Mechanistic Definition of Trimethylstannylation of 1,4-Dihalobicyclo[2.2.1]heptanes: Bridgehead Nucleophilic Substitution Mediated by the Intermediacy of Radicals, Radical Anions, Carbanions, and [2.2.1]Propellane[1]

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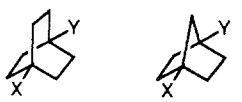
A series of 1,4-dihalobicyclo[2.2.1]heptanes (2; X = Y = halogens) have been synthesized, characterized, and treated with (trimethylstannyl)lithium (Me_3SnLi) in the absence and presence of *tert*-butylamine (TBA). The product distributions of these reactions have been established by ^{13}C and ^{119}Sn NMR spectroscopy and vapor-phase chromatographic analyses. The results clearly indicate that a polar mechanism involving the formation of a carbanion can compete effectively in these systems against a free-radical chain process ($S_{RN}1$). The latter mechanism was previously shown to dominate the stannlyation reactions of 1,4-dihalobicyclo[2.2.2]octanes (1; X = Y = halogens). Most of the initially formed (4-halo(X)bicyclo[2.2.1]hept-1-yl)lithium derivatives (2; X = halogen, Y = Li) collapse partially (X = Cl) or completely (X = Br and I) to yield the highly reactive [2.2.1]propellane, which serves as a transient intermediate in the stannylation process. Most importantly, the competition between the radical and polar mechanisms in 2 is shown to be dependent not only on the nature of the leaving group (Y = Br or I) but also on the substituent (X = H, F, Cl, Br, or I). Factors governing the partitioning between the two mechanisms are considered.

Recently,[2] based on the product distribution results of a specific deuterium labeling experiment and, as well, a radical trapping experiment with dicyclohexylphosphine,[3,4] we proposed that the reaction of 1-bromo-4-iodobicyclo-[2.2.2]octane (1; X = Br, Y = I) with (trimethylstannyl)-



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lithium (Me_3SnLi) in THF at 0 °C occurs by a radical chain mechanism (Scheme I; $m = 8$, $n = 12$; X = Br, Y = I) similar to the $S_{RN}1$ mechanism.[5] A major difference, however, is an additional propagation step involving iodine atom abstraction from 1 (X = Br, Y = I) by the 4-(trimethylstannyl)bicyclo[2.2.2]oct-1-yl radical intermediate (Scheme I, step 5).[6] This mechanistic proposal (Scheme I) is strongly corroborated by the fact that the unusual results of a product distribution analysis of a series of 1,4-dihalobicyclo[2.2.2]octanes[2] becomes readily intelligible on the basis of this dissociative electron-transfer-initiated process. It should be noted that almost simultaneous to our publication,[2] Ashby et al.[7] presented strong evidence for a somewhat similar electron-transfer process involving radical intermediates in the reaction of Me_3SnNa with primary alkyl halides.

The key feature of the mechanism (Scheme I) is the formation (step 2) and subsequent fate (steps 3 and 4) of the halo tin radical anion ($[XC_mH_nSnMe_3]^{\bullet-}$). This species decomposes by two competitive pathways (bimolecular intermolecular electron transfer (step 3) and unimolecular fragmentation induced by intramolecular electron transfer (step 4)) whose relative rates ($k_t[XC_mH_nY]$ vs k_f, respectively) depend importantly on both operational (concentration, rate and order of addition of reactants, extent of reaction, etc.) and intrinsic parameters. The product distribution results[2] suggest that there is essentially no competition between steps 3 and 4 for system 1 (Scheme I; $m = 8$, $n = 12$; $k_t[XC_8H_{12}Y] \gg k_f$ or $k_f \gg k_t[XC_8H_{12}Y]$) when X = F, Y = Br or I and X = Br, Y = Br or X = I, Y = I, respectively. However, the situation appears to be competitive for 1 ($k_t[XC_8H_{12}Y] \approx k_f$) when X = Cl, Y = Br or I and X = Br, Y = I. Interestingly, we discovered inadvertently that if a THF solution of the chloro iodide (1; X = Cl, Y = I) is added dropwise to the Me_3SnLi reagent at 0 °C (the usual order of addition is the reverse mode), the product is almost exclusively the ditin compound (1; X = Y = $SnMe_3$) rather than a mixture dominated by the chloro tin derivative (1, X = Cl, Y = $SnMe_3$).[2] This result implies that under these conditions step 3 is unable to compete effectively against step 4 ($k_f \gg k_t[XC_8H_{12}Y]$) because of the lack of an effective electron acceptor (concentration of $ClC_8H_{12}I$ very low). It is important to remember that the chloro tin derivative is unreactive toward Me_3SnLi under the conditions,[2] and, therefore, is not an intermediate in the formation of the ditin compound.

In view of the current interest in electron-transfer-induced processes involving organic systems,[5,8,9] we have

(1) (a) Reported in part at the VIII IUPAC Conference on Physical Organic Chemistry, Tokyo, Japan, August 24–29, 1986. (b) Physical Organic Chemistry 1986, A Collection of the Invited Lectures Presented at the 8th IUPAC Conference on Physical Organic Chemistry; Kobayashi, M., Ed.; Tokyo, Japan, August 24–29, 1986. *Studies in Organic Chemistry*; Elsevier Science Publishers B.V.: Amsterdam, 1987; Vol. 31, pp 227–234.

(2) Adcock, W.; Iyer, S. W.; Kitching, W.; Young, D. *J. Org. Chem.* **1985**, *50*, 3706.

(3) (a) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833. (b) Alnejjar, M. S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416.

(4) (a) The presence of *tert*-butylamine (carbanion trap)[3] has no effect on the product distribution of the reaction between 1-bromo-4-iodobicyclo[2.2.2]octane (1; X = Br, Y = I) and Me_3SnLi.[4b] (b) Iyer, S. V. Ph.D. Dissertation, The Flinders University of South Australia, 1986.

(5) For reviews, see: (a) Kornblum, N. *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1982; Supplement F, Chapter 10. (b) Rossi, R. A.; de Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*; *ACS Monograph 178*; American Chemical Society: Washington, DC, 1983. (c) Norris, R. K. *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1983; Supplement D, Chapter 16.

(6) (a) The rate constants of the forward and back reactions for the equilibrium between alkyl radicals and alkyl iodides are normally very fast ($>10^6$ M^{-1} s^{-1}). Further, the position of the equilibrium is essentially governed by the relative stability of the two radicals.[6b] (b) Hawari, J. A.; Kanabus-Kaminska, J. M.; Wayner, D. D. M.; Griller, D. *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; D. Reidel Publishing Co.: Dordrecht, 1986; pp 91–105.

(7) Ashby, E. C.; Su, W. Y.; Pham, T. N. *Organometallics* **1985**, *4*, 1493.

