J. Am. Chem. Soc. 1990, 112, 3140–3145

Through-Bond Transmission of Substituent Effects in the Bicyclo[2.2.2]octane Ring System: Solvolysis of 4-Deuterio- and 4-Metalloidal ($M(CH_3)_3$, M = Si, Ge, and Sn)-Substituted Bicyclo[2.2.2]oct-1-yl *p*-Nitrobenzenesulfonates and Methanesulfonates

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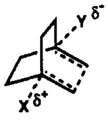
Abstract: 4-Deuterio- and 4-metalloidal ($M(CH_3)_3$, M = Si, Ge, and Sn)-substituted bicyclo[2.2.2]oct-1-yl *p*-nitrobenzenesulfonates and methanesulfonates, respectively, have been synthesized, and their solvolyses at 25 °C in aqueous ethanol and trifluoroethanol solvents have been examined. An extraordinarily large δ-deuterium isotope effect (k_H/k_D) is observed. Moreover, large rate enhancement factors are observed for the metalloidal substituents. These findings indicate through-bond coupling (or double hyperconjugation) to be a significant mode of cation stabilization in the bicyclooctyl system. The formation of some fragmentation product in a subsequent step is an analogous manifestation of the proposed long-range electronic interaction.

As part of a major study of polar substituent effects on carbocation mediated reactions in saturated systems,[1] Grob et al.[2] reported the rates of solvolysis of an extensive series of 4-substituted (X) bicyclo[2.2.2]-oct-1-yl *p*-nitrobenzenesulfonates (**1a**).

1



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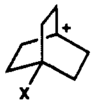
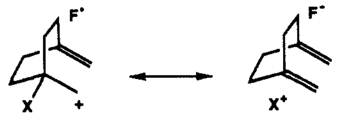


3

1a Y = $p\text{-}NO_2C_6H_4SO_3$
1b Y = CH_3SO_3
1c Y = F



4 **5**

By necessity these substrates solvolyze without back-side solvent nucleophilic assistance to ionization. Moreover, as a result of their symmetry and rigidity and the remoteness of the substituent, they are not complicated by steric and conformational phenomena. Hence, they serve as excellent model substrates for delineating quantitatively the response of unimolecular ionization reactions in saturated systems to polar substituent effects.

In general, Grob et al.[2] found that the solvolysis rates of **1a** correlate well against an inductive constant ($\sigma_I{}^q$) derived from the pK_a values of 4-substituted (X) quinuclidinium perchlorates.[3] However, the data for several substituents (X = H, COO^-, $CONH_2$, CH_2OH, and CH_2NH_2), described by Grob et al.[2] as being electrofugal, were significantly deviant. The apparent enhanced solvolysis rates of the deviant groups were ascribed to a phenomenon called 2-fold or double hyperconjugation involving the C–X and the three ethano bonds as illustrated in **2** (for one bridge only).[4] In addition, Grob et al.[2] suggested that the "anomalous" rate order for the alkyl substituents (H > $t\text{-}C_4H_9$ > $i\text{-}C_3H_7$ > C_2H_5 > CH_3) in **1a** may also be a manifestation of this hyperconjugative phenomena. It should be noted that Schleyer and Woodworth[5] have previously observed the same sequence from a very limited study of the acetolysis of **1** (Y = $p\text{-}BrC_6H_4SO_3$) but ascribed the anomalous position of hydrogen to substituent-induced structural distortions.

Subsequently, Wenke and Lenoir[6] presented ab initio calculations (STO-3G) of 4-substituted (X) bicyclo[2.2.2]oct-1-yl cations (**3**), in particular, the parent system (X = H), which did not corroborate the postulate of double hyperconjugation. Furthermore, these workers attributed the decreased solvolysis rate associated with the methyl substituent (vide supra) to steric hindrance to solvation in the transition state leading to the cation intermediate.

More recently, Adcock et al.[7] reported that the ^{19}F substituent chemical shifts (SCS, charge density monitors) of 4-substituted (X) bicyclo[2.2.2]oct-1-yl fluorides (**1c**) seem dependent on both electrostatic field (σ_F)[3c] and electronegativity (σ_X) effects. Initially, after canvanssing several possible factors, the origin of the latter contribution was tentatively ascribed to a "through-three-bond" electron delocalization mechanism (TB-3 effect; a σ resonance or σ–σ hyperconjugative effect), which couples the C–X and C–F bond MOs through the intervening ethano σ bonds. The prevailing orbital interactions governing this resonance effect have been attributed essentially to $\sigma^*_{CF}\text{–}\sigma_{CC}\text{–}\sigma_{CX}$. In valence bond terminology, the TB-3 effect in **1c** may be denoted by canonical

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[1] Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426–431 and references cited therein.

[2] (a) Grob, C. A.; Rich, R. *Tetrahedron Lett.* **1978**, 663–666. (b) Grob, C. A.; Rich, R. *Helv. Chim. Acta* **1979**, *62*, 2793–2801. (c) Bielmann, R.; Grob, C. A.; Küry, D.; Yao, G. W. *Helv. Chim. Acta* **1985**, *68*, 2158–2164.

[3] It is significant to note that Fischer et al.[3b] have demonstrated that, provided the CO_2^- substituent is excluded, the quinuclidinium data ($\sigma_I{}^q \equiv pK_H - pK$) exhibit an excellent correlation (r = 0.988) with σ_I (although the hydrogen datum point is deviant). An even better correlation (r = 0.992) was obtained when the datum point for hydrogen was excluded. (b) Fischer, A.; King, M. J.; Robinson, F. P. *Can. J. Chem.* **1978**, *56*, 3072–3077. (c) The symbol σ_F is probably best employed in place of σ_I in view of the overwhelming evidence that σ_I is a manifestation of polar field effects.[3d] (d) Reynolds, W. F.; Gomes, A.; Maron, A.; MacIntyre, D. W.; Tanin, A.; Hamer, G. K.; Peat, I. R. *Can. J. Chem.* **1983**, *61*, 2376–2384 and references cited therein.

[4] Except for X = H, all the so-called electrofugal substituents (X = COO^-, $CONH_2$, CH_2OH, and CH_2NH_2) are chemically active functions as far as solvent interactions are concerned. All are good hydrogen bond acceptors and, in the case of the three neutral dipolar groups, also good hydrogen bond donors. Thus, the deviations observed for these groups may be readily ascribed to solvation factors. Most importantly, it should be remembered that the substituent effects of charged substituents vary widely (e.g. COO^-)[3b] and do not generally fit linear free energy relationships.

