq 1). Pure

$$[W(\eta\text{-}C_5H_5)_2(C_2H_4)H]^+ + I_2 \rightarrow [W(\eta\text{-}C_5H_5)_2(CHCH_3)I]^+ + HI \quad (1)$$

salts of $\mathbf{2}^+$ can only be isolated under carefully controlled conditions, since the I^- generated tends to complex I_2,[5] leading to mixed PF_6^-/I_3^- salts which cannot be readily purified. Pure **2**-PF_6 was, however, obtained by adding 2.4 molar equiv of 0.073 M I_2 in THF dropwise to a suspension of **1**-PF_6 in THF (0.90 mmol in 150 mL). After 3.5 h the filtered red solution was concentrated to dryness and the black crystals obtained were washed with THF. Extraction with acetonitrile gave a green solution from which microcrystalline green **2**-PF_6[6] (55% yield) was precipitated by slow addition of diethyl ether.

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(1) (a) Awang, M. R.; Jeffery, J. C.; Stone, F. G. A. *J. Chem. Soc., Chem. Commun.* **1983**, 1426. (b) Casey, C. P.; Marder, S. R.; Fagan, P. J. *J. Am. Chem. Soc.* **1983**, *105*, 7197. (c) Forrow, N. J.; Knox, S. A. R. *J. Chem. Soc., Chem. Commun.* **1984**, 679.

(2) (a) Cutler, A.; Fish, R. W.; Giering, W. P.; Rosenblum, M. *J. Am. Chem. Soc.* **1972**, *94*, 4354. (b) Fischer, E. O.; Held, W. *J. Organomet. Chem.* **1976**, *112*, C59. (c) Casey, C. P.; Albin, L. D.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1977**, *99*, 2533. (d) Marsella, J. A.; Folting, K.; Huffman, J. C.; Caulton, K. G. *J. Am. Chem. Soc.* **1981**, *103*, 5596. (e) Casey, C. P.; Miles, W. H.; Tukada, H.; O'Conner, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 3761. (f) Kremer, K. A. M.; Kuo, G.-H. O'Connor, E. J.; Helquist, P.; Kerber, R. C. *J. Am. Chem. Soc.* **1982**, *104*, 6119. (g) Brookhart, M.; Tucker, J. R.; Husk, G. R. *J. Am. Chem. Soc.* **1983**, *105*, 258. (h) Hatton, W. G.; Gladysz, J. A. *J. Am. Chem.* **1983**, *105*, 6157.

(3) (a) Grubbs, R. H. In "Comprehensive Organometallic Chemistry"; Wilkinson, G. W., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982, Vol. 8, Chapter 54. (b) Rooney, J. J.; Stewart, A. *Catalysis (London)* **1977**, *1*, 277.

(4) Benfield, F. W. S.; Green, M. L. H. *J. Chem. Soc., Daltron Trans.* **1974**, 1324.

(5) The formation constant of I_3^- is large in nonaqueous solvents: (a) Popov, A. I. in "Halogen Chemistry"; Gutmann, V., Ed.; Academic Press: London, 1967; Vol. 1, p 225. (b) Nelson, I. V.; Iwamoto, R. T. *J. Electroanal. Chem.* **1964**, *7*, 218.

0002-7863/85/1507-0709$01.50/0