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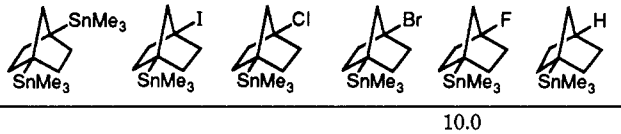
Table I. Product Distribution Analysis of the Reaction between 1,4-Dihalobicyclo[2.2.1]heptanes (2) and (Trimethylstannyl)lithium in THF and Some Mixed Solvents

entry no.	compound	equiv of Me_3-SnLi	additive[b]	solvent[c]	product distribution ratios[a] 	extent of reaction,[d] %
1	2; X = F, Y = I	1.5	none	THF	10.0 1.0	85
2	2; X = F, Y = I	1.5	TBA	THF	1.1 1.0	100
3	2; X = Cl, Y = I	1.5	none	THF	8.0 16.0 6.0 1.0 1.3	88
4	2; X = Cl, Y = I	2.0	none	THF	5.1 2.1 2.3 1.0 1.0	98
5	2; X = Cl, Y = I	1.5	TBA	THF	1.0 trace 1.7 6.8	80
6	2; X = Br, Y = I	1.5	none	THF	10.0 19.0 trace 1.0 1.1	80
7	2; X = Br, Y = I	1.7	none	THF	2.4 2.6 trace 1.0 1.5	90
8	2; X = Br, Y = I	1.5	TBA	THF	1.0 trace 7.3 8.0	84
9	2; X = I, Y = I	1.5	none	THF	6.0 10.0 2.0 1.0	82
10	2; X = I, Y = I	2.0	none	THF	9.0 9.3 4.5 1.0	100
11	2; X = I, Y = I	1.5	TBA	THF	1.0 trace 10.0 2.5	88
12	2; X = Cl, Y = Br	1.5	none	THF	2.7 3.9 1.0 1.1	62
13	2; X = Cl, Y = Br	2.0	none	THF	3.1 6.4 1.3 1.0	84
14	2; X = Cl, Y = Br	1.5	TBA	THF	1.6 3.7 1.0 4.3	82
15	2; X = Cl, Y = Br	1.5	none	THF	14.0 6.4 trace 1.0 trace	80
16	2; X = Cl, Y = Br	1.5	TBA	THF	1.8 2.6 1.0 4.7	84
17	2; X = Br, Y = Br	1.5	none	THF	13.0 1.7 4.7 1.0	60
18	2; X = Br, Y = Br	2.0	none	THF	4.7 1.6 4.4 1.0	80
19	2; X = Br, Y = Br	1.5	TBA	THF	1.0 trace 8.7 1.9	60
20	2; X = Cl, Y = I	1.5	none	THF + TG[e]	6.3 1.3 4.3 1.0 10.4	75
21	2; X = Br, Y = I	1.5	none	THF + TG[e]	4.1 1.0 2.4 1.8	70
22	2; X = I, Y = I	1.5	none	THF + TG[e]	1.0 3.0 1.0	75
23	2; X = Cl, Y = Br	1.5	none	THF + TG[e]	1.7 1.8 trace 1.0 3.5	80
24	2; X = Cl, Y = Br	1.5	none	THF + DOD[e]	12.0 8.4 1.0[f] 1.0	80
25	2; X = Br, Y = Br	1.5	none	THF + TG[e]	2.3 trace 1.0 4.0	60
26	2; X = Br, Y = Br	1.5	none	THF + DOD[e]	7.1 1.0 1.0[f] trace	65

[a] The VPC product ratios were determined by comparison of peak areas by using the cut and weight technique, giving errors of about 4%. Peak areas were not corrected for appropriate response factors; therefore, the results must be viewed as being semiquantitative rather than quantitative. [b] TBA = *tert*-butylamine (10 molar equiv). [c] TG ≡ tetraglyme; DOD ≡ dodecane. [d] Based on the relative amount of unreacted starting material (±10%). [e] Me_3SnLi reagent in THF (ca. 5 mL) added to TG or DOD solution (ca. 5 mL). [f] Estimated from ^{119}Sn NMR spectrum. Could not be determined by VPC because retention time coincident with that for dodecane.

extended our trimethylstannylation studies to a series of 1,4-dihalobicyclo[2.2.1]heptanes (**2**) in order to test the scope and generality of the aforementioned chain mechanism (Scheme I) with respect to some other polycycloalkane substrates.

(8) (a) Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer-Verlag: Berlin-Heidelberg, 1987; Reactivity and Structure, Vol. 25. (b) Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212. (c) Chanon, M. *Acc. Chem. Res.* **1987**, *20*, 214. (d) Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414.
(9) Santiago, A. N.; Iyer, V. S.; Adcock, W.; Rossi, R. A. *J. Org. Chem.* **1988**, *53*, 3016 and references cited therein.

Herein we report the results of our study.

Results and Discussion

The results of the product distribution analysis of the reaction between Me_3SnLi and various 1,4-dihalobicyclo[2.2.1]heptanes (**2**; X = Y = halogen) in THF and some mixed solvent systems at 0 °C are assembled in Table I. Hexamethyldistannane, which is not listed, was identified as a significant reaction product in all instances. The product mixtures, which were all very clean and remarkably free of byproducts, were all fully characterized by ^{13}C

Scheme I[a-e]

$XC_mH_nY + Me_3Sn^- \rightarrow XC_mH_n^{\bullet} + Y^- + Me_3Sn^{\bullet}$ (step 1)

$XC_mH_n^{\bullet} + Me_3Sn^- \rightarrow [XC_mH_nSnMe_3]^{\bullet -}$ (step 2)

$[XC_mH_nSnMe_3]^{\bullet -} + XC_mH_nY \xrightarrow{k_3} XC_mH_nSnMe_3 + XC_mH_n^{\bullet} + Y^-$ (step 3)

$[XC_mH_nSnMe_3]^{\bullet -} \xrightarrow{k_4} X^- + {}^{\bullet}C_mH_nSnMe_3$ (step 4)

$XC_mH_nY + {}^{\bullet}C_mH_nSnMe_3 \rightleftharpoons YC_mH_nSnMe_3 + XC_mH_n^{\bullet}$ (step 5)

${}^{\bullet}C_mH_nSnMe_3 + Me_3Sn^- \rightarrow [Me_3SnC_mH_nSnMe_3]^{\bullet -}$ (step 6)

$[Me_3SnC_mH_nSnMe_3]^{\bullet -} + XC_mH_nY \xrightarrow{k_7} Me_3SnC_mH_nSnMe_3 + XC_mH_n^{\bullet} + Y^-$ (step 7)

${}^{\bullet}C_mH_nSnMe_3 + SH \rightarrow Me_3SnC_mH_{n+1} + S^{\bullet}$ (step 8)

$2Me_3Sn^{\bullet} \rightarrow Me_3SnSnMe_3$ (step 9)