[5] Schleyer, P. v. R.; Woodworth, C. A. *J. Am. Chem. Soc.* **1968**, *90*, 6528–6530.

[6] Wenke, G.; Lenoir, D. *Tetrahedron Lett.* **1979**, 2823–2826.

[7] Adcock, W.; Abeywickrema, A. N. *Tetrahedron Lett.* **1981**, *22*, 1135–1138. Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2957–2966.

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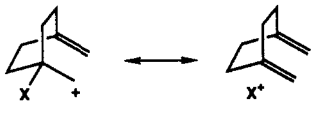
structures **4** and **5** (depicted for only one of the three bonds). Subsequent model system studies[8-11] have corroborated the strong regulation of the ^{19}F SCS of **1c** by the TB-3 effect. Clearly, this effect is simply double hyperconjugation in another guise. Hence, since it is generally accepted that hyperconjugative interactions are more pronoucned in excited or electron deficient species such as carbocations than in the neutral ground state, the aforementioned ^{19}F chemical shift studies strongly suggest that double hyperconjugation should be an important mode of cation stabilization in the bicyclo[2.2.2]octyl system (**3**) as illustrated by canonical structures **6** and **7**.



6 **7**

In the present paper we report solvolysis rates for several new derivatives of **1a** (X = D) and **1b** (X = SiMe$_3$, GeMe$_3$, and SnMe$_3$). There were two main reasons for selecting these particular substituents for study.[12] First, the pronounced ^{2}H/^{1}H isotope effect on the ^{19}F chemical shift of **1c**,[9] which is the largest isotope shift over five single bonds ever observed in a neutral system, strongly suggests that a large δ-deuterium isotope effect on the rates of solvolysis of **1a** should be observed.[13] Confirmation of this prediction would provide experimental evidence in support of double hyperconjugation in **3** (X = H) since secondary kinetic deuterium isotope effect measurements are an established tool for probing hyperconjugative electron demand in carbocation-like transition states of solvolysis reactions.[14] Second, the ^{19}F SCS of **1c** for alkyl substituents, which are predominantly manifestations of the TB-3 effect, are *negative*, implying σ-electron withdrawal relative to hydrogen.[7,10] This result is concordant with the observed rate-retarding effects of these groups (vide supra) on the solvolysis rates of **1** (Y = p-NO$_2$C$_6$H$_4$SO$_3$ or p-BrC$_6$H$_4$SO$_3$). Hence, since the sign of the ^{19}F SCS of the metalloidal groups (MMe$_3$; M = Si, Ge, and Sn)[7,10] is diametrically opposed (*positive*) to that for the alkyl substituents and, moreover, since the shifts are also predominantly manifestations of the dominant TB-3 effect,[7,10] significant accelerative effects (Sn $\gg$ Ge > Si > H) on the rates of solvolysis of **1b** are suggested for these σ-electron-donor groups. Substantiation of this δ effect for the metalloidal substituents would strongly implicate the participation of the C–M bond during cleavage of the C–O bond via a long-range σ-conjugative mechanism.

Herein we report the results of our study.

Results and Discussion

The rate constants for the solvolysis of the 4-substituted (X) bicyclo[2.2.2]octyl sulfonate esters **1a** and **1b** in several solvents are listed in Table I. It should be noted that we initially set out to extend the Grob et al.[2] study by examining the p-nitrobenzenesulfonate derivatives **1a** of the metalloidal substituents. However, it soon became apparent from an unsuccessful attempt to synthesize the silyl derivative (**1a**: X = SiMe$_3$; see Experimental Section) that a less active nucleofuge (CH$_3$SO$_3$) was required to render the substrates tractable for preparation and isolation. This was the first sign that the metalloidal substituents would indeed significantly enhance solvolytic reactivity of the bicyclo[2.2.2]octyl substrates.

Table I Solvolysis Rate Constants[a] for 4-Substituted (X) Bicyclo[2.2.2]octyl Derivatives (**1a** and **1b**)

			solvent[b]				
	X	T, °C	97T	50E	60E	80E	90E
1a	H	25.000	33.72			1.652	
	D	25.000	32.13			1.576	
1b	H	15.000	0.466				
		25.000	1.659	1.460	0.465	0.032	
		35.000	5.451				
	Me$_3$Si	25.000	80.7		6.60	0.603	0.110
	Me$_3$Ge	25.000	117.9		8.90	0.832	
	Me$_3$Sn	−14.55	41.0				
		−10.00	72.5				
		0.000	273.9				
		10.000	906.0				
		25.000	(4713)[c]		278.5	25.34	4.865

[a] First-order rate constants in units of 10^{-5} s^{-1} for the average of at least two determinations. [b] 50E, 60E, 80E, and 90E are 50, 60, 80, and 90 vol % ethanol with 50, 40, 20, and 10 vol % water while 97T is 97 wt % trifluoroethanol–3 wt % water. [c] Extrapolated from rates observed at lower temperatures, see Experimental Section.

4-(Trimethylstannyl)bicyclo[2.2.2]octyl mesylate reacts too rapidly in 97T at 25 °C for the rate constant to be determined by our conductance technique. Therefore, the solvolysis rate constants were determined in this solvent at four lower temperatures and the 25 °C value was obtained by extrapolation with the Arrhenius equation. The activation parameters were as follows: $A = 1.61 \times 10^{-12}$ s^{-1}; E_a = 18.46 kcal/mol; ΔH^* = 17.92 kcal/mol; ΔS^* = −4.49 cal/(mol deg^{-1}) at 273 K. The activation parameters were also determined for the solvolysis of the unsubstituted analogue; as expected, the activation energy (21.37) and the enthalpy (21.33) are both larger than those for the trimethylstannyl analogue while the activation entropy is more negative (−8.85), presumably reflecting the stronger demand for transition state solvation for the less reactive ester.

