same metal are π donors. Therefore Arg is particularly likely to bind metals in conjunction with Cys or Tyr. Our research on guanidyl complexes and on new heavy-atom tags for Arg residues continues.

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Supplementary Material Available: Attempts at direct identification of the Arg binding site by peptide mapping and by blocking, lability of the $[Pt(trpy)L]^{n+}$ complexes in acid, and ^{13}C NMR evidence for the Arg coordination via its guanidyl group (4 pages). Ordering information is given on any current masthead page.

Calculations of the Geometric and Electronic Structure of Trichloromethyltitanium: Is There an Agostic Hydrogen Interaction?

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A complete geometry optimization on Cl_3TiCH_3 shows no flattening of the methyl hydrogens toward the metal and no titanium–hydrogen interaction. From the optimized geometry of calculations at several different wave functions, we predict a Ti–C–H bond angle of 107 ± 1° which is significantly larger than the electron diffraction (ED) result of 101 ± 2°. The anomalously low methyl rock frequency of the titanium complex in comparison to the germanium complex is correctly predicted by the full second derivatives of the energy and is shown to be due to titanium's empty d-orbitals, which allow rehybridization of the carbon–metal bond during the rocking motion. The naturally weak scattering by hydrogen atoms, which hinders accurate determination of hydrogen positions, could account for the observed difference between the ED and theoretical Ti–C–H angle.

A recent preliminary communication on the ED[1] of Cl_3TiCH_3 suggests that the methyl hydrogens are symmetrically "flattened" away from a normal tetrahedral geometry by 8.5° (2.2°), which was interpreted as evidence of an agostic hydrogen interaction between the methyl hydrogens and titanium. Spectroscopic data show a very low-energy methyl rocking vibration for Cl_3TiCH_3, in comparison to Cl_3GeCH_3, which Berry et al.[1] interpreted as the result of hydrogen flattening. Eisenstein and Jean[2] using extended Huckel calculations found that rocking the methyl in both staggered and eclipsed conformations of H_3TiCH_3 is weakly destabilizing. Here, we report the results of Hartree–Fock–Roothaan (HFR) calculations which were done to determine if there is a large degree of flattening of the three hydrogens and if not, why there is a large difference in methyl rocking vibrational frequency between Cl_3TiCH_3 and Cl_3GeCH_3.

We optimized the geometry of Cl_3TiCH_3 by using four different basis sets. Basis set I is a "double ζ" modified Huzinaga basis set used in previous geometry optimizations.[3] Basis sets II–IV have the same Ti basis, but different basis for Cl, C, and H. The Ti basis is a (5333-53-5)[4] modified to a (533211-5211-3111) by splitting off the most diffuse s, p, and d functions and adding additional s, p, and d functions with exponent values one third the value of the most diffuse functions. Basis set II is Cl-(5321-521), C(331-31), and H(31)[4], basis set III is Cl(531111-4211), C(721-41), and H(31),[5] and basis set IV is basis set II with polarization functions[4] added. The geometry optimizations were done in C_{3v} symmetry in a staggered conformation. Basis set I was used for all calculations on H_3TiCH_3 and H_3GeCH_3. The generalized valence bond (GVB) calculations involved perfect-pairing for all seven σ bonds.[6]

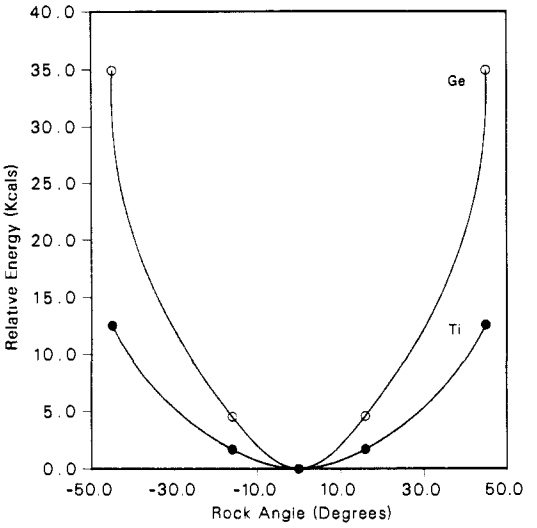

Figure 1. Relative energy of H_3TiCH_3 and H_3GeCH_3 for the methyl rock.

The results of complete geometry optimizations on Cl_3TiCH_3 using basis sets I–IV gave calculated bond lengths and bond angles which varied slightly (see Table I). The addition of polarization functions to basis set II (basis set IV) shortened the Ti–Cl distance and increased the Cl–Ti–C angle closer to the ED values; however, the Ti–C–H angle did not change. The calculated bond lengths from the GVB optimizations are larger than the SCF bond lengths, which is expected for this level of electron correlation. As a result of the long Ti–C distance, the $TiCl_3$ and CH_3 moieties favor a more radical-like flattened geometry as seen by the decrease of the Ti–C–H and C–Ti–Cl angles. However, when the Ti–C, Ti–Cl, and C–Ti–Cl parameters are fixed at the ED values, the Ti–C–H angle increased by 2.7°. Further calculations show that the major parameter influencing the Ti–C–H angle is the Ti–C bond distance. If any hydrogen flattening were due to direct titanium–hydrogen interactions, one would expect the Ti–C–H angle to increase as the Ti–C bond lengthened; however, the GVB results showed the opposite; thus, we conclude there to be no direct interaction between Ti and H.