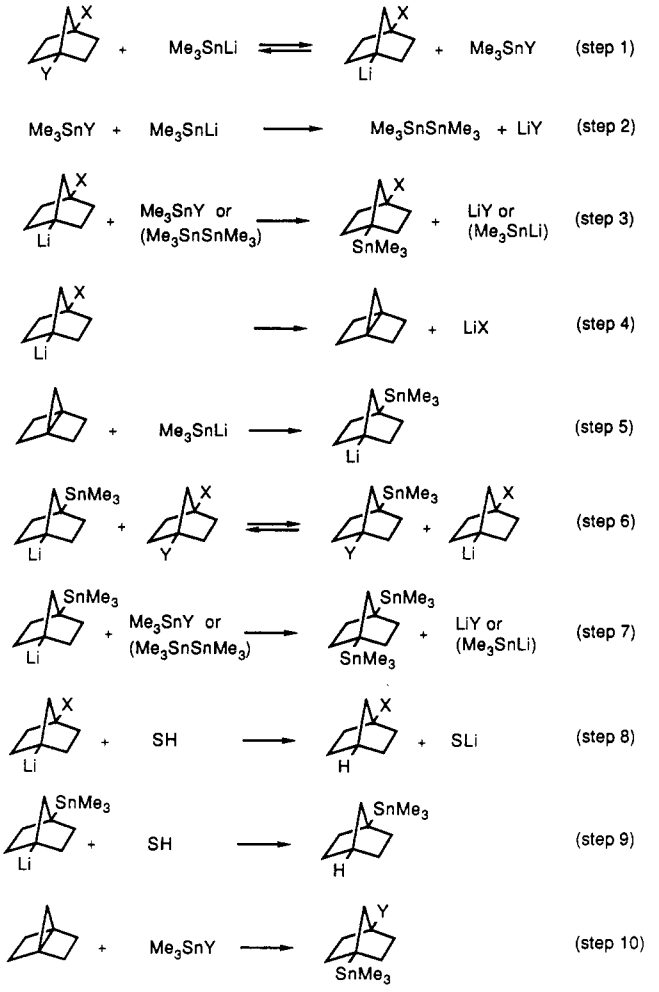
$XC_mH_n^{\bullet} + Me_3Sn^{\bullet} \rightarrow XC_mH_nSnMe_3$ (step 10)

[a] C_mH_n ≡ polycycloalkane; X = F, Cl, Br, or I; Y = Br or I. [b] Li^+ is understood to be present as the counter ion. [c] For expedience, the formation of a radical–halide anion adduct is understood to occur prior to steps 1, 3, and 7. [d] The tin reagent is given as being monomeric for the sake of pictorial clarity. However, it should be remembered that its state of aggregation is unknown. [e] Solvent ≡ SH.

and ^{119}Sn NMR and vapor-phase chromatography (VPC). In the case of the ^{119}Sn NMR and VPC analyses, the availability from another investigation[10] of authentic samples of 1-(trimethylstannyl)bicyclo[2.2.1]heptane (**2**; X = $SnMe_3$, Y = H) and 1,4-bis(trimethylstannyl)bicyclo[2.2.1]heptane (**2**; X = Y = $SnMe_3$) facilitated their identification in the various mixtures. The ^{13}C and ^{119}Sn NMR data for the tin derivatives of **2** have been presented elsewhere in connection with another study[10] and need not be reiterated here. It is important to note that although there were some significant discrepancies between the product distribution ratios determined by ^{119}Sn NMR and those by VPC, the trends from both analyses were obviously similar and quite unambiguous. Only the results of the VPC analyses are listed in Table I.

A scrutiny of the results (Table I) brings to light several noteworthy features. Firstly, it can be seen that the product mixtures obtained from the chloro and bromo iodides (entries 3 and 6, respectively) are not in accord with expectations based on the nucleofugality (or nucleofugicity) of the bridgehead halogen groups (I > Br ≫ Cl). Note that in both cases the iodo tin derivative (**2**; X = I, Y = $SnMe_3$) is clearly the dominant compound in each mixture. Thus, taken at face value, these results imply that both chlorine and bromine are better leaving groups than iodine in this nucleophilic substitution reaction. In fact, we have found that 1-chlorobicyclo[2.2.1]heptane is inert toward Me_3SnLi.[11a] A similar outcome has been reported for 1-apocamphyl chloride.[11b] At higher conversion levels of the chloro and bromo iodide reactants (entries 4 and 7), it can be seen (Table I) that the relative amount of the iodo tin compound in both mixtures decreases since it is consumed by the Me_3SnLi reagent to yield the ditin derivative (**2**; X = Y = $SnMe_3$). However, when both these reactions are effected in the presence of excess (10 molar equiv) *tert*-butylamine (TBA; entries 5 and 8), an excellent carbanion trapping agent,[3] only trace amounts of the iodo tin compound are observed in the product mixtures.[4a] The dominant compounds are now 1-chlorobicyclo[2.2.1]heptane for the chloro iodide case (entry 5) and 1-bromobicyclo[2.2.1]heptane together with the monotin compound (**2**; X = $SnMe_3$, Y = H) for the bromo iodide reaction (entry 8).

Scheme II[a-c]



[a] X = F, Cl, Br, or I; Y = Br or I. [b] See footnote *d* to Scheme I. [c] Solvent = SH.

Secondly, it can be seen that similar to the observations noted above for the chloro and bromo iodides, the product mixtures for the diiodo (entries 9 and 10) and dibromo compounds (entries 17 and 18) are also profoundly perturbed when the reactions are carried out in the presence of TBA (entries 11 and 19, respectively). For the latter reactions, the monotin compound (**2**; X = $SnMe_3$, Y = H) is clearly predominant in the product mixtures.

Finally, it can be seen that although the product mixtures obtained from the fluoro iodo and chloro bromo compounds (entries 1 and 12 or 13, respectively) are also significantly effected by the presence of TBA (entries 2 and 14 or 16), the perturbation is not nearly as pronounced as for the other aforementioned compounds.

(10) Adcock, W.; Gangodawila, H.; Kok, G. B.; Iyer, V. S.; Kitching, W.; Drew, G. M.; Young, D. *Organometallics* **1987**, *6*, 156.

(11) (a) We previously reported[2] that 1-chloro-4-methylbicyclo[2.2.2]octane does not react with Me_3SnLi (2 molar equiv) in THF at 0 °C over a 48 h period.[4b] Subsequently, we have found that this compound will react slowly at room temperature (40% conversion in 12 h) with excess Me_3SnLi to give a mixture of the tin and reduction product (30% and 10%, respectively). An intermolecular entrainment reaction was not observed when a mixture of the chloro methyl compound and 1-iodo-4-phenylbicyclo[2.2.2]octane was treated with Me_3SnLi (2 molar equiv) in THF at 0 °C (Krstic, A. R. Unpublished work). (b) Koermer, G. S.; Hall, M. L.; Traylor, T. G. *J. Am. Chem. Soc.* **1976**, *98*, 6764.