To analyze the effects of solvent changes on the solvolysis reaction rates, ethanol–trifluoroethanol plots of log k(**1b**) vs log k(1-adamantyl methanesulfonate)[15] were examined.[16] The slopes for the ethanol–water points and the distance in log units of the 97T point from the ethanol–water correlation line are as follows for the 4-substituted (X) bicyclo[2.2.2]octyl mesylates: X = H, m_E = 1.01, Δ97T = 0.23; X = trimethylsilyl, m_E = 0.92, Δ97T = −0.36; X = trimethylgermyl, m_E = 0.91, Δ97T = −0.40; X = trimethylstannyl, m_E = 0.92, Δ97T = −0.50. Surprisingly the 97T point falls below the ethanol line (slower) for the parent compound. A plot of log k(bicyclo[2.2.2]octyl tosylate) vs log k(2-adamantyl tosylate) has been reported for a much more extensive range of solvents and showed a linear correlation in all solvents.[17] Our plots show that the 4-metalloidal-substituted bicyclooctyl esters all have similar slopes near 0.90, slightly lower than the one for the parent ester. This could be due to a dispersal of the cationic charge to the metalloidal atom, which lessens the demand for solvation and causes a slightly lower response to Y_{OMs}. The 97T points are significantly *above* the ethanol–water line for all three metalloidal compounds. The fact that the rates in 97T are faster than predicted by the Y_{OMs} correlation might also be explained by the ability of the metalloids to disperse the transition state

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(12) (a) The field mechanism (σ_F effect),[3c] which involves the direct electrostatic interaction between the substituent and probe group (dipole or charge), is so dominant for reactivity probes[12b] that relatively small through-bond effects tend to be swamped and, hence, camouflaged. Thus, the unambiguous delineation of the latter effects is best confined to groups with negligible field influences ($\sigma_F \sim 0$). D and MMe$_3$ groups (M = C, Si, Ge, Sn) fit this category.[9,10] Although the MMe$_3$ groups are all very polarizable, the relatively large fall-off factor with distance (r^{-4}) of substituent polarizability[12c,d] precludes this phenomena being significant in 1 (r > 2.5 Å). (b) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1983**, *14*, 165–203. (c) Hehre, W. J.; Pau, C. F.; Headley, A. D.; Taft, R. W.; Topsom, R. D. *J. Am. Chem. Soc.* **1986**, *108*, 1711–1712. (d) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1–84.

(13) See footnote 48 of ref 14a.

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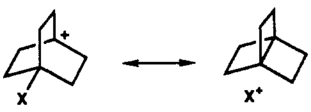
Table II Relative Solvolysis Rates for 4-Substituted (X) Bicyclo[2.2.2]octyl Mesylates at 25 °C

solvent	Me_3Si/H	Me_3Ge/H	Me_3Sn/H	Me_3Sn/Me_3Si	Me_3Ge/Me_3Si
90E				44	
80E	18.6	25.7	781	42	1.38
60E	14.2	19.01	599	42	1.35
97T	48.6	71.1	2841	58	1.45

positive charge away from C1; this implies that trifluoroethanol favors charge dispersal within a molecule slightly more than ethanol–water solvents of the same *Y* value, i.e. that differences in transition-state charge dispersal can be a cause of small deviations from *mY* correlations.

The first two entries in Table I show that the involvement of the C_4–H bond in the solvolysis is unexpectedly large (k_H/k_D = 1.048 in 80E and 1.050 in 97T). It is of interest to note that this effect is considerably larger than the corresponding β-isotope effect (1.02) on the dediazonization of phenyldiazonium ions, which leads to the phenyl cation.[18] Furthermore, it is larger than the γ-isotope effects (1.03 and 1.041) observed for the solvolysis of 3-substituted (X) adamant-1-yl derivatives (**10**: Y = Br and $p\text{-}CH_3C_6H_4SO_3$) in 80T and 96E, respectively,[14] and of 1.044 observed for the solvolysis of 5-deuteriobicyclo[3.1.1]heptyl bromide.[19] We believe that the origin of the isotope effect in **1a** can only be ascribed to lowering of the C–H force constant by double hyperconjugation as predicted (see introduction; illustrated by structures **6** and **7**, X = H). An alternative explanation in terms of homohyperconjugation or back lobe (percaudal)[20] participation through space[21] (illustrated by structures **8** and **9**, X = H) is not supported by model system studies utilizing ^{19}F chemical shifts as the probe.[8-11] The dramatic accelerative effects due to double hyperconjugation involving the C–M bonds, particularly for tin (Sn ≫ Ge ~ Si > H), are clearly seen from the relative rates listed in Table II. Note that in 97T the stannyl compound is nearly 3000 times more reactive than the parent. The enhanced reactivities are more pronounced in 97T because charge dispersal within the cation of the transition state is larger in this medium and, hence, more demand is placed on the conjugative abilities of the C–M bonds. An alternative rationale of these very significant δ-metalloidal substituent effects in terms of polar field or polarizability phenomena[12] is not plausible. Interestingly, in the case of 3-substituted (X) 1-bromoadamantanes (**10**: Y = Br), a model system whose solvolytic reactivity is determined by polar field effects as well as σ-inductive perturbation of C–C hyperconjugation and homohyperconjugation,[22,23] rate enhancement factors of 8.6[23] and 58[24] have been reported for Me_3Si and Me_3Sn in 80E, respectively. Note that these γ effects in **10** are much smaller than the corresponding δ effects in **1** (18.6 and 781, respectively; taken from Table II). The differences between these two systems cannot be ascribed to polar inductive effects since the ρ value for **1** (Y = $p\text{-}NO_2C_6H_4SO_3$, $\rho = -1.09$)[2] is somewhat smaller than that for **10** (Y = Br, $\rho = -1.14$)[24] in 80E. Furthermore, MM2 calculations give a C_1–C_3 internuclear distance in the 1-adamantyl cation (2.33 Å), which is approximately the same as the C_1–C_4 distance in the 1-bicyclo[2.2.2]octyl cation (2.36 Å); if a through-space interaction were operative in **1** as is proposed for **10**,[25] more similar rate acceleration factors would be expected. Instead, stannyl substitution in the bicyclooctyl system produces an acceleration factor that is more than 10 times that observed in the 1,3-adamantyl system.



