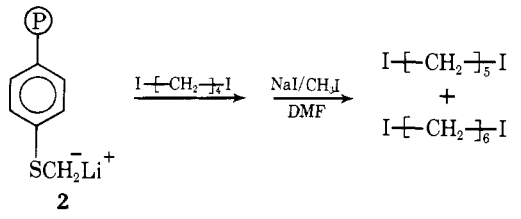

2

nomeric and polymeric[7] forms of phenylthiomethyllithium are shown in Table I. Interestingly, the use of a polymer with ca. 22% ring substitution (reaction 2; 1.85 mequiv of S/g) produced a high preponderance of the product (1,6-diiodohexane) resulting from reaction at both terminal iodides. A lower concentration of functional groups (reaction 1, 0.87 mequiv of S/g, ca. 10% ring substitution) again failed to provide a selective reaction at only one of the terminal iodides. In addition, the use of a lower bath temperature (reaction 3), increased number of equivalents of sulfide (reaction 4), or the utilization of a copper derivative[9] (reaction 5) all resulted in the formation of nearly equal amounts of the $n + 1$ and $n + 2$ homologues of 1,4-diiodobutane. A control reaction with phenylthiomethyllithium (reaction 7) run under the same conditions of temperature and concentration as several of the polymer runs resulted in a high yield of products, with the major component being 1,5-diiodopentane. Comparison of longer reaction times for both the monomeric and polymeric phenylthiomethyllithium reagents (compare reactions 6 and 8) indicated a marked similarity of product ratios except for the presence of significant amounts of starting material common to most of the experiments utilizing the polymeric reagent.[10] It is clear from the results presented in Table I that extensive interaction of polymer-bound functional groups is occurring under these conditions.

An interpretation of these results can be formulated from a comparison of the homologation of 1,4-diiodobutane with the previously reported[3e] oxidation of 1,7-heptanediol as displayed in Table II. A number of similarities can be drawn between the two transformations: (1) the fact that both polymeric reagents are prepared from the same insoluble thioanisole,[7] (2) the same level of cross-linking is present, (3) both reactions utilize solvents with similar swelling properties for the matrix,[1c,d] (4) the concentration of polymer functional groups is nearly the same, (5) the same equivalents of sulfide are employed in each case, (6) reaction times and temperatures are comparable, and (7) overall conversion to products is similar. *Surprisingly, the selectivities appear to be reversed.* The reaction employing polymeric phenylthiomethyllithium results in a preponderance of site interaction, while the evidence obtained for the oxidation of 1,7-heptanediol via the chlorosulfonium reagent **4** (see Table II) indicates significant site isolation.[11]

Polymers bearing anionic groups bound to the backbone (i.e., styrene–acrylate copolymers) have been shown to exist in solution with extensive ionic clustering.[5] The presence of such domains would be expected to lead to restricted mobility of polymer chains,[5] while simultaneously providing regions of high concentrations of functional groups. Similar behavior of the insoluble phenylthiomethyllithium **2** might therefore be expected to resemble concentrated solutions of reactants, thus leading to extensive interaction of polymer-bound functional groups, even with fairly low polymer substitution. Lower reaction temperatures should assist this behavior. Conversely, it is reasonable to assume that positively charged functional groups bound to the polymer backbone will not be induced into forming charge clusters through the agency of a counterion such as chloride, but rather lead to an extension of polymer chains due to repulsion of like charges.[12] Thus, the chlorosulfonium polymer **4** will provide an environment for site isolation, when the concentration of these sites is not too high. Lower temperatures should also assist such behavior.

Even though lightly cross-linked polymer chains have the capacity for significant mobility in the swollen state, our results emphasize the necessity to further consider the interaction of polymer-bound functional groups in light of individual reaction conditions and mechanism. The presence of charged sites can have pronounced effects as shown above. Other studies suggest that polymer transformations leading to increased levels of covalent cross-linking (i.e., chloromethylation) will result in reduced mobility of polymer chains.[2,13] Still other investigations have shown that polymer chain mobility is affected by the swelling capacity of the reaction media.[1c,d] Low reaction temperatures and concentrations of polymer-bound functional groups can be expected to enhance the apparent isolation of reactive sites. Thus, the interaction of polymer chains can be controlled under appropriate conditions.

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(8) The reaction of 1,4-diiodobutane with **2** was carried out under slightly different conditions. Prior to reaction with 1,4-diiodobutane, **2** was washed free of excess *n*-BuLi at −70 °C, followed by the addition of fresh solvent containing appropriate reagents such as DABCO or CuI. The reaction with 1,4-diiodobutane was terminated by addition of MeOH. Washings of the resulting resin were examined for unreacted starting material by GLC. The absence of any 1,5- or 1,6-diiodo product at this point in the reaction sequence was also confirmed by GLC.