We believe a combination of the mechanistic pathways outlined in Schemes I[2] and II allows a complete rationalization of the above-mentioned observations as well as other nuances of the trimethylstannylation results (Table I) of the 1,4-dihalobicyclo[2.2.1]heptanes (2; X = Y = halogen). The first step in the polar mechanism (Scheme II) involves halogen–metal exchange (HME) between the dihalide and Me_3SnLi to form the appropriate (4-halo(X)bicyclo[2.2.1]hept-1-yl)lithium derivative (2; X = F, Cl, Br, or I; Y = Li). Such a metathetical exchange process is well known to readily occur for iodine at the bridgehead of bicyclo[2.2.1]heptane (BCH)[12,13] but not for bromine.[13] In fact it has been reported that 1-bromobicyclo[2.2.1]-heptane (2; X = Br, Y = H) and 1,4-dibromobicyclo-[2.2.1]heptane (2; X = Y = Br) are inert toward *tert*-butyllithium.[13] In view of our contrary observations in this study with the dibromo and chloro bromo derivatives, we were prompted to repeat the reaction between the dibromo compound and *tert*-butyllithium (see the Experimental Section). Although we did not carry out a complete product analysis, it is clear that lithium–bromine exchange occurs readily. The major product of the reaction is 1-*tert*-butylbicyclo[2.2.1]heptane, presumably formed via [2.2.1]propellane as an intermediate (see below).

The key feature of the polar mechanism (Scheme II) is the fate of the intermediate carbanion formed in step 1. It can be seen that this species can either react with Me_3SnY (Y = Br or I) or $Me_3SnSnMe_3$[14] to form the appropriate halo tin derivative (step 3) or undergo unimolecular fragmentation to yield [2.2.1]propellane (step 4). This highly reactive latter species has been invoked as an intermediate in various chemical[13,15] and electrochemical[16] studies, and, more recently, the compound has been trapped in a nitrogen matrix at ca. 30K and unambiguously characterized.[17] These studies suggest that [2.2.1]propellane, which possesses very high strain energy and, therefore, an extremely weak central bond (<20 kcal/mol), is exceptionally reactive toward nucleophiles, electrophiles, free radicals, and electrons.[18] Thus, it can be readily envisaged that [2.2.1]propellane will react facilely with Me_3SnLi, a super nucleophile,[19] to form (4-(trimethylstannyl)bicyclo[2.2.1]hept-1-yl)lithium (2; X = $SnMe_3$, Y = Li) (step 5). This new carbanion species can then either undergo rapid HME to form the appropriate bromo or iodo tin derivative (step 6) or react with Me_3SnY (Y = Br or I) or $Me_3SnSnMe_3$ to yield the ditin compound (step 7). It is significant to note that no bibicyclo[2.2.1]heptyl derivatives were identified in the various product mixtures. This suggests that the carbanions formed in steps 1 and 5 appear not to react significantly with the propellane. In contrast, Wiberg et al. observed such reactions on treatment of the bromo iodo and diiodo compounds with *tert*-butyllithium.[13] We believe this highlights the supernucleophilicity of Me_3SnLi compared to the latter reagent and bicyclo[2.2.1]hept-1-yl carbanions.

An alternative mode of trapping the propellane is by reaction with an available electrophile (Me_3SnY) to form the bromo or iodo tin derivatives directly (step 10). However, we favor step 5 over step 10 in Scheme II. The other minor competing steps (8 and 9) of the mechanism involve abstraction of a proton from the solvent (THF) by the carbanion intermediates to form reduction products. Alkyllithium compounds, being relatively strong bases, are well known to undergo such a reaction with ethers.[20]

The invocation of the elusive [2.2.1]propellane as an intermediate in the polar mechanism (Scheme II) is necessary in order to explain the aforementioned anomalous nucleofugality of the halogens in the stannylation of the chloro and bromo iodo derivatives. For both of these compounds, the product distribution ratios (Table I) suggest that steps 4 and 6 are faster than steps 3 and 7, respectively. It follows that this must also be the case for the diiodo compound as well. However, for the dibromo derivative, the product ratios (Table I, entries 17 and 18) clearly indicate that step 7 is faster than step 6. Interestingly, for the latter compound an additional consequence of step 6 (Y = Br) being relatively slow is that reduction appears to become relatively more important (steps 8 and 9) compared to the iodides (2; X = Cl, Y = I; X = Br, Y = I; X = Y = I) where step 6 (Y = I) is fast.

The formation of significant amounts of the chloro tin derivative (which is unreactive toward Me_3SnLi) in the product mixture of the chloro iodide (Table I, entries 3 and 4) indicates that step 3 is competitive with step 4 when X = Cl. However, this is not the case when X = Br, and presumably also when X = I, since only trace amounts of the bromo tin derivative is formed from the bromo iodide (Table I, entries 6 and 7). Only in the case of the fluoro iodide (Table I, entry 1) is step 4 obviated (indicated by the complete absence of the monotin (2; X = $SnMe_3$, Y = H) and ditin (2; X = Y = $SnMe_3$) compounds) and the course of the reaction predominantly governed by step 3. It is important to note though that fragmentation of (4-fluorobicyclo[2.2.1]hept-1-yl)lithium to [2.2.1]propellane is observed if it is generated in the absence of an efficient trapping agent, namely, by treating the fluoro iodide with *tert*-butyllithium (see the Experimental Section). Thus, the observed competition between steps 3 and 4 reflects the anticipated kinetic stability of the 4-halo(X)bicyclo-[2.2.1]hept-1-yl anions (X = F > Cl > Br > I). That these anions do not undergo a Grob-like fragmentation[21] is confirmed by the absence of 1,3-dimethylenecyclopentane[5c] in any of the various product mixtures.

In the presence of TBA, quenching of the initially formed carbanion is dominant (step 8). Hence, steps 3–7 of Scheme II are precluded. However, it is possible that when X = Br or I step 4 may still compete effectively with step 8 under these conditions, and, therefore, an additional quenching step (step 9) may also be important. It is significant that if [2.2.1]propellane is produced in the presence of TBA it appears not to react with this relatively strong nucleophile.

If it is assumed that TBA functions with unit efficiency, then the formation of significant amounts of the halo tin or ditin compound (or both) under these circumstances is

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(15) (a) Wilcox, C. F.; Leung, C. *J. Org. Chem.* **1968**, *33*, 877. (b) Stohrer, W. D.; Hoffmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 779. (c) Wiberg, K. B.; Bailey, W. F.; Jason, M. E. *J. Org. Chem.* **1976**, *41*, 2711.

(16) (a) Carroll, W. F.; Peters, D. G. *Tetrahedron Lett.* **1978**, 3543. (b) Carroll, W. F.; Peters, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 4127.

(17) Wiberg, K. B.; Michl, J.; Walker, F. H. *J. Am. Chem. Soc.* **1982**, *104*, 2056.

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indicative of an additional mechanistic pathway. Based on the results of the 1,4-dihalobicyclo[2.2.2]octanes,[2] it seems reasonable to assume that we are dealing with a competing $S_{RN}1$ type process (Scheme I). The fact that the chloro tin compound (**2**; X = Cl, Y = $SnMe_3$) is inert toward Me_3SnLi and, therefore, is not an intermediate in the formation of the ditin compound (**2**; X = Y = $SnMe_3$) in the case of the chloro iodo and chloro bromo derivatives (Table I, entries 3–5 and 12–16, respectively) constitutes powerful evidence for this free radical chain pathway (Scheme I).