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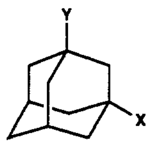

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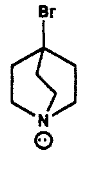

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It is of interest to note that the germyl compound is only slightly more reactive (ca. 1.5 times) than the corresponding silyl derivative (see Table II). Although this is essentially in accord with expectations based on the appropriate ^{19}F SCS data of **1c**,[10] it is considerably less than the corresponding relative rates where the C–M bond is β disposed to partial positive charge. For example, solvolysis studies of esters of *cis-* and *trans-*2-(trimethylsilyl and trimethylgermyl)cyclohexanols give relative rates (Ge/Si) of ca. 14 and 18, respectively.[26] This apparent discrepancy is probably related to the fact that the β effect involves *direct* interaction of the C–M bond with the developing charge whereas for the δ effect the interaction is *indirect*. For the former interaction, the resonance effect is probably dominated by ΔE (orbital energy gap between the appropriate orbitals).[27] However, for the latter ΔE is probably offset to a considerable degree by $C^2\beta^2$ [10] (C is the coefficient at the carbon atom of attachment and β is the resonance integral associated with the appropriate orbitals).[27]

The products of solvolysis of the silyl and germyl compounds **1b** in perdeuterated 80E and of the stannyl compound in perdeuterated 80E, 100E, and 97T were determined by analysis of the proton NMR of the spent reaction mixtures (see Experimental Section). Only direct substitution products were identified in the reactions of the silyl and germyl derivatives. This is in accord with the observations of Grob et al.[2] for a diverse number of substituted derivatives of **1a**. However, in the case of the stannyl derivative, 1,4-dimethylenecyclohexane was identified. This fragmentation product accounts for about 15% and 16% of the yield in 80E and 100E, respectively, and for 36% of the yield in 97T, the remainder being direct substitution. While it is possible that 1,4-dimethylenecyclohexane arises from ring opening of a fleeting [2.2.2]propellane,[28,29] trapping experiments for (4-halobicyclo[2.2.2]oct-1-yl)lithium derivatives, which readily yield 1,4-dimethylenecyclohexane, failed to indicate the intermediacy of [2.2.2]propellane.[10,30] Thus, the situation for the tin compound is somewhat akin to that of 4-bromoquinuclidine (**11**), which solvolyzes 10^5 times faster than 1-bromobicyclo[2.2.2]octane and gives rise exclusively to fragmentation products. The observations for **11** have been ascribed to through-bond coupling of the incipient cation orbital and the nitrogen lone pair.[31] A molecular orbital study of this phenomenon has defined the electronic prerequisites for fragmentation.[32] Clearly, enhanced through-bond coupling

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leads to increased fragmentation. A major difference in the behavior of the tin compound (**1b**, X = Me_3Sn) and **11** is that whereas the latter compound fragments in a concerted fashion with the departure of the leaving group (frangomeric acceleration), the former undergoes fragmentation via the intermediate cation. We believe that the results for the tin compound of **1b** confirm through-bond coupling (double hyperconjugation or TB-3 effect) as the origin of the δ-deuterium isotope rate effect observed in this study.[33]

We are currently extending our studies in an attempt to delineate the kinetic and stereochemical consequences of through-bond coupling between the 2 and 5 positions in the adamantane ring system. This is pertinent since several recent papers by le Noble and co-workers have reported on the effectiveness of 2,5-disubstituted adamantanes as model systems for delineating the electronic effects of substituents on the stereoselectivity of addition reactions to trigonal carbon.[34] Preliminary results have shown that (*E*)-5-Me_3M-2-adamantyl brosylate esters (M = Si and Sn) show large solvolytic rate enhancements of the same magnitude seen in the bicyclooctyl system.

Experimental Section

General Methods. Melting and boiling points are uncorrected. All liquid samples were distilled on a Kugelrohr apparatus (Büchi GKR-50). Hence, the boiling points quoted pertain to the glass oven temperature of this equipment. Mass spectra were obtained on an AEI M530 spectrometer with an ionizing energy of 70 eV. Analytical vapor-phase chromatographic analyses were performed on a Perkin-Elmer 8410 gas chromatograph with a 6-ft column of silicone-OV17 on 100/120 Chromosorb WHP.

The broad-band proton-decoupled ^{13}C NMR spectra (22.53 and 75 MHz) were recorded in the pulse Fourier transform mode on JEOL FX-90Q and Varian XL-300 instruments, respectively. ^1H NMR spectra were measured with Varian EM-360 (60 MHz) or Nicolet-360 (360 MHz) instruments.

Synthesis. Bicyclo[2.2.2]octan-1-ol (1: X = OH, Y = H). By use of the procedure of Suzuki et al.,[35] a solution of 1-methoxybicyclo[2.2.2]octane (15.0 g, 0.11 mol; prepared in the manner previously indicated)[36] in acetic anhydride (50 mL) was treated with a few drops of boron trifluoride etherate and stirred at 50 °C until VPC analysis indicated that all the starting material had been consumed (29 h). The reaction mixture was poured on to ice/H_2O and extracted with ether. The combined extract was washed with saturated sodium bicarbonate solution and dried, and the solvent was removed to afford the crude 1-acetoxybicyclo[2.2.2]octane as an orange oil, 18.0 g (97%). A sample was distilled to afford a colorless oil (bp 70 °C/0.6 mm), which solidified: mp 34–36 °C; ^1H NMR (CCl_4) δ 1.4–2.3 (16 H, m).

A mixture of crude acetate (20.2 g, 0.12 mol), sodium methoxide (13.0 g, 0.24 mol), and absolute methanol (100 mL) was refluxed with stirring for 2 h. The resulting slurry was poured on to ice/water and extracted with ether. The extracts were combined and dried, and the solvent was evaporated. Sublimation of the residue gave the title alcohol as a white solid (10.6 g, 70%): mp 195–197 °C (sealed capillary; lit.[37] mp 214–216 °C); ^1H NMR (360 MHz, $CDCl_3$) δ 2.69–3.37 (12 H, m), 1.04 (1 H, br s).

4-Bromobicyclo[2.2.2]octan-1-ol (1: X = OH, Y = Br). By use of the procedure of Rubottom et al.,[38] as described by Adcock et al.,[11,39] for the conversion of 4-iodo- and 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid to 1-acetyl-4-iodobicyclo[2.2.2]octane and 1-acetyl-4-methoxybicyclo[2.2.2]octane, respectively, 4-bromobicyclo[2.2.2]octane-1-carboxylic acid[40] (22.79 g, 0.098 mol) was converted to 1-acetyl-4-bromobicyclo[2.2.2]octane, which was obtained as a very pale yellow solid (21.4 g, 95%) after sublimation: mp 79–80.5 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.40 (12 H, m, CH_2CH_2), 2.0 (3 H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 42.53 (C1), 30.43 (C2), 36.81 (C3), 62.01 (C4), 25.13 (CH_3), 212.13 (CO).

