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CHLORIDE FOR BROMIDE SUBSTITUTIONS ON CARBON UTILIZING TRI-n-BUTYLTIN CHLORIDE

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Summary

A new halogen for halogen substitution reaction on carbon utilizing tri-n-butyltin halides is reported. The substitutions proceed to equilibrium positions rather than to completion. Mechanistic investigations indicate, at least for benzhydryl and secondary benzyl type bromides, that the substitutions using tri-n-butyltin chloride proceed via rate determining organotin halide assisted alkyl halide ionization for both the forward and reverse reactions.

Introduction

We have recently uncovered a new substitution reaction on carbon utilizing organotin reagents. As an example of this reaction, when benzhydryl bromide is heated at 50°C with tri-n-butyltin chloride in a 1/1 mol ratio for 2 h in the absence of a solvent, a 70% conversion to benzhydryl chloride is observed*:

$$(C_6H_5)_2CHBr + Bu_3SnCl \rightarrow (C_6H_5)_2CHCl + Bu_3SnBr$$

This substitution resembles the alkoxide for halide [1] and amino group for halide [2] substitutions on carbon using organotin reagents discovered by Pommier, Delmond, and coworkers. For the alkoxide for halide case, they have shown that a free-radical mechanism appears unlikely [1*a*]. Also, at least in intramolecular reactions with simple secondary alkyl halides, they have shown that backside displacement on carbon appears to be favored [1*h*,*k*,*l*].

Although the reaction of benzhydryl bromide with tri-n-butyltin chloride in a 1/1 mol ratio in the absence of a solvent was completed within several hours

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* In preliminary studies of the reaction of benzhydryl bromide with di-n-butyltin dichloride in n-heptane solution an analogous rapid chloride for bromide substitution on carbon was found to take place which utilizes both chlorines on tin.

at 50°C, under the same conditions but at 150°C benzyl bromide required approximately 10 h for 30% reaction. Also, 1-bromooctane or 2-bromooctane showed no detectable reaction after 100 h at 100°C. Thus, the chloride for bromide substitutions with tri-n-butyltin chloride seem to proceed readily only with those systems usually considered as being highly reactive in reactions proceeding via carbonium ion or free-radical intermediates.

Although the halogen for halogen substitution reactions on carbon utilizing trialkyltin halides appeared not to be of general utility, the preliminary results did indicate an interesting area for mechanistic study. The results of our initial mechanistic investigations are described below.

Results and discussion

For our present mechanistic studies of the halogen for halogen substitution reactions on carbon utilizing organotin reagents, we chose primarily to use benzhydryl bromide and tri-n-butyltin chloride as model substrates. This was because of their ready availability, and because their reactions were found to proceed smoothly at low temperatures and with good reproducibility. Also, their reactions could be followed conveniently by NMR. Thus, these could be carried out on small scale and analyzed directly without any workup being required.

To determine whether or not the substitution process is free radical in character, the effects of addition of free-radical initiators and inhibitors on the rate of substitution were examined. The reaction of benzhydryl bromide with tri-n-butyltin chloride, neat, in a 1/1 mol ratio at 85°C required about 7 min for 30% benzhydryl chloride formation under normal conditions in the absence of any additives and also under irradiation with ultraviolet light or in the presence of 4 mol % azobisisobutyronitrile or 20 mol % *p*-benzoquinone. Thus, as is the case with the alkoxide for halide substitutions [1*a*], the chloride for bromide substitution with benzhydryl bromide does not proceed via a free-radical mechanism and therefore must be ionic.