(9) The disappearance of suspended copper(I) iodide and the development of brownish gray coloration in the polymer beads were taken as strong evidence for the formation of a polymer bound copper reagent.

(10) The failure to consume all starting material is probably due to the inaccessibility of a portion of the "reactive" sites.

(11) As additional support for this conclusion we have found (unpublished results) that an oxidation of 1,7-heptanediol conducted with the thioanisole–chlorine complex under conditions identical with the polymer version given in Table II produced 5.2% of the monoaldehyde and 37.9% of the dialdehyde, along with 4.5% starting material and 52.4% of a mixture of chlorides.

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The Similarity of Solvent Effects on Carbocations[1]

Sir:

Evidence is accumulating which suggests that the relative energies of simple,[3] isomeric secondary and tertiary carbonium ions are similar in the gas phase and in solution.[4-6] Specifically,

Table I. LUMO Charges, LUMO Energies, and Specific Solvation Factors for Carbonium Ions and Stabilization Energies for $R^+ \cdots ClH$

Carbonium ion	$Q_L(C^+)$[a]	$-\epsilon_L(R^+)$, eV[a]	f_s[a]	ΔE_s[a,b]	ΔE_s[est g]
Methyl	1.000	9.30	0.355	53.4	38.1
Ethyl[c]	0.951[c]	7.80	0.220	33.0	23.6
Isopropyl	0.758	7.15	0.153	15.6	16.4
tert-Butyl	0.726	6.77	0.136	13.2	14.6
Cyclopentyl	0.769	6.88	0.147	16.5	15.8
1-Methylcyclopentyl[d]	0.728	6.48	0.129	11.5	13.8
Bicyclo[3.1.0]-hex-3-yl[d]	0.776	6.76	0.145	16.6	15.5
Bicyclo[3.1.0]-hex-2-yl	0.507	5.83	0.081	9.4	8.7
Trishomocyclopropenyl[d]	0.526	3.87	0.064	<7[f]	6.9
Homocubyl[d]	0.720	5.46	0.108	14.8	11.6
1,3-Dimethylallyl	0.443	6.49	0.079	7.8[e]	8.5
α-Methylbenzyl	0.427	6.17	0.072	<7[f]	7.7

[a] MINDO/3 results with complete geometry optimization except as noted. $Q_L(C^+)$ is the electron density for the carbonium carbon in the LUMO (eq 4). ϵ_L is the orbital energy of the LUMO. f_s is defined in eq 2. [b] ΔE_s in kcal/mole as defined in eq 1. [c] Bisected ($\theta = 100°$) ion used in reference. See ref 11, 19. [d] C_s symmetry assumed. [e] Unsymmetrical complex. [f] Hydrogen bonding preferred to specific solvation. [g] Calculated using eq 3 with $a = 107.2$.

the enthalpy difference between isomeric secondary and tertiary ions in the gas phase is usually 12–17 kcal/mol.[4,7,8] This range has been entered in superacid by Arnett's recent finding[6a] that the *sec* → *tert*-butyl enthalpy difference is 14.5 ± 0.5 kcal/mol and by Saunders value of 11–15 kcal/mol for the 2-methylpent-3-yl → 2-methylpent-2-yl difference.[6b] The range has also been approached under less severe conditions by Schleyer and co-workers who studied solvolyses leading to secondary and tertiary 2-adamantyl cations.[4] They determined an α-CH_3/H rate ratio of $10^{8.1}$ for acetolysis which corresponds to an activation difference of about 11 kcal/mol at 25 °C. These results have fostered the notion that the extent of solvation must vary little between such carbonium ions.[4,6a] Work by Taft et al.[5] also implied that the solvation of a wide variety of aryl carbocations in aqueous media is similar due to a uniform "absence of exposed atomic sites with appreciable positive charge". Thus, only general solvation of the resonant ions is anticipated rather than solvation at specific carbons.

A straightforward theoretical model for specific solvation is presented here which is consistent with the above experimental observations. However, the model predicts that the relative energies of isomeric carbonium ions may vary appreciably from solution to the gas phase. The proper conditions for variance are significantly different charge delocalization for the ions under comparison and the presence of counterions or solvent molecules that are good electron donors.