A solution of 1-acetyl-4-bromobicyclo[2.2.2]octane (21.4 g, 0.093 mol) in dry chloroform was treated with *m*-chloroperbenzoic acid (48 g, 0.28 mol) as previously described for the conversion of 1-acetyl-4-methoxybicyclo[2.2.2]octane to 1-acetoxy-4-methoxybicyclo[2.2.2]octane.[11] The crude bromoacetate was obtained as a pale yellow solid (22.9 g, 95%). Sublimation afforded a white solid: mp 132–135 °C; ^1H NMR ($CDCl_3$) δ 1.88 (3 H, s, $OCOCH_3$) 1.93–2.58 (12 H, m, CH_2CH_2); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 76.85 (C1), 32.37 (C2), 38.22 (C3), 60.13 (C4), 22.29 (CH_3), 170.08 (CO).

1-Acetoxy-4-bromobicyclo[2.2.2]octane (22.9 g, 0.093 mol) was hydrolyzed to the title compound in the same manner described above for the conversion of 1-acetoxybicyclo[2.2.2]octane to bicyclo[2.2.2]octan-1-ol. Sublimation of the crude product afforded a white solid (17.9 g, 94%): mp 158–159 °C (lit.[39] 163–164 °C, 163–165 °C[41]).

1-Bromo-4-(trimethylsiloxy)bicyclo[2.2.2]octane (1: X = Br, Y = $OSi(CH_3)_3$). By use of the procedure of Strating et al.,[42] freshly distilled chlorotrimethylsilane (5.8 g, 0.053 mol) was added dropwise to a well-stirred solution of 4-bromobicyclo[2.2.2]octan-1-ol (9 g, 0.044 mol) in anhydrous pyridine (50 mL) under an atmosphere of nitrogen. The reaction mixture was then refluxed for 1 h before being allowed to stir overnight at ambient temperature. Following workup as prescribed by Strating et al.,[42] the crude silyl ether was distilled (75 °C/0.2 mm) to afford a white solid (12.05 g, 99%): mp 42–44 °C; ^1H NMR ($CDCl_3$) δ 0.00 (9, s, $SiMe_3$), 1.50–2.48 (12 H, m, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 61.66 (C1), 38.86 (C2), 37.00 (C3), 69.24 (C4), 2.63 ($OSiMe_3$).

4-Deuteriobicyclo[2.2.2]octan-1-ol (1: X = D, Y = OH). A solution of 1-acetoxy-4-bromobicyclo[2.2.2]octane (2.6 g, 0.011 mol; obtained as an intermediate in the preparation of 4-bromobicyclo[2.2.2]octan-1-ol (see above)) in tri-*n*-butyltin deuteride (3.6 g, 0.012 mol; prepared by treating tri-*n*-butyltin chloride with $LiAlD_4$) containing several milligrams of azobis(isobutyronitrile) (AIBN) was irradiated with a 450-W medium-pressure Hanovia lamp for 4 h.[43] Ether (160 mL) was then added and the solution was washed with 10% aqueous potassium fluoride. The latter was then extracted thoroughly with ether. The combined ether extracts were washed with an aqueous sodium bicarbonate solution and dried, and the solvent was evaporated. The residue was distilled to afford 1-acetoxy-4-deuteriobicyclo[2.2.2]octane as a colorless solid (1.78 g, 96%): mp 34–36 °C, mass spectrum, *m/e* 169 (M^+). The mass spectrum indicated >99.5% deuterium incorporation.

The acetate (1.78 g, 0.011 mol) was hydrolyzed to the title compound in the manner outlined above for the hydrogen analogue. Sublimation of the crude product afforded a white solid (1.1 g, 83%): mp 198–200 °C (sealed capillary); ^{13}C NMR ($CDCl_3$) δ 69.06 (C1), 33.80 (C2), 27.09 (C3), 23.64 (C4; t, J_{CD} = 20.51 Hz).

4-(Trimethylsilyl)bicyclo[2.2.2]octan-1-ol (1: X = $SiMe_3$, Y = OH). By use of a procedure outlined by Shippey and Dervan,[44] a solution of (trimethylsilyl)sodium was prepared by adding hexamethyldisilane (13.6 g, 0.093 mol) dropwise to a suspension of freshly prepared sodium methoxide (3.1 g, 0.057 mol) in dry hexamethylphosphoric triamide (HMPA; 45 mL) under a nitrogen atmosphere. After the resulting red solution was stirred for 4 h at 20 °C, a solution of 1-bromo-4-(trimethylsiloxy)bicyclo[2.2.2]octane (3.9 g, 0.014 mol) in dry HMPA was then added dropwise over a period of ca. 10 min and the reaction mixture was then allowed to stand overnight with stirring. The mixture was then quenched with aqueous acetic acid (70 mL) and allowed to stand for a further 1 h before being extracted thoroughly with pentane (3×) and ether (3×), respectively. The extracts were washed thoroughly with iced water (3×) and dried, and the solvents were evaporated.

Kugelrohr distillation (60 °C/0.7 mm) of the ether extract residue afforded the reduction product bicyclo[2.2.2]octan-1-ol (0.35 g, 40%). Similar distillation of the pentane extract residue gave two fractions: (1) a mixture of the reduction product and various silicon-containing by-products (50–60 °C/0.7 mm); (ii) a mixture of the title compound and its silyl ether derivative (80 °C/0.07 mm). The latter fraction was

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[33] (a) The results of this study suggest that the deviation of the datum point for hydrogen from the correlation line for the quinuclidinium data ($\sigma_I{}^q$ versus σ_I)[3a,b] is a consequence of through-bond coupling. In addition, through-bond interactions may also be responsible for some of the discrepancies between $\sigma_I{}^q$ and σ_F values[3c] defined from the ^{19}F SCS of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes.[7-10,32b,c] The latter model system is not complicated by such interactions. (b) Adcock, W.; Khor, T.-C. *J. Org. Chem.* **1978**, *43*, 1272–1275. (c) Adcock, W.; Aldous, G. L.; Kitching, W. *J. Organomet. Chem.* **1980**, *202*, 385–399.

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treated with methanol–dry HCl gas to effect complete desilylation. The crude silyl alcohol (1.6 g, 58%) was recrystallized (3×) from hexane and then sublimed to afford a white solid: mp 133.5–134 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 69.56 (C1), 34.00 (C2), 27.83 (C3), 16.49 (C4), −4.64 ($SiMe_3$). Anal. Calcd for $C_{11}H_{22}SiO$: C, 66.60; H, 11.18. Found: C, 66.15; H, 11.06.