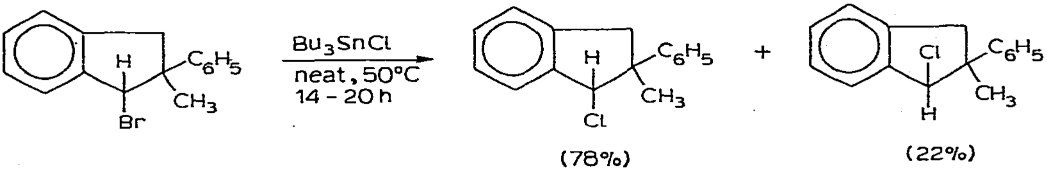
Preliminary studies had suggested that the chloride for bromide substitution on benzhydryl bromide with tri-n-butyltin chloride proceeded not to completion but rather to an equilibrium mixture. To substantiate this, individual reactions of benzhydryl bromide with tri-n-butyltin chloride, neat, at 50°C in 1/1, 1/2 and 1/4 mol ratios were allowed to proceed until they were unchanged on further heating. The percentages of benzhydryl chloride produced in each of these cases were 71 ± 1, 88 ± 1 and 95 ± 1, respectively; all corresponding within experimental error to an average equilibrium constant of 5.9. When the reverse reaction of a 1/1 mol ratio mixture of benzhydryl chloride and tri-n-butyltin bromide was heated at 50°C, an equilibrium mixture was obtained containing 70 ± 1% benzhydryl chloride.

The observation that these chloride for bromide substitutions proceed to equilibrium positions of the magnitude observed must mean that the C—Br to C—Cl bond dissociation energy difference in the benzhydryl halide system is almost identical to the Sn—Br to Sn—Cl bond dissociation energy difference in the tri-n-butyltin halide system. That this is not unreasonable is seen from consideration of the appropriate bond dissociation energy values reported for the benzyl (55 and 69 kcal/mol) [3] and trimethyltin (61 and 75 kcal/mol) [4] bromides and chlorides, respectively, where the differences in question are found to be identical*.

A brief study of the stereochemistry of the chloride for bromide substitution process was undertaken next. Because of the problems associated with isolation of reactive alkyl halides, we chose to employ a rigid cyclic bromide for this study rather than an optically active bromide. Studies with an optically active bromide would provide more information regarding the intimate details of the substitution reaction stereochemistry. However, studies with a cyclic bromide are sufficient to provide the most important information of whether the substitution proceeds with complete retention or inversion of configuration at carbon, or if it is at least partly non-stereospecific.

Initial stereochemical studies were attempted using isomeric *cis*- and *trans*-1-bromo-2-methylindanes. However, these were unsuccessful owing to the tendency of the bromides to undergo dehydrobromination rather than substitution upon heating with tri-n-butyltin chloride. Thus, for the purpose of the study a tailor-made bromide, 1-bromo-2-methyl-2-phenylindane, was prepared in which dehydrobromination is rendered impossible by the lack of any β-hydrogens.

Unfortunately, we were unable to prepare isomerically pure samples of either the *E* or *Z* isomers of this bromide for study. Only an isomeric mixture predominating in the *E* isomer could be obtained. However, the results of our studies with this isomeric mixture, which are summarized in Table 1, do clearly show that the substitution here proceeds neither with clean retention nor clean inversion of configuration at carbon. It is reasonable to assume that similar behavior should be exhibited by the benzhydryl system. Thus, it is seen that the *E* bromide undergoes substitution more rapidly than does the *Z* bromide. In the early stages of the reaction where essentially none of the *Z* bromide has reacted and only the *E* bromide has undergone substitution, an approximately 78/22 mixture of the isomeric *E* to *Z* chlorides is produced. This isomeric chloride ratio of kinetic product control remains fairly constant even after significant amounts of the *Z* bromide have reacted (91 h). Late in the reaction, however, the differing chloride ratio begins to reflect the thermodynamic stabilities of the isomeric chlorides. On continued heating of the reaction mixture the *E*/*Z* chloride ratio would most likely have approached the 56/44 ratio observed for the corresponding isomeric bromides, which must be an equilibrium value for this system.



Based on the stereochemical results obtained at this point, several of the ionic mechanisms which we originally considered as possibilities for the chloride for bromide substitution process could be excluded. These are: a mechanism involv-

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* The reaction of benzyl bromide with tri-n-butyltin chloride, neat, in a 1/1 mole ratio at 150°C gives 65 ± 1% benzyl chloride at equilibrium.