The frequency of the methyl rock for Cl_3TiCH_3 in comparison to the analogous frequency in Cl_3GeCH_3 is anomalously low. Berry et al.[1] presumed this anomalously low frequency to result from flattening of the hydrogens. After optimizing the geometries of the model complexes H_3TiCH_3 and H_3GeCH_3, we calculated the vibrational frequencies of each complex (see Table II) by taking finite differences of energy gradients. Although these absolute frequencies show the error expected of results at the HFR level, comparison of the change in frequency when changing the metal from Ge to Ti are in good agreement with the experimental values. The calculated difference of the methyl rocking modes between the germanium and titanium hydride complexes of 401 cm^{-1} is much larger than the differences of other modes which was the observation made by Berry et al. for the germanium and

(1) Berry, A.; Dawoodi, Z.; Derome, A. E.; Dickinson, J. M.; Downs, A. J.; Green, J. C.; Green, M. L. H.; Hare, P. M.; Payne, M. P.; Rankin, W. H.; Robertson, H. E. *J. Chem. Soc., Chem. Commun.* **1986**, 519.
(2) Eisenstein, O.; Jean, Y. *J. Am. Chem. Soc.* **1985**, *107*, 1177.
(3) Williamson, R. L.; Hall, M. B. *Int. J. Quantum Chem.: Quan. Chem. Symp. 21* **1987**, 503. This basis set was shown to give geometric parameters for transition-metal complexes to similar accuracy as a 3-21G basis set for organic molecules.
(4) *Gaussian Basis Sets for Molecular Calculations*; Huzinaga, S., Ed.; Elsevier: Amsterdam, 1984.
(5) Dunning, T. H., Jr.; Hay, P. J. In *Methods of Electronic Structure Theory*; Schaefer, H. F., Ed.; Plenum Press: New York, Vol. 4, 1977; Chapter 1.
(6) Bobrowicz, F. W.; Goddard, W. A. In *Methods of Electronic Structure Theory*; Schaefer, H. F., Ed.; Plenum Press: New York, Vol. 4, 1977; Chapter 4.

0002-7863/88/1510-4428$01.50/0

Table I. Geometric Parameters for X_3MCH_3 in Å and deg

M	X	basis	method	M-C	M-X	C-H	M-C-H	C-M-X
Ti	Cl	I	SCF	2.009	2.213	1.087	108.0	101.3
Ti	Cl	II	SCF	2.013	2.251	1.092	108.3	103.4
Ti	Cl	III	SCF	2.012	2.258	1.095	108.2	103.2
Ti	Cl	IV	SCF	2.016	2.219	1.091	108.3	103.7
Ti	Cl	III	GVB	2.180	2.296	1.108	103.8	99.3
Ti	Cl	III	GVB[a]	2.042	2.185	1.111	106.5	105.2
Ti	Cl	exp.	ED[b]	2.042	2.185	1.158	101.0	105.2
Ti	H	I	SCF	2.035	1.710	1.092	109.9	108.3
Ge	H	I	SCF	1.959	1.533	1.086	110.7	110.3

[a] The Ti-Cl, Ti-C, andd C-Ti-Cl distances are fixed at the electron diffraction distances. [b] Reference 1.

Table II. Vibrational Frequencies for X_3MCH_3 in cm^{-1}

	calculated (X = H)			experimental[a] (X = Cl)		
mode	Ge	Ti	diffrnce	Ge	Ti	diffrnce
e CH_3 rock	978	577	401	825	580	245
a_1 CH_3 def	1468	1360	108	1246	1052	194
e CH_3 def	1611	1564	47	1403	1375	28
a CH_3 stretch	3190	3122	68	2940	2894	46
e CH_3 stretch	3270	3208	62	3019	2980	39

[a] Reference 1.

titanium chloride complexes. Thus, the large differences in rocking frequency is not a result of the flattening since the calculations, which predict this difference, predict no flattening of the hydrogens. Why then is there this large difference in the germanium and titanium complexes methyl rocking mode frequency?

Point-by-point calculations of the methyl rocking motion for the germanium and titanium hydride complexes show, as expected, the energy surface for the titanium complex to be flatter than the energy surface of the germanium complex (see Figure 1). As the methyl ligand rocks 45° to one side, the titanium complex is destabilized by 12.9 kcal mol^{-1}, whereas the germanium complex is destabilized by 34.9 kcal mol^{-1}. Deformation density plots of the titanium complex show rehybridization of the titanium–carbon bond as the methyl rocks. Analogous plots of the germanium complex show no rehybridization because germanium has used its s and p orbitals and the empty d orbitals are at very high energy; therefore, no empty orbitals are available for rehybridization. However, titanium has low-lying empty d orbitals that allow facile rehybridization of the metal–carbon bond. Thus, we observed a much lower methyl rocking frequency for the titanium complex than for the germanium complex.