In a repeat preparation of the title compound the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ether, and the resulting product was desilylated with tetrabutylammonium fluoride as described below for the corresponding tin compound. The mixture of 4-(trimethylsilyl)bicyclo[2.2.2]octan-1-ol (ca. 60%) and bicyclo[2.2.2]octan-1-ol (ca. 40%) was then separated by HPLC (silica gel column) with 30% ethyl acetate–hexane as the eluent.

4-(Trimethylgermyl)bicyclo[2.2.2]octan-1-ol (1: X = GeMe$_3$, Y = OH). A solution of 1-bromo-4-(trimethylsiloxy)bicyclo[2.2.2]octane (3 g, 0.011 mol) in HMPA (20 mL) under a nitrogen atmosphere was added to a solution of (trimethylgermyl)lithium[45] (prepared from Me_3GeBr (2.12 g, 0.011 mol) and lithium (1 g, 0.144 mol) in HMPA (40 mL); the reagent was allowed to stand with stirring for 8.5 h before use). The reaction mixture was allowed to stir for 48 h at room temperature before being quenched with saturated aqueous ammonium chloride. A standard workup afforded a mixture of the title compound (ca. 98%) and bicyclo[2.2.2]octan-1-ol (ca. 2%). The unexpected isolation of the alcohols rather than the corresponding silyl ethers is probably a consequence of the inadvertent use of excess lithium in the preparation of Me_3GeLi. The HMPA reaction mixture contains solvated electrons and, hence, is apparently able to effect reductive desilylation. Fractional sublimation of the alcohol mixture followed by recrystallization from hexane afforded 4-(trimethylgermyl)bicyclo[2.2.2]octan-1-ol as a white solid (2.1 g, 80%): mp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 0.00 (9 H, s, $GeMe_3$), 1.58 (12 h, s, CH_2CH_2), 1.72 (1 H, s, OH); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 68.87 (C1), 34.16 (C2), 28.68 (C3), 20.20 (C4), −5.70 ($GeMe_3$). Anal. Calcd for $C_{11}H_{22}GeO$: C, 54.39; H, 9.13. Found: C, 54.47; H, 9.09.

4-(Trimethylstannyl)bicyclo[2.2.2]octan-1-ol (1: X = SnMe$_3$, Y = OH). A solution of 1-bromo-4-(trimethylsiloxy)bicyclo[2.2.2]octane (4.9 g; 0.018 mol) in anhydrous THF (30 mL) was added dropwise to a solution of (trimethylstannyl)lithium (0.07 mol) in anhydrous THF at 0 °C under a nitrogen atmosphere. The latter reagent was prepared in a standard way.[46] A standard workup afforded the crude product as a pale yellow liquid (6.36 g). Following a procedure by Corey et al.,[47] a 1 M solution of anhydrous tetrabutylammonium fluoride (TBAF)[48] in THF (53 mL) was added over 10 min to a well-stirred solution of the crude stannylation product (6.36 g) in THF (30 mL) at 0 °C under a nitrogen atmosphere. The solution was then stirred at room temperature until VPC analysis indicated that desilylation was complete (ca. 9–10 h). A standard workup afforded a mixture of the title compound (ca. 96%) and bicyclo[2.2.2]octan-1-ol (ca. 4%). Fractional Kugelrohr distillation/sublimation followed by recrystallization from aqueous ethanol afforded 4-(trimethylstannyl)bicyclo[2.2.2]octan-1-ol as a white solid (4.5 g, 88%): mp 123–124 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ −0.16 (9 H, s), 1.05 (1 H, br s), 1.40–1.48 (6 H, m), 1.62–1.78 (6 H, m); ^{13}C NMR ($CDCl_3$), relative to Me_4Si) δ 68.48 (C1), 35.00 (C2), 31.51 (C3), 21.65 (C4), −12.43 ($SnMe_3$). Anal. Calcd for $C_{11}H_{22}SnO$: C, 45.72; H, 7.67. Found: C, 45.90; H, 7.90.

Initially, we attempted to prepare the title alcohol by treatment of 4-bromobicyclo[2.2.2]octan-1-ol with excess Me_3SnLi in THF. However, this led to a mixture consisting mainly of the reduction product (>95%) and only a small amount of the desired stannyl alcohol (<5%). In our second attempt, we converted 4-iodobicyclo[2.2.2]octan-1-ol to the corresponding trimethylstannyl ether by treatment with NaH/Me_3SnCl. The ether was then treated with Me_3SnLi in tetraglyme which, after a standard workup, afforded a mixture of the title alcohol (ca. 30%) and bicyclo[2.2.2]octan-1-ol (ca. 70%). The mixture was readily separated by HPLC (silica gel (column) with 30% ethyl acetate–hexane as the eluent.

The varying amounts of substitution versus reduction observed in the aforementioned stannylation reactions highlights the importance of the substituent in these syntheses. The reaction of bridgehead bicyclo[2.2.2]octyl bromides and iodides occurs by a radical chain mechanism in which a key step is the combination of the initially formed bicyclo[2.2.2]oct-1-yl radical with Me_3Sn^- to form a radical anion.[30c] Any retardation of this step will promote the competing step of hydrogen atom abstraction from the solvent to increase the reduction product. Thus, we believe the predominance of reduction in the case of the stannylation of the bromo alcohol is due to an initial rapid reaction to give lithium 4-bromobicyclo[2.2.2]octoxide and Me_3SnH. However, it should be pointed out that based on the relatively slow reaction between *tert*-butyl alcohol and Me_3SnNa[49] this was not expected. The field effect of the negative pole substituent ($-O^-Li^+$) must have a profound rate-retarding effect on the formation of the key radical anion. Conversion of the hydroxyl group to a siloxy substituent (a weakly dipolar electron-withdrawing group) precludes this disadvantageous influence.

Bicyclo[2.2.2]oct-1-yl *p*-Nitrobenzenesulfonate (1a: X = H). By use of the procedure of Grob et al.[37] for the preparation of 4-methylbicyclo[2.2.2]oct-1-yl *p*-nitrobenzenesulfonate (**1a**: X = CH_3), bicyclo[2.2.2]octan-1-ol was treated with *p*-nitrobenzenesulfonyl chloride in dry pyridine as described. The crude product (60% yield) was recrystallized (3×) from a CCl_4/hexane mixture to afford very pale yellow needles: mp 131–132 °C (lit.[37] mp 115.5–117 °C); ^{1}H NMR (CCl_4) δ 1.50–2.30 (13 H, m, aliphatic), 8.30 (4 H, q, aromatic); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 95.50 (C1), 31.49 (C2), 27.43 (C3), 23.40 (C4), 145.51 (C1′), 128.48 (C2′), 124.24 (C3′), 150.24 (C4′). Anal. Calcd for $C_{14}H_{17}O_5SN$: C, 54.01; H, 5.50. Found: C, 53.90; H, 5.49.