TABLE 1

REACTION OF AN ISOMERIC MIXTURE OF 1-BROMO-2-METHYL-2-PHENYLINDANES WITH TRI-n-BUTYLTIN CHLORIDE, NEAT, IN A 1/1 MOL RATIO AT 50°C[a]

Reaction time (h)	Composition of reaction mixture[b]					
	E—Br (%)	*Z*—Br (%)	*E*—Cl (%)	*Z*—Cl (%)	*E*—Br/*Z*—Br ratio	*E*—Cl/*Z*—Cl ratio
0	77	23	0	0	77/23	—
14	39	24	29	8	62/38	78/22
19	32	23	35	10	58/42	78/22
20	31	21	38	10	60/40	79/21
53	17	15	53	15	53/47	78/22
91	16	13	54	17	55/45	76/24
186	14	11	52	23	56/44	70/30
377	15	12	50	23	56/44[c]	68/32

[a] The data are taken from two separate runs. [b] Percentages given are estimated from NMR integrations run at least in triplicate to be accurate to about ±2%. [c] In a reaction of the 77/23 *E* to *Z* bromide mixture in a 1/1 mol ratio, neat, at 50°C with tri-n-butyltin bromide, after 330 h the composition of the bromides had also changed to a constant 55/45 *E* to *Z* ratio.

ing concerted bimolecular backside displacement at carbon; and one involving concerted bimolecular frontside displacement via a four-centered activated complex. Only mechanisms involving product formation via reaction with an intermediate carbonium ion remained as likely possibilities. This might have been expected in light of the known propensity of benzhydryl and secondary benzyl halides to undergo substitution via initial rate-determining ionization rather than via concerted bimolecular processes.

Of the remaining ionic mechanisms, one involves rate determining alkyl halide ionization for the forward and reverse processes. A substitution proceeding via this mechanism would be expected to exhibit reversible-first-order kinetic behavior. A second possible mechanism, however, might involve rate determining tri-n-butyltin halide promoted alkyl halide ionization for the forward and reverse processes. Support for the suggestion that such a mechanism could be operative comes from the report that $SnCl_4$ promotes racemization of optically active 1-chloroethylbenzene in CCl_4 solution [5]. At one extreme for a mechanism of this type the rather unlikely assumption could be made that tri-n-butyltin chloride is specific for assisting in ionization of the alkyl bromide and that tri-n-butyltin bromide is specific for assisting in ionization of the alkyl chloride. For this case the reaction would be expected to follow reversible-second-order kinetic behavior. If the tri-n-butyltin halides are only partially specific for assisting in ionization of the respective alkyl halides, a complex kinetic behavior would be anticipated. However, if at the other extreme either tri-n-butyltin chloride or bromide can serve with approximately equal facility in promoting either the alkyl bromide or the alkyl chloride ionization process, then reversible-pseudo-first-order kinetic behavior should be followed for the substitution.

In accord with the latter suggestion, when kinetic studies were carried out on the chloride for bromide substitution in the benzhydryl bromide/tri-n-butyltin chloride system at 50°C in the absence of a solvent, the data were found to give good straight line fits when plotted graphically assuming reversible-first-order rate behavior [6]. However, the first-order rate constants calculated for the forward process for individual runs in which the initial mol ratios of tri-n-butyltin chloride to benzhydryl bromide were changed were not the same. This is shown by the data given in Table 2. If the reaction was simply reversible first-order and in the absence of other effects, these numbers would all be expected to be the same within experimental error. However, if one divides the reversible first-order rate constants obtained for the differing initial mole ratios of tri-n-butyltin chloride to benzhydryl bromide by initial tri-n-butyltin chloride concentration, the resulting second-order rate constants obtained are in much better agreement. These are also shown in Table 2. This is the treatment to be used if, as mentioned earlier, both tri-n-butyltin chloride or bromide could serve with similar facility for promoting ionization of either benzhydryl bromide or chloride.

The fact that the second-order rate constants calculated using the method described above are still not identical within experimental error must be due to a solvent effect resulting from the considerable changes in the composition of the reaction medium produced by changing the mol ratios of the reactants in these neat reactions. Support for this explanation comes from the observation that the second-order rate constants calculated for runs in n-heptane or acetonitrile solvent using differing mol ratios of reactants are in quite good agreement. These data are also shown in Table 2.