The strongest interactions between solvent and a simple carbonium ion may be anticipated to occur in the immediate vicinity of the carbonium carbon. In an intimate ion pair the dominant interaction should involve the solvated leaving group while it would involve one or perhaps two solvent molecules in a solvent separated ion pair or solvated free ion.[9] In the case where strong interaction with two solvent molecules is preferred, e.g., one on each side of the trigonal center, the strength of the first interaction could be expected to be a gauge for the extent of the second interaction. Thus, calculation of the structures and stabilization energies for complexes of carbonium ions with a solvated leaving group or a single solvent molecule might provide insight into the relative extent of specific solvation for the cations.

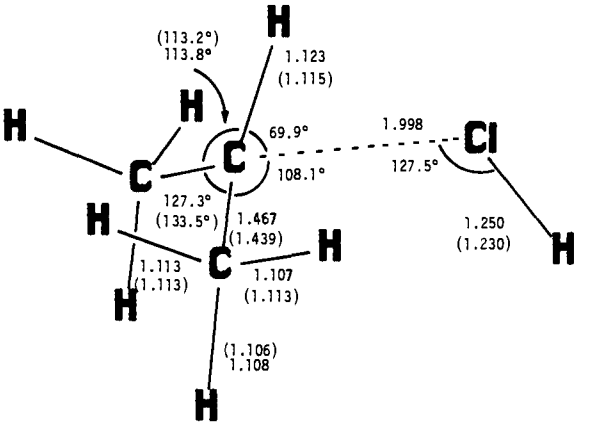


Figure 1. Important structural parameters calculated for (isopropyl-ClH)$^+$. The complex has C_s symmetry. Values for separated isopropyl cation and HCl in parentheses.

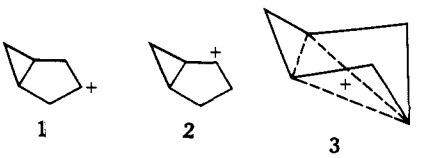
Operationally, selection of a solvent molecule for these bimolecular complexes depends on the degree of interaction that is desired. To avoid potential steric effects and to attempt to take into account the decreased electron demand expected for a fully solvated ion, a solvent molecule that would interact relatively weakly with the carbonium ion seemed desirable. The methyl cation affinities reported by Holtz et al.[10a] revealed that hydrogen halides should be appropriate choices.

This idea has been pursued using MINDO/3[11] and perturbation theory calculations for a broad selection of complexes between carbonium ions and HCl. The stabilization energies, ΔE_s (eq 1), for the complexes calculated by MINDO/3 are listed in the fifth column of Table I.

$$\Delta E_s \equiv \Delta H_f(R^+) + \Delta H_f(HCl) - \Delta H_f(R + \cdots ClH) \quad (1)$$

Typical calculated equilibrium C–Cl distances for primary, secondary, and tertiary cations are 1.9, 2.0, and 2.1 Å, respectively, as compared with 1.75 Å in methyl chloride. For further illustration the structure of the isopropyl ClH complex is shown in Figure 1.

There are several striking features that emerge from the ΔE_s's. (1) High electron demand places methyl and ethyl in a class by themselves showing substantial bonding to chlorine. These species may properly be called protonated alkyl chlorides. Experimental estimates for the ΔE_s's of CH_3ClH^+ and $C_2H_5ClH^+$ can be calculated from the proton affinities of the parent alkyl chlorides.[10] The resulting values are 51 and 27 kcal/mol which agree well with the MINDO/3 predictions in Table I.[12] (2) The interaction of isopropyl with HCl is found to be only 2.4 kcal/mol of 15% more stabilizing than between *tert*-butyl and HCl. This is consistent with the proposal that specific solvation of the two species is similar. The ΔE_s difference for cyclopentyl and 1-methylcyclopentyl is somewhat greater (5 kcal/mol). However, this is reasonable in view of the enhanced propensity for hydride loss of 1-methylcyclopentane that has been previously ascribed to relief of steric (B–) strain.[14] (3) The results for the isomeric series **1**–**3**[2] are



important because they indicate that specific solvation becomes less favorable with increasing charge delocalization. Consequently, the calculated reaction profile for the interconversion of **1** and **3** is substantially flattened by the addition of HCl (Figure 2).[2a] In fact, C—H···Cl—H (nearly linear) hydrogen

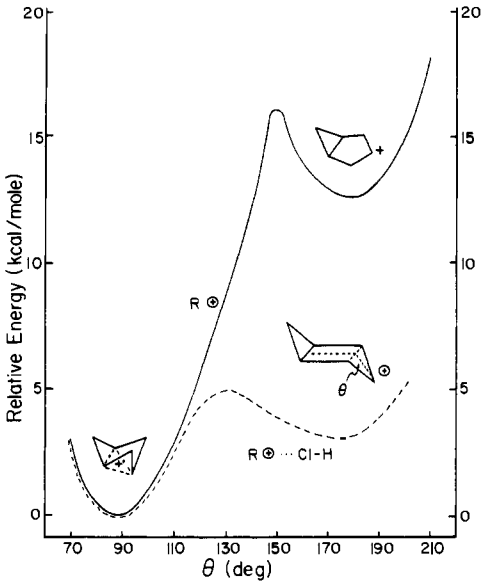


Figure 2. Calculated reaction profiles for the interconversion of **1** and **3** assuming C_s symmetry. The solid line is for the rearrangement of the free ions. The dashed line represents the interconversion of the ions in the presence of one HCl molecule.

bonding is preferred in **3** to solvation at a carbon. The only minima found for **3**-ClH were the three hydrogen bond possibilities each with a bond energy of 7.0 ± 0.1 kcal/mol. Similar hydrogen bond energies were found for all other carbonium ions tested except for the highly charged, bridging hydrogen in ethyl (10.4 kcal/mol). For example, the hydrogen bond energies for isopropyl cation range from 7.5 to 9 kcal/mol and several resonant isomers of homocubyl also have hydrogen bond energies of ca. 7 kcal/mol. The constancy of the hydrogen bond energies argues against the idea that by adding more solvent molecules the initial discrepancy between the specific solvation of simple and resonant isomers, e.g., **1** and **3**, could be eradicated.[15] This conclusion is also supported by calculations on ethyl cation polyhydrochlorides which reveal a nearly constant preference for bisected rather than bridged species in the presence of from one to five solvent molecules.[16c] In any event, consistent with Taft's[5] results, resonant ions such as **3** and α-methylbenzyl are not expected to benefit from specific solvation at carbons, but may only experience general solvation, such as C—H···X hydrogen bonding, which is relatively indiscriminate.

A remarkably simple model may be used to probe the origin of the ΔE_s values in Table I. Frontier orbital theory predicts that the important stabilizing interaction in the complexes occurs between the HOMO of the electron donating solvent molecule (or solvated counterion) and the LUMO of the cation. The interaction energy should then conform to the second-order perturbation theory[17] expression (eq 2–4) where Q_L is the sum of the orbital coefficients squared for the carbonium carbon in the LUMO of the cation.

$$\Delta E_s \propto \frac{Q_L(C^+)}{\epsilon_L(R^+) - \epsilon_H(S} \equiv f_s \qquad (2)$$

$$\Delta E_s^{est} = af_s \qquad (3)$$

$$Q_L(C^+) = \sum_i c_{iL}^2(C^+) \qquad (4)$$

For simple carbonium ions, Q_L is dominated by the contribution from the vacant 2p orbital. ϵ_L (R +) and ϵ_H (S) are the orbital energies for the LUMO of the cation and HOMO of the solvent molecule, respectively. f_s is then defined as the "specific solvation factor" and should provide an estimate of ΔE_s through a proportionality constant, a. Using the Q_L values and ϵ_L (R +)'s compiled in Table I and the MINDO/3 value for the ionization potential of HCl (12.11 eV; experimental, 12.7 eV[18]), the f_s values in the fourth column of Table I are determined. A least-squares fit was made to the calculated ΔE_s's for the secondary and tertiary cations except **3** and α-methylbenzyl yielding a value of 107.2 for a. The mean error for the eight points is 1.36 kcal/mol. The estimated values for ΔE_s using eq 3 are given in the last column of Table I.

Use of eq 2 helps provide several interesting observations. (1) Although charge delocalization in *tert*-butyl is greater than in isopropyl as witnessed by the smaller Q_L and higher LUMO energy, the difference is not substantial and the f_s values mirror the ΔE_s's. (2) For α-methylbenzyl the low f_s is primarily due to charge delocalization (low Q_L), while for **3** it is due to the high energy of the LUMO, a general feature of homoaromatics. (3) Change in the electron donating ability of the solvent or counterion is reflected in eq 2 by ϵ_H (S). Electron donors with low ionization potentials, e.g., chloride, bromide, or alkyl or aryl sulfonate anions, are the most stabilizing, while less labile species with high IP's compress the range of ΔE_s. The latter situation may prevail in superacid media with counterions like SbF_6^-.

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(12) The calculated ΔE_s values and hydrogen bond energies are anticipated to be uniformly too large by ca. 5 kcal/mol based on these results and the MINDO/3 stabilization energies for CH_4–ClH (5 kcal/mol) and HCl dimer (9 kcal/mol). Better estimates of the latter quantities are ~1 and 2 kcal/mol, respectively.[13] Calculations with fluorine were not attempted due to the propensity of fluorine to be dicoordinate in MINDO/3 