4-Deuteriobicyclo[2.2.2]oct-1-yl *p*-nitrobenzenesulfonate (1a: X = D) was prepared from 4-deuteriobicyclo[2.2.2]octan-1-ol as indicated above for the corresponding hydrogen analogue. The crude product (60% yield) was recrystallized (5×) from a CCl_4/hexane mixture to afford a white microcrystalline solid: mp 132–133 °C; ^{1}H NMR (CCl_4) δ 1.55–2.35 (12 H, m, aliphatic), 8.25 (4 H, q, aromatic); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 95.52 (C1), 31.44 (C2), 27.30 (C3), 22.95 (C4; t, J_{C-D} = 20.02 Hz), 145.51 (C1′), 128.48 (C2′), 124.24 (C3′), 150.24 (C4′). Anal. Calcd for $C_{14}H_{16}DO_5SN$: C, 53.83; H, 5.81. Found: C, 53.95; H, 5.57.

Attempted Synthesis of 4-(Trimethylsilyl)bicyclo[2.2.2]oct-1-yl *p*-Nitrobenzenesulfonate (1a: X = SiMe$_3$). An attempt was made to prepare the title compound from the corresponding alcohol (**1**: X = $SiMe_3$, Y = OH) by utilizing the method indicated above for the parent derivative (**1a**: X = H). The crude product was recrystallized (3×) from a $CHCl_3$/hexane mixture to afford white flakes: mp 216.5–217.5 °C; ^{1}H NMR ($CDCl_3$) δ −0.04 (9 H, s, $SiMe_3$), 1.60–2.0 (6 H, m, CH_2CH_2), 2.0–2.50 (6 H, m, CH_2CH_2) 8.10–8.60 (7 H, m, aromatic), 9.35–9.60 (2 H, m, aromatic); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 72.08 (C1), 32.21 (C2), 27.33 (C3), 17.09 (C4), 148.17 (C1′), 128.85 (C2′), 123.44 (C3′), 152.85 (C4′), 142.37 (Cα), 127.39 (Cβ), 144.97 (Cγ). The NMR date are clearly not in accord with the structure of the title compound. The solvolysis product *N*-(4-(trimethylsilyl)bicyclo[2.2.2]oct-1-yl)-pyridinium *p*-nitrobenzenesulfonate anion ($(C_{16}H_{26}N\ Si)^+(C_6H_4SNO_5)^-$) appears to fit the data. Anal. Calcd for $C_{22}H_{30}N_2SSiO_5$: C, 57.10; H, 6.53; N, 6.08; S, 6.93; Si, 6.07. Found: C, 55.24; H, 6.70; N, 5.87; S, 6.80; Si, 5.6. An analysis of the compound by Fast Atom Bombardment Mass Spectrometry (FAB-MS) in both positive and negative ion modes confirmed the structure. The measured accurate mass of the positive ion was 260.18251 ($C_{16}H_{26}NSi$). Negative ion chemical ionization provided a significant peak at m/z 202, which corresponds to the suspected anion ($C_6H_4SNO_5$).

Preparation of Mesylates of 1b (X = H, SiMe$_3$, GeMe$_3$, and SnMe$_3$). By use of the procedure of Crossland and Servis,[50] triethylamine (0.11 g, 1.08 mmol) and methanesulfonyl chloride (0.07 g, 0.65 mmol) were added to a methylene chloride solution of the appropriate alcohol (**1**, Y = OH; 0.496 mmol) at 0 °C. After a standard workup, the mesylates were all purified by HPLC (Prepacked silica gel column) with 20% ethyl acetate–hexane as the eluent. All were subsequently recrystallized from light petroleum ether to afford white crystals. Melting points and NMR data for the mesylates **1b** are as follows: X = H, mp 48.5–51.5, ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.96 (3 H, s, CH_3SO_3), 2.17–2.04 (6 H, m), 1.80–1.70 (6 H, m), ^{13}C NMR (75 MHz, $CDCl_3$) proton coupled δ 92.06 (s, C1), 31.22 (t, C2), 37.18 (t, C3), 23.30 (d, C4), 40.82 (q, CH_3SO_3); X = $SiMe_3$, mp 114.5–116 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.97 (3 H, s, CH_3SO_3), 2.10–1.98 (m, 6 H), 1.75–1.65 (m, 6 H), −0.04 (s, 9 H, Me_3Si), ^{13}C NMR (75 MHz, $CDCl_3$) proton decoupled δ 93.04 (C1), 31.45 (C2), 28.04 (C3), 16.21 (C4), 40.97 (CH_3SO_3), −4.77 (Me_3Si); X = $GeMe_3$, mp 115.5–117.5 °C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.93 (3 H, s, CH_3SO_3) 2.09–2.00 (6 H, m, CH_2CH_2), 1.74–1.62 (6 H, m, CH_2CH_2), −0.02 (9 H, s, Me_3Ge), ^{13}C NMR (75 MHz, CCl_3) δ 92.35 (C1), 31.74 (C2), 28.95 (C3), 19.66 (C4), 40.86 (CH_3SO_3), −5.69 (Me_3Ge); X = $SnMe_3$, mp 87–89 °C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.93 (3 H, s, CH_3SO_3) 2.09–2.00 (6 H, m, CH_2CH_2), 1.90–1.80 (6 H,

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m, CH_2CH_2), −0.06 (9 H, s, Me_3Sn), ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.07 (C1), 32.48 (C2), 31.62 (C3), 20.65 (C4), 40.91 (CH_3SO_3), −12.45 (Me_3Sn).

Conductance Kinetics Procedure. Solvolysis rates were measured conductometrically following the proceudure published earlier.[51] For reactions having half-lives of several hours or longer the reactant was dissolved in the solvent, mixed outside the bath, and the solution was added to an unstirred cell of approximately 10-mL volume that was placed in the bath and allowed about 20 min to come to temperature. For faster reactions, 100-mL magnetically stirred cells filled with solvent were allowed to temperature equilibrate in the bath for about 20 min or longer before the reactant was added. Reactant concentrations were about 10^{-3} M. Two- to four-hundred resistance readings were taken at intervals of approximately equal reaction over about 2 half-lives in the range of 10% to 90% reaction. Concentrations derived from the resistance readings using the limiting conductance law with experimentally determined constants for the particular product acid in the particular solvent fit the first-order rate law with standard deviations in the derived rate constants of 0.1% or better.