The data for the reactions run in n-heptane and acetonitrile solvents also provide additional support for the tri-n-butyltin halide promoted benzhydryl halide ionization mechanism. In the reactions in n-heptane where the initial benzhydryl bromide concentration was held constant but the initial tri-n-butyltin chloride concentration was varied, the reversible first-order rate constants obtained

TABLE 2

REACTIONS OF TRI-n-BUTYLTIN CHLORIDE WITH BENZHYDRYL BROMIDE UNDER VARIOUS CONDITIONS

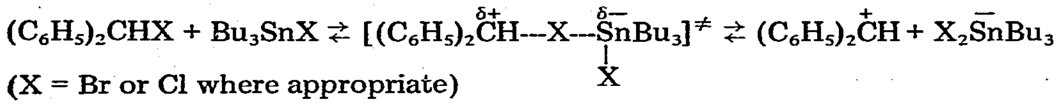
Solvent	Temp. (°C)	Mol ratio SnCl/RBr	[RBr] (M)	[SnCl] (M)	% RCl at equil.	$10^4 k$ (sec^{-1})[a]	$10^4 k$ (M^{-1} - sec^{-1})[b]
Neat	50	1/1	2.34	2.34	70	3.7	1.6[c]
					71	4.0	1.7
		2/1	1.46	2.92	87	6.7	2.3
					88	6.7	2.3
		4/1	0.81	3.24	95	10	3.1
					95	9.1	2.8
	65	1/1	2.34	2.34	70	7.0	3.0
					71	7.5	3.2
	80	1/1	2.34	2.34	69	13	5.6
					70	14	5.9
n-C_7H_{16}	50	1/1	0.456	0.456	71	0.091	0.20
			0.457	0.457	69	0.082	0.18
		4/1	0.449	1.80	94	0.40	0.22
			0.465	1.86	96	0.41	0.22
CH_3CN	50	1/1	0.455	0.460	71	9.7	21
			0.411	0.405	68	8.1	20
		1/2	0.800	0.400	47	9.6	24
			0.804	0.400	46	8.8	22

[a] Calculated graphically for the forward process assuming reversible firstorder rate behavior. [b] Calculated by dividing the first-order rate constants by the initial tri-n-butyltin chloride concentration. [c] $\Delta H^{\ddagger}_{323}$ = 8.7 ± 1.6 kcal mol^{-1}, $\Delta S^{\ddagger}_{323}$ = —49 ± 5 eu.

for the reactions changed considerably. However, for the reactions in acetonitrile where the initial benzhydryl bromide concentrations were varied but the initial tri-n-butyltin chloride concentrations were held constant, the reversible first-order rate constants obtained for the reactions were identical within experimental error. This is precisely what would be expected if the reactions are pseudo-first-order in benzhydryl halide.

Finally a study was made of temperature effects on the rate of chloride for bromide substitution on benzhydryl bromide utilizing tri-n-butyltin chloride. The rate of the 1/1 mol ratio reaction, as shown by the data in Table 2, showed only a rather small dependence on temperature resulting in a small positive enthalpy of activation and a large negative enthropy of activation. The latter result is in accord with that expected for a bimolecular reaction having a highly ordered activated complex, such as would be expected for a rate determining tri-n-butyltin halide promoted benzhydryl halide ionization process.

In conclusion, the results of this investigation clearly support the suggestion that the halide substitutions, at least on highly reactive benzhydryl and secondary benzyl halides with tri-n-butyltin halides, proceed via rate determining trialkyltin halide promoted alkyl halide ionization. A reasonable overall mechanism involving this process is shown below for the benzhydryl halide case.



$$(C_6H_5)_2CHX + Bu_3SnX \rightleftarrows [(C_6H_5)_2\overset{\delta+}{C}H\text{--}X\text{--}\underset{X}{\overset{\delta-}{Sn}}Bu_3]^{\neq} \rightleftarrows (C_6H_5)_2\overset{+}{C}H + X_2\overset{-}{Sn}Bu_3$$

(X = Br or Cl where appropriate)

Work is continuing in our laboratories on investigations of the details of the organotin halide promoted alkyl halide ionization process, and on the synthetic utilities and mechanisms of other substitution reactions on carbon utilizing organotin reagents [7].