Although it is not possible to accurately quantify the apportionment of each mechanism to the overall reaction in each case, it is clear that the carbanion trapping experiments suggest that the halogen–metal exchange (HME) pathway (Scheme II) is overwhelmingly predominant (ca. 85 ± 10%) for the dibromo, bromo iodo, and diiodo compounds, clearly predominant (ca. 70 ± 10%) for the chloro iodo compound, and very significant (ca. 50 ± 10%) for the fluoro iodo and chloro bromo derivatives. It is noteworthy that we discovered inadvertently that the composition of the product mixture from stannylation of the chloro bromo compound is variable (cf. entry 15 to entries 12 and 13). We ascribe this phenomenon to operational parameters (dilution, rate of addition of Me_3SnLi, etc.) impinging on the competition between the two key steps (step 3 vs step 4) of the radical chain mechanism (Scheme I), which contributes significantly (ca. 50%) to the overall reaction of this compound. Alternatively, the Me_3SnLi reagent may contain varying amounts of unreacted $Me_3SnSnMe_3$ which impinges on the competition between steps 3 and 4 of the polar mechanism (Scheme II).

In connection with the mechanistic dissections given above for the dihalo derivatives of **2** it is of interest to note the results of stannylation of 1-bromo- and 1-iodobicyclo[2.2.1]heptane in the absence and presence of TBA. Treatment of both compounds in THF at 0 °C with 2 molar equiv of Me_3SnLi led to complete reaction to yield (bicyclo[2.2.1]hept-1-yl)trimethylstannane and bicyclo[2.2.1]heptane in the following ratios (determined by VPC): 7:1 (no TBA) and 6.8:1 (TBA) for the *bromide* and 7.4:1 (no TBA) and 1:1 (TBA) for the *iodide*. Thus, whereas 1-bromobicyclo[2.2.1]heptane appears to react exclusively by the radical pathway, 1-iodobicyclo[2.2.1]heptane reacts by both the radical (ca. 60%) and HME (ca. 40%) pathways. The latter dissection is based on the reasonable assumption that the reduction product formed in the absence of TBA is the consequence of hydrogen atom abstraction from the solvent by the highly reactive bicyclo[2.2.1]hept-1-yl radical[22] rather than the less reactive corresponding anion.[12] A comparison of these results for the 1-halobicyclo[2.2.1]heptanes with those disclosed above for the corresponding 4-halo derivatives leads to the important conclusion that the degree of HME (Scheme II) vs radical reaction (Scheme I) for stannylation of **2** (X = Y = halogen) is markedly substituent dependent in the order I ~ Br > Cl ≫ F.

Finally, it is of interest to note the product distribution results of stannylation of the 1,4-dihalobicyclo[2.2.1]heptanes in some mixed solvents (Table I, THF + tetraglyme (TG) and THF + dodecane (DOD)). These experiments were specifically carried out with the express purpose of determining whether or not an increase in viscosity of the solvent would promote trapping of the initially formed reactive species (carbanion or radical). It is known that if the latter are formed in a solvent cage, coupling within the cage is enhanced by increasing the viscosity of the medium.[3b,7,23] It can be seen (Table I) that the relative amounts of the appropriate halo tin compounds (**2**; X = Cl, Br, or I; Y = $SnMe_3$) for the mixed solvents are not increased compared to the corresponding results in THF. Thus, a significant cage effect is not apparent. However, there is no doubt that the product distribution is markedly influenced by the nature of the solvent. In particular, note that in the presence of TG the relative amounts of reduction products (**2**; X = $SnMe_3$, Y = H and X = halogen, Y = H) are significantly increased (see entries 20–23 and 25 in Table I). This result can probably be ascribed to the better cation chelating ability of TG compared to THF,[3b,7] which consequently enhances the basicity of the (bicyclo[2.2.1]hept-1-yl)lithium derivatives and, therefore, leads to steps 8 and 9 being relatively more important. It is worth noting that by changing the viscosity of the solvent without changing the cation chelation ability (THF + DOD; entries 24 and 26, Table I) and, in addition, also lowering the proton (and hydrogen atom) donating ability of the medium, the relative amounts of reduction products are significantly decreased. An additional interesting feature of the results in TG is the dramatic reduction in the relative amount of the iodo tin derivative (**2**; X = I, Y = $SnMe_3$) in the case of the chloro and bromo iodide and diiodide compounds (entries 20–22; Table I). Apparently, in the presence of TG, step 6 of Scheme II is now unfavorable compared to the other competitive steps. We are unable to offer a satisfactory explanation for this phenomenon except to point out that it may be related to the important role that the solvent plays in determining the reduction potential of alkyl halides.[24] Alternatively, a significant change in the mechanism may be responsible. We did not perform appropriate trapping experiments to test this particular possibility.

Conclusion

This study has revealed that substitution by Me_3Sn^- at the bridgehead of 1,4-dihalobicyclo[2.2.1]heptanes (**2**) can occur by an $S_{RN}1$ type mechanism (Scheme I) as previously proposed for 1,4-dihalobicyclo[2.2.2]octanes (**1**).[2] However, whereas the latter compounds appear to react almost exclusively by this mechanism, a polar mechanism involving the formation of a carbanion and, subsequently, [2.2.1]-propellane can compete effectively against the $S_{RN}1$ process in the former systems. Perhaps the most important revelation to emerge from this study is that the competition between the radical and polar mechanism in **2** is dependent not only on the nature of the leaving group (Y = Br or I) but also on the substituent (X = H, F, Cl, Br, or I). The former result was expected on the basis of other studies concerned with the mechanism of halogen–metal exchange.[25] However, the latter result, to the best of our knowledge, is unprecedented and highlights that the

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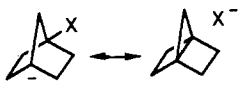
preference for one pathway over the other is delicately balanced in both systems. We believe that this fine tuning between the two mechanisms by such subtle structural changes strongly implies that the transition state for both processes must be fairly similar. By use of the configuration mixing model (CM) developed by Pross, Shaik, and others,[26] a model which has proved to be extremely useful in providing an understanding of the relationship between radical and polar pathways for nucleophilic substitutions at carbon centres,[8a,26] an appreciation of this conclusion can be attained. This requires invoking that both mechanisms involve a single electron shift in the transition state region. Thus, on this basis, a valence bond configurational description of the transition state for trimethylstannylation of bridgehead-substituted polycyclic alkyl halides is as shown in Scheme III. The relative magnitude of the

Scheme III

$$Me_3Sn^{\bullet}\ (Y^{-\bullet}\text{—}R\text{—}X)^{-} \equiv a(Me_3Sn^{\bullet}\ {}^{\bullet}Y\ {:}R\text{—}X) \leftrightarrow b(((Me_3Sn^{\bullet}\ {:}Y^{-}\ {}^{\bullet}R\text{—}X)$$

(R = polycyclic alkyl system; X = H, F, Cl, Br, or I; Y = Br or I)