The resistance residuals were generally in the range of ±0.08% and showed no systematic trends greater than ~0.10% through the course of the reaction; reproducibility of the rate constants was generally ±0.5% or better. Temperatures of the thermostat baths for the reaction rate experiments were determined with a Mueller bridge and a calibrated platinum resistance thermometer with an accuracy of ±0.001 °C. The bath temperature control was also in the range of ±0.001 °C except at the two lower temperatures where control was more difficult and was maintained in the range of ±0.007 °C.

Since 4-(trimethylstannyl)bicyclo[2.2.2]octyl mesylate was too reactive in 97% trifluoroethanol–3% water (97T) for its rate to be measured by our conductance technique at 25 °C, this rate constant was obtained by extrapolation from rates measured at lower temperatures.

Conductance parameters for methanesulfonic acid in 97T at temperatures below 25 °C were determined by the "kinetic" method[52] with 4-(trimethylstannyl)bicyclo[2.2.2]octyl mesylate. The required "infinity" concentrations were determined from the conductance of the cell at 25 °C after the end of the reaction and corrected for the change in density of the sovlent with temperature.

The values for the temperatures, densities, limiting conductances (Λ_0) and slopes (S_α) were as follows: −14.545, 1.4336, 8.06, 34.71; −10.000, 1.4266, 9.96, 57.88; 0.000, 1.4105, 14.27, 66.33; 10.000, 1.3956, 18.75, 69.98; 25.000, 1.3726, 28.5, 119.3; 35.000, 1.3570, 32.67, 130.3. The conductance parameters for the temperatures other than 25 °C are probably accurate to only about ±10% but should be good enough to give satisfactory rate constants. The Arrhenius plot for the trimethylstannyl compound gives a correlation coefficient of 0.99988 and the standard deviation in the rate constant projected to 25 °C is ±5%.

Product Determination. The products of solvolysis of the silyl, germyl, and stannyl mesylates (**1b**: X = $SiMe_3$, $GeMe_3$, and $SnMe_3$, respectively) in perdeuterated 80E, 100E, and 97T were determined by analysis of the proton NMR in the following manner. A solution of the ester (0.1 M) in perdeuterated solvent, buffered with 2,6-lutidine, was put in an NMR tube, capped lightly, and allowed to stand for 10 half-lives after which the NMR spectra were taken. Resonances due to direct substitution were easily identified by comparison to spectra of the authentic alcohols **1** (Y = OH, X = Me_3M). 1,4-Dimethylenecyclohexane was assigned to the resonances at 2.00 and 4.49 ppm (relative area 1:1) in 80E. This is in agreement with the literature values of 2.27 and 4.74 ppm for the same compound in vinyl chloride solution.[53] The destannylation product, $(CH_3)_3SnOR$, was assigned to the singlet at 0.41 ppm (J = 68.4 Hz).

Acknowledgment. Support of the work at Indiana University from the National Science Foundation, Grants No. CHE-85-06682 (project support) and No. CH-81-05004 (NMR Instrumentation), is gratefully acknowledged. We also thank the Australian Research Council for financial support.

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Simultaneous Hydrogen Bonding and Metal Coordination Interactions in the Two-Point Fixation of Amino Acids with a Bifunctional Metalloporphyrin Receptor[1]

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Abstract: The organometallic acetone–Rh(III) derivative of 5,15-*trans*-bis(2-hydroxy-1-naphthyl)octaethylporphyrin (**1b**) reversibly forms two-point adducts in $CHCl_3$ with *o*-aminobenzoic acid (**2b**, a rigid β-amino acid) and its methyl ester (**2a**) via simultaneous Rh(III)–NH_2– coordination and OH–CO_2R hydrogen bonding (R = H or CH_3). The weaker interaction, hydrogen bonding (HB), was characterized from spectroscopic as well as thermodynamic viewpoints: for adduct **1b–2a**, K_{HB} = 9.5 and $\Delta G°_{HB}$ = −1.3 kcal/mol at 288 K ($\Delta H°_{HB}$ = −2.8 kcal/mol and $\Delta S°_{HB}$ = −5.3 cal/mol·K); for adduct **1b–2b**, K_{HB} = 107 and $\Delta G°_{HB}$ = −2.7 kcal/mol at 288 K ($\Delta H°_{HB}$ = −3.6 kcal/mol and $\Delta S°_{HB}$ = −3.0 cal/mol·K), where K_{HB} is the selectivity factor due to the hydrogen bonding. α-Amino esters also form similar two-point adducts; for the phenylalanine methyl ester adduct, K_{HB} = 42 and $\Delta G°_{HB}$ = −2.1 kcal/mol at 288 K. The importance of hydrogen bonding, however, sharply decreases in going from flexible β- through γ- to ε-amino ester adducts. The intermolecular hydrogen bonding of **1b** and methyl acetate (K_{HB} = 0.38 M^{-1} and $\Delta G°_{HB}$ = 0.56 kcal/mol at 288 K) ($\Delta H°_{HB}$ = −2.4 kcal/mol and $\Delta S°_{HB}$ = −10.2 cal/mol·K) is a weak interaction. On the other hand, the hydrogen bonding in adduct **1b–2a** is essentially intramolecular in nature and takes place much more readily owing to a less unfavorable entropy change; it thus makes a significant contribution to the stability and selectivity of the resulting adduct. Such α-amino acids as phenylalanine, leucine, isoleucine, and 2-aminohexanoic acid (norleucine) are readily extracted from neutral aqueous solutions into $CHCl_3$ upon formation of similar two-point **1b**–(amino acid) adducts, in marked contrast to alanine, serine, and 6-aminohexanoic acid, which are not extractable; sufficient lipophilicities of amino acids as well as intramolecular hydrogen bonding in the adducts play crucial roles. Selective transport of lipophilic α-amino acids through a $CHCl_3$ liquid membrane was also achieved with **1b** as a carrier.

Multipoint interaction plays an essential role in the functions of proteins as biological catalysts, receptors, and carriers. Much recent interest in the host–guest associations[4] has been directed to the multipoint molecular recognition of polar organic compounds

0002-7863/90/1512-3145$02.50/0