Experimental

General comments

Melting points and boiling points are uncorrected. NMR spectra were run on a Varian A-60A instrument, and chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Materials

Benzhydryl bromide; m.p. 43-44°C (lit. m.p. 42°C [8]) was prepared by NBS bromination of diphenylmethane and purified by reduced pressure distillation. Benzyl bromide, 1-bromooctane, 2-bromooctane, benzhydryl chloride, n-heptane, acetonitrile and tri-n-butyltin chloride were obtained commercially and redistilled before use. Tri-n-butyltin bromide, b.p. 108°C/0.5 mm, n_D^{25} 1.5010 (lit. [9] b.p. 122°C/1.6 nm [9], n_D^{25} 1.5022) was prepared by the reaction of tri-n-butyltin hydride with ethyl bromide under UV irradiation.

1-Bromo-2-methyl-2-phenylindanes

2-Methyl-2-phenyl-indan-1-one [10] (10 g, 0.045 mol) was reduced with 0.95 g (0.025 mol) of lithium aluminum hydride in 30 ml of dry tetrahydrofuran at 0°C for 30 min. Workup and reduced pressure distillation gave 8.0 g (80%) of an isomeric mixture of 2-methyl-2-phenylindan-1-ols, estimated by NMR to contain 55% of the *E* isomer and 45% of the *Z* isomer [b.p. 160-185°C/0.5 mm; NMR (CCl_4) δ 1.1 (s, 1.35H, $C\underline{H}_3$ for *Z* isomer), 1.3 (s, 1.65 H, $C\underline{H}_3$ for *E* isomer), 3.0 (m, 2H, $C\underline{H}_2$), 3.3 (bs, 1H, $O\underline{H}$), 4.6 (s, 0.45H, $C\underline{H}OH$ for *Z* isomer), 5.0 (s, 0.55H, $C\underline{H}OH$ for *E* isomer) and 7.0 ppm (bs, 9H, arom)]. This mixture of alcohols (4.0 g, 0.02 mol) was dissolved in 50 ml of n-pentane, cooled to −50°C, and HBr gas was bubbled through the solution for 5 min. Workup and distillation gave 3.0 g (60%) of an isomeric mixture of 1-bromo-2-methyl-2-phenylindanes determined by NMR to contain 77% of the *E* isomer and 23% of the *Z* isomer. [m.p. ca. 35°C; n_D^{23} 1.6181; NMR (CCl_4) δ 1.2 (s, 0.69H, $C\underline{H}_3$ for *Z* isomer), 1.4 (s, 2.21H, $C\underline{H}_3$ for *E* isomer), 3.2 (m, 2H, $C\underline{H}_2$), 5.2 (s, 0.23H, $C\underline{H}Br$ for *Z* isomer), 5.5 (s, 0.77H, $C\underline{H}Br$ for *E* isomer), and 7.0 ppm (m, 9H, arom.).

Anal. Found: C, 66.81; H, 5.22. $C_{16}H_{15}Br$ calcd.: C, 66.91; H, 5.26%.

Reaction Studies

All reactions were run on small scale in NMR tubes. The reagents were carefully weighed into the tubes which were placed into a constant temperature bath maintained within ±0.2°C. At appropriate intervals, the tubes were withdrawn from the bath and the contents analyzed using quantitative NMR or GLPC (for 1-bromooctane and 2-bromooctane only) techniques. The products of the reactions were identified by comparison with authentic samples or with analogous known compounds. The chemical shift values of the absorptions used during NMR analysis of the various substitution reaction mixtures were: benzhydryl bromide (δ 6.2, s, $C\underline{H}Br$), benzhydryl chloride (δ 6.1, s, $C\underline{H}Cl$), benzyl bromide (δ 4.3, s, $C\underline{H}_2Br$), benzyl chloride (δ 4.4, s, $C\underline{H}_2Cl$) 1-bromo-2-methyl-2-phenylindane, *Z* isomer (δ 5.3, s, $C\underline{H}Br$), *E* isomer (δ 5.5, s, $C\underline{H}Br$), and 1-chloro-2-methyl-2-phenylindane, *Z* isomer (δ 5.2, s, $C\underline{H}Cl$), *E* isomer (δ 5.4, s, $C\underline{H}Cl$). These values varied slightly in different reaction mixtures and thus should only be taken as indicative of the general pattern of absorption.

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