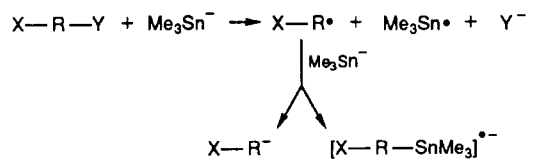
weighting factors (a and b) will govern the partitioning between the two mechanisms. When a carbanion mechanism is predominant, then $a \gg b$. For a dominant radical pathway, then $b \gg a$. The results of this study suggest that the relative magnitude of a and b can be significantly perturbed by three structural factors: (i) a increases relative to b when the leaving group (Y) is changed from Br to I. This is as expected on electronegativity grounds.[26a] (ii) a increases relative to b on increasing the s character of the appropriate exocyclic bridgehead orbital of R (cf 1 vs 2). This is understandable in terms of the electron being increasingly more delocalized between Y and R when R is more electronegative.[26a] (iii) a increases relative to b in the order I > Br > Cl > F ~ H for 2 (Y = Br and I). A consideration of the various possible substituent factors (polar field effect, polarizability, and homohyperconjugation) leads us to tentatively attribute the observed substituent dependency of the mechanistic competition to the latter phenomenon (denoted by canonical structures 3 and 4 for system 2). This has the effect of increasing the



3 4

delocalization of the electron[27] and, therefore, increasing a relative to b.[26a] The order of ability of the halogens to effect delocalization by homohyperconjugation should parallel their leaving-group ability (I > Br > Cl > F).[28] The relatively large fall-off factor with distance of substituent polarizability[29] effects precludes this phenomenon as a likely possibility. Polar field effects (characterized by σ_F (or σ_I) parameters) were discarded as a possible explanation because σ_F values for the halogens are virtually the same.[30]

Scheme IV



An alternative mechanistic description of the partitioning can be advanced based on the idea that a common free-radical intermediate mediates both pathways (Scheme IV). It can be seen that in this proposal the carbanion is formed by two successive electron transfers from Me_3Sn^-. The reducing power of the stannyl anionoid is sufficient to effect such a reduction.[8a,31] However, a serious deficiency of Scheme IV is that it is unable to accommodate the different apportionments between the two pathways observed for the chloro bromo and chloro iodo derivatives of 2 (see above). This conclusion is based on the fact that tin substitution products appear not to be formed significantly by in-cage or out-of-cage coupling of radical species (nonchain process).

Experimental Section

General. Melting and boiling points are uncorrected. Liquid samples were purified by distillation in a Kuhelrohr apparatus (Büchi: GKR-50). Hence, the boiling points quoted pertain to the glass-oven temperature of the latter equipment. Analytical vapor-phase chromatographic (VPC) analyses were performed on Varian 1740 and Perkin-Elmer Sigma 3B gas chromatographs using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W and a 6-ft column of 10% Carbowax 20M on Chromosorb G, respectively. Preparative VPC were carried out on a Shimadzu (GC-9A) gas chromatograph. Mass spectra were obtained on an AEI MS30 spectrometer with an ionizing energy of 70 eV.

The broad-band proton-decoupled ^{13}C and ^{119}Sn NMR spectra were recorded at 22.53 and 33.34 MHz, respectively, in the pulse Fourier transform mode on a JEOL FX-90Q spectrometer. The same instrument was employed for recording proton-decoupled ^{19}F NMR spectra. Routine ^1H NMR spectra were measured with a Varian EM-360 (60 MHz).

Tetrahydrofuran and tetraglyme were distilled from sodium benzophenone ketyl and sodium, respectively, under an atmosphere of dry nitrogen. *tert*-Butylamine was dried over potassium hydroxide and distilled immediately before performing the reactions. The trimethylstannylation reactions were performed under argon in flame-dried glassware.

Compounds. Literature procedures were followed in the preparation of 1-chloro-[32] and 1-iodobicyclo[2.2.1]heptane[12b] and 1-fluoro-4-iodobicyclo[2.2.1]heptane.[33] (Bicyclo[2.2.1]hept-1-yl)trimethylstannane[10] and 1,4-bis(trimethylstannyl)bicyclo-[2.2.1]heptane[10] were available from another study. A sample of 1-bromobicyclo[2.2.1]heptane was kindly donated by Dr. E. W. Della.

4-Carbomethoxybicyclo[2.2.1]heptane-1-carboxylic Acid (2; X = COOH, Y = $COOCH_3$). A solution of dimethyl bicyclo[2.2.1]heptane-1,4-dicarboxylate (2; X = Y = $COOCH_3$;[34] 10.5 g, 0.05 mol), barium hydroxide octahydrate (7.53 g, 0.024 mol), methanol (100 mL), and water (22 mL) was stirred for 42 h at ambient temperature. The resulting suspension was diluted with water and then extracted with ether to remove the unreacted diester (2; X = Y = $COOCH_3$; 1.2 g). The aqueous phase was acidified with concentrated hydrochloric acid and then extracted with carbon tetrachloride (4 × 1). Drying and removal of the solvent in vacuo followed by sublimation (95 °C/0.05 mm) of the

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pale yellow residue afforded the half-ester (2; X = COOH, Y = $COOCH_3$) as a colorless solid (5.7 g, 78% yield based on consumed starting material): mp 101–105 °C (lit.[15a] mp 114–115 °C); ^1H NMR (CCl_4) δ 1.67–2.17 (10 H, m, CH_2CH_2 and CH_2), 3.73 (3 H, s, CH_3), 8.33 (1 H, broad s, COOH); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 52.82 (C1), 32.88, 32.99 (C2 and C3), 52.50 (C4), 44.96 (C7), 175.50 ($COOCH_3$), 181.48 (COOH), 51.74 ($COOCH_3$).

The acidic aqueous phase was saturated with sodium chloride and reextracted with ether. The ether extracts were dried and the solvent removed to afford bicyclo[2.2.1]heptane-1,4-dicarboxylic acid (1.4 g).

4-Chlorobicyclo[2.2.1]heptane-1-carboxylic Acid (2; X = Cl, Y = COOH). The half-ester (2; X = COOH, Y = $COOCH_3$; 8.5 g, 0.043 mol) was treated with thionyl chloride in a standard manner to give the acid chloride (2; X = COCl, Y = $COOCH_3$). By use of the procedure of Barton et al.,[35] a solution of the acid chloride in carbon tetrachloride (10 mL) was added slowly to a well-stirred fine suspension of *N*-hydroxypyridine-2-thione sodium salt (7.05 g, 47.3 mmol) in the same solvent (100 mL) at reflux containing a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine. After the evolution of carbon dioxide had ceased, the reaction mixture was worked up in a standard manner to afford an oil. Treatment of the oil with aqueous ethanolic potassium hydroxide in the manner previously outlined for the hydrolysis of the methyl and ethyl esters of 4-methoxy-2-oxobicyclo[2.2.2]octane-1-carboxylic acid[36] gave, after sublimation, the desired chloro acid as a colorless solid (2; X = Cl, Y = COOH; 5.85 g, 78%). A sample was recrystallized from methanol to afford colorless needles: mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 1.77–2.27 (10 H, m, CH_2CH_2 and CH_2), 8.7 (1 H, broad s, COOH); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 49.60 (C1), 33.70 (C2), 38.46 (C3), 68.45 (C4), 49.49 (C7), 181.29 (COOH). Anal. Calcd for $C_8H_{11}O_2Cl$: C, 55.02; H, 6.35. Found: C, 55.35; H, 6.20.

1-Bromo-4-chlorobicyclo[2.2.1]heptane (2; X = Cl, Y = Br). The chloro acid (2; X = Cl, Y = COOH; 2.3 g, 13.2 mmol) was treated with red mercuric oxide and bromine in dichloromethane as previously described for the preparation of 1-bromo-4-fluorobicyclo[2.2.2]octane.[36] A standard workup, followed by Kugelrohr distillation (90 °C/7 mm), afforded the title compound as a colorless solid (2.46 g, 89%). A sample was recrystallized from methanol: mp 74.5–75.5 °C; ^1H NMR (CCl_4) δ 1.93–2.27 (m); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 56.28 (C1), 41.26 (C2), 40.37 (C3), 65.36 (C4), 55.00 (C7). Anal. Calcd for $C_7H_{10}BrCl$: C, 40.13; H, 4.81. Found: C, 40.26; H, 4.65.

1-Chloro-4-iodobicyclo[2.2.1]heptane (2; X = Cl, Y = I). The chloro acid (2; X = Cl, Y = COOH; 1.55 g, 8.9 mmol) was treated with *tert*-butyl hypoiodite and then irradiated in the same manner as previously described for the preparation of 1-fluoro-4-iodobicyclo[2.2.2]octane.[36] A standard workup, followed by careful sublimation (1.56 g, 69%) and recrystallization from methanol, gave the title compound as colorless leaflets: mp 40–41 °C; ^1H NMR (CCl_4) δ 1.87–2.5 (m); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 64.81 (C1), 40.93 (C2), 44.47 (C3), 30.55 (C4), 57.40 (C7). Anal. Calcd for $C_7H_{10}ClI$: C, 32.78; H, 3.93. Found: C, 33.15; H, 4.26.

4-Bromobicyclo[2.2.1]heptane-1-carboxylic Acid (2; X = Br, Y = COOH). The half-ester (2; X = COOH, Y = $COOCH_3$; 4 g, 20.2 mmol) was treated with red mercuric oxide and bromine in dichloromethane as previously described for the preparation of 1-bromo-4-fluorobicyclo[2.2.2]octane.[36] A standard workup, followed by hydrolysis with aqueous ethanolic potassium hydroxide as indicated above for the corresponding chloro derivative (2; X = Cl, Y = COOH), gave the crude bromo acid (2.8 g, 63%). Sublimation afforded a colorless solid: mp 142–144 °C (lit.[15a] mp 148 °C); ^1H NMR ($CDCl_3$) δ 2.0–2.2 (10 H, m, CH_2CH_2 and CH_2), 9.73 (1 H, broad s, COOH).

1,4-Dibromobicyclo[2.2.1]heptane (2; X = Y = Br). The bromo acid (2; X = Br, Y = COOH; 1.5 g, 6.8 mmol) was bromodecarboxylated in the same manner as described above for the preparation of 1-bromo-4-chlorobicyclo[2.2.1]heptane (see above). After sublimation, the dibromide (2; X = Y = Br; 1.1 g, 63%) was obtained as a colorless solid: mp 73 °C (lit. mp 73 °C,[37] 73.5–74 °C[15c]); ^1H NMR (CCl_4) δ 1.97–2.35 (m); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 56.06 (C1, C4), 41.78 (C2, C3), 55.99 (C7).

1-Bromo-4-iodobicyclo[2.2.1]heptane (2; X = Br, Y = I). The bromo acid (2; X = Br, Y = COOH; 1.0 g, 4.57 mmol) was iododecarboxylated in the same manner as described above for the preparation of 1-chloro-4-iodobicyclo[2.2.1]heptane (see above). Sublimation of the crude product, followed by recrystallization from a mixture of hexane and methanol, afforded the bromo iodide (2; X = Br, Y = I; 0.83 g, 60%) as a colorless solid. A sample was purified by preparative gas chromatography: mp 65 °C (lit.[13] mp 64.5–65 °C); ^1H NMR (CCl_4) δ 1.98–2.37 (m); ^{13}C NMR ($CDCl_3$) δ 55.50 (C1), 42.30 (C2), 44.94 (C3), 30.27 (C4), 58.40 (C7).

4-Iodobicyclo[2.2.1]heptane-1-carboxylic Acid (2; X = I, Y = COOH). The half-ester (2; X = COOH, Y = $COOCH_3$; 5.5 g, 0.028 mol) was converted to methyl 4-iodobicyclo[2.2.1]heptane-1-carboxylate (2; X = I, Y = $COOCH_3$) by the iododecarboxylation procedure indicated above for the preparation of 1-chloro-4-iodobicyclo[2.2.1]heptane (see above). Kugelrohr distillation (105 °C/0.5 mm) afforded the iodo ester (2; X = I, Y = $COOCH_3$) as a colorless oil (5.91 g, 76%): ^1H NMR (CCl_4) δ 1.58–2.15 (10 H, m, CH_2CH_2 and CH_2), 3.77 (3 H, s, $COOCH_3$); ^{13}C NMR ($CDCl_3$) δ 49.89 (C1), 35.35 (C2), 43.29 (C3), 34.92 (C4), 53.52 (C7), 173.95 ($COOCH_3$), 51.84 ($COOCH_3$).

The iodo ester (2; X = I, Y = $COOCH_3$; 5.0 g, 0.018 mol) was hydrolyzed to the iodo acid (2; X = I, Y = COOH) via the procedure indicated above for the corresponding chloro derivative (see above). The crude pale yellow iodo acid was sublimed to afford a white solid (4.0 g, 84%). A sample was recrystallized from aqueous methanol to afford colorless plates: mp 120–121 °C; ^1H NMR ($CDCl_3$) δ 2.0–2.22 (10 H, m, CH_2CH_2 and CH_2), 8.77 (1 H, broad s, COOH); ^{13}C NMR ($CDCl_3$) δ 49.89 (C1), 35.21 (C2), 43.23 (C3), 34.59 (C4), 53.52 (C7), 180.51 (COOH). Anal. Calcd for $C_8H_{11}O_2I$: C, 36.09; H, 4.17. Found: C, 36.36; H, 4.10.

1,4-Diiodobicyclo[2.2.1]heptane (2; X = Y = I). The iodo acid (2; X = I, Y = COOH; 1.8 g, 6.8 mmol) was iododecarboxylated in the same manner as described above for the preparation of 1-chloro-4-iodobicyclo[2.2.1]heptane (see above). Sublimation afforded the diiodide (2; X = Y = I; 1.42 g, 60%) as a colorless solid: mp 98 °C (lit.[37] mp 101 °C, 102–103 °C[15c]); ^1H NMR (CCl_4) δ 1.92–2.43 (m); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 29.93 (C1, C4), 45.55 (C2, C3), 60.94 (C7).

Trimethylstannylation of 1-Halo- and 1,4-Dihalobicyclo[2.2.1]heptanes. The procedure was identical with that previously described[2] for the stannylation of the 1,4-dihalobicyclo[2.2.2]-octanes (1, X = Y = halogen).

Trimethylstannylation of 1-Halo- and 1,4-Dihalobicyclo[2.2.1]heptanes in the Presence of *tert*-Butylamine. The procedure was identical with that indicated above except that 10 molar equiv of dry *tert*-butylamine was added.

Treatment of 1-Fluoro-4-iodobicyclo[2.2.1]heptane (2; X = F, Y = I) with *tert*-Butyllithium. A solution of the fluoro iodide (2; X = F, Y = I; 0.21 g, 0.86 mmol) in dry diethyl ether (3 mL) was cooled to −80 °C and treated with 1.15 mL of 1.5 M *tert*-butyllithium (1.72 mmol) in pentane. After 10 min, the reaction mixture was allowed to warm to 0 °C (ca. 40 min), and then a solution of trimethylstannyl chloride (0.68 g, 3.44 mmol) in ether (5 mL) was added slowly. After stirring for 20 min at 0 °C, the reaction mixture was brought to reflux for 30 min and then cooled before quenching with saturated aqueous ammonium chloride. After a standard workup, the crude product mixture was analyzed by ^{19}F and ^{119}Sn NMR. No 1-fluorobicyclo[2.2.1]heptane, 1-fluoro-4-(trimethylstannyl)bicyclo[2.2.1]heptane or starting material could be detected. This analytical result indicates that lithiation and decomposition of the subsequent lithium derivative (2; X = F, Y = Li) was complete.

A repeat experiment was performed in which, after lithiation of the fluoro iodide (0.5 g, 2.1 mmol) at −80 °C and allowing the reaction mixture to warm to 0 °C, freshly distilled acetaldehyde (0.20 g, 4.2 mmol) was added dropwise. After a standard workup, the crude product mixture was analyzed by VPC, mass spectrometry, and NMR). The major product was 1-(4-*tert*-butylbicyclo[2.2.1]hept-1-yl)ethanol: mass spectrum, *m/e* 151 (M^+ –

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45). No starting material or 1,3-dimethylenecyclopentane could be detected. However, the presence of a small amount of 1-fluorobicyclo[2.2.1]heptane was confirmed by ^{19}F NMR. The remaining four components of the crude product mixture could not be unambiguously identified.

Treatment of 1,4-Dibromobicyclo[2.2.1]heptane (2; X = Y = Br) with *tert*-Butyllithium. A solution of the dibromide (2; X = Y = Br; 0.37 g, 1.45 mmol) in dry diethyl ether (5 mL) was treated with *tert*-butyllithium (2 equiv) as described above for the fluoro iodide (2; X = F, Y = I). After allowing the reaction mixture to warm to room temperature, saturated aqueous ammonium chloride was added followed by a standard workup. The crude reaction product was analyzed by VPC, mass spectrometry, and ^{13}C NMR. No starting material could be detected. The major product was 1-*tert*-butylbicyclo[2.2.1]heptane: mass spectrum, *m/e* 152 (M^+); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 54.50 (C1), 30.12 (C2), 30.94 (C3), 37.03 (C4), 38.40 (C7), 27.20 ($C(CH_3)_3$), 31.64 ($C(CH_3)$).

A small amount of 1-bromobicyclo[2.2.1]heptane was also detected.

Registry No. 2 (X = Y $COOCH_3$), 15448-76-7; 2 (X = COOH, Y = $COOCH_3$), 15448-77-8; 2 (X = Cl, Y = CO_2H), 123463-09-2; 2 (X = Cl, Y = Br), 123463-10-5; 2 (X = Cl, Y = I), 123463-11-6; 2 (X = Y = Br), 40950-22-9; 2 (X = Br, Y = I), 62947-51-7; 2 (X = Y = I), 40950-21-8; 2 (X = Br, Y = COOH), 15448-85-8; 2 (X = I, Y = $COOCH_3$), 123463-12-7; 2 (X = I, Y = COOH), 123463-13-8; 2 (X = F, Y = I), 84553-45-7; 2 (X = $CH(OH)CH_3$, Y = $C(CH_3)_3$), 123463-14-9; 2 (X = H, Y = $C(CH_3)_3$), 29339-31-9; Me_3SnLi, 17946-71-3; acetaldehyde, 75-07-0.

Interactive Computer Modeling of the Octant Rule: Applications to the CD of Floppy Molecules

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Computer-assisted structure–property studies of molecules involves the computer construction of a model and the use of this model to deduce the properties of a real molecule. Computer graphics, molecular mechanics, and conformation search methods have been combined with rule-based techniques to assist the prediction of CD properties from the geometric characteristics of a molecule. A computer package for CD–structure relationship studies has been developed which includes two main modules: CDexpert and RELATE. The octant rule for ketones has been implemented and tested on a number of rigid molecules. Application to CD studies of conformationally flexible molecules using the auxilliary program RELATE on the Boltzmann distribution of low-energy conformations allows excellent correlation with the temperature dependance of the CD.

Circular dichroism (CD)[1,2] is a common chiroptical method used to determine the absolute configuration of a compound as well as in conformational analysis,[3] and for determination of secondary structural changes in proteins or nucleic acids.[4] Interpretation of the CD spectrum involves the correlation of the CD with a geometric property such as absolute configuration. Most chemists use Dreiding models to construct the structural models.

We report in this paper a new computer package for CD studies which combines computer graphics and molecular mechanics with rule-based techniques to assist the prediction of CD properties from the three-dimensional structure of a molecule. Although computer programs have been used to calculate wave functions and transition moments in theoretical studies of CD,[5-7] no computer program for CD exists to make full use of techniques developed in recent years, such as interactive computer graphics and molecular mechanics. Our CDexpert program is a graphical implementation of empirical rules built around the well-known molecular modeling program MODEL.[8] An example of using CDexpert to predict the CD sign for a simple ketone is illustrated by the graphics output from an actual run on 2-decalone (Figure 1).

True theoretical approaches, except for quite simple molecules, usually do not give reliable numerical estimates of the Cotton effect or even the correct sign.[2] Our approach is a qualitative one and a natural implementation of the empirical rules. These rules predict the CD sign of a molecule based on certain geometric characteristics.[9]

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(9) Sector rules divide the space into certain sectors divided by the nodal surfaces of the chromophore. Examples are the "octant rule" for ketones,[1] the "left-handed octant rule" for chiral olefins[10] and the "lactone sector rule" for the five- and six-membered lactones.[11] Helicity rules relate the helicity of the structure or part of the structure to the CD sign an example being the rule for α,β-unsaturated ketones,[12] which relates the CD sign to the helicity of the C=CC=O chromophore. Chirality rules relate certain chiral characteristics of the geometry to the CD sign. Two rules which belong to this group are the allylic axial chirality rule[10] for chiral cyclohexene and "Ogura sign rule" for seven-membered lactams and lactones.[13] The exciton chirality method[17] developed by Nakanishi is an unique rule for relating the CD sign to the geometry of a molecule. It is derived from the molecular exciton theory[14] and deals with the Cotton effect resulting from the spatial interactions between two or more chromophores.

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