A possible cause of the differences between the ED and theoretical results can be found by comparing interatomic distances. The interatomic distances involving atoms other than hydrogen show small differences; however, those distances with H atoms show large discrepancies of up to 0.282 Å for the H–Cl distance. As noted by Berry et al.[1], the ED radial distribution curve shows that the "Ti–H peak at 253 pm is partially obscured by the major Ti–Cl and Ti–C peaks". Because the H atoms scatter electrons weakly, the location of H–X peaks can be difficult to determine to high accuracy. This uncertainty could account for the discrepancies in the Ti–H, C–H, Cl–H, and H–H distances, which would then convert to an error in the Ti–C–H bond angle and C–H bond length.[10]

Note Added in Proof: Geometry optimizations at the CASSCF level with an active space containing orbitals involving C–H and C–Ti bonds (eight electrons, 11 orbitals) gave a Ti–C bond length of 2.106 Å and a Ti–C–H bond angle of 106.2°.[11]

(11) Williamson, R. L.; Hall, M. B. *ACS Symp. Ser.*, to be submitted for publication.

(7) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395.
(8) Dawoodi, Z.; Green, M. L. H.; Mtetwa, V. S. B.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1982**, 802.
(9) Dawoodi, Z.; Green, M. L. H.; Mtetwa, V. S. B.; Prout, K.; Schultz, A. J.; Williams, J. M.; Koetzle, T. F. *J. Chem. Soc., Dalton Trans.* **1986**, 1629.
(10) We thank the National Science Foundation (Grant no. CHE 83-09936 and CHE 86-19420) for support of the work. This research was conducted with use of the Cornell National Supercomputer Facility, a resource for the Center for Theory and Simulation in Science and Engineering at Cornell University, which is funded in part by the National Science Foundation, New York State, and the IBM Corporation, and of a CRAY X-MP at Cray Research in Mendota Heights, MN. We also thank Cray Research for a grant of computer time and Dr. Martyn Guest for making his version of GAMESS available.

New Inhibitors of Cysteine Proteinases. Peptidyl Acyloxymethyl Ketones and the Quiescent Nucleofuge Strategy[1]

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Cathepsin B (EC 3.4.22.1)[3] is a clinically relevant cysteine proteinase that has been implicated in the pathogenesis of a number of diseases.[4] The most potent small molecule inhibitors of cysteine proteinases are the affinity labels with reactive leaving groups (Y),[4,5] many of which (i.e., Z-PheNHCHR(C=O)CH_2Y) have been developed by Shaw.[6] Recently, peptidyl fluoromethyl ketones have been introduced as inhibitors of cathepsin B and have proven to be affinity labels with low chemical reactivity.[7]

Conceptually, an ideal affinity label would be one in which the peptide moiety serves to transport a nucleofuge[8] on a carbon center that is uniquely reactive toward an active-site nucleophile of the target enzyme and quiescent in the presence of other bionucleophiles under physiological conditions. Hence, we sought to develop new inhibitors with difficultly displaceable leaving groups whose reactivity could be controlled by substituent effects and which might undergo rapid displacement in the enzyme inhibitor complex, by virtue of their proximity to a powerfully nucleophilic active site residue.

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(3) Barrett, A. J.; Kirschke, H. *Methods Enzymol.* **1981**, *80*, 535-561.
(4) Rich, D. H. In *Proteinase Inhibitors*; Barrett, A. J., Salvesen, G., Eds.; Elsevier: New York, 1986; pp 153-178.
(5) Shaw, E. In *Enzyme Inhibitors as Drugs*; Sandler, M., Ed.; University Park Press: Baltimore, MD, 1980; pp 25-42.
(6) (a) Shaw, E.; Kettner, C. *Acta Biol. Med. Ger.* **1981**, *40*, 1503-1511. (b) Leary, R.; Larsen, D.; Watanabe, H.; Shaw, E. *Biochemistry* **1977**, *16*, 5857-5861.
(7) (a) Rasnick, D. *Anal. Biochem.* **1985**, *149*, 461-465. (b) Rauber, P.; Angliker, H.; Walker, B.; Shaw, E. *Biochem. J.* **1986**, *238*, 633-640. (c) Shaw, E.; Angliker, H.; Rauber, P.; Walker, B.; Wikstrom, P. *Biomed. Biochem. Acta* **1986**, *45*, 1397-1403.
(8) Mathieu, J.; Allais, A.; Valls, J. *Angew. Chem.* **1960**, *72*, 71-74.

0002-7863/88/1510-4429$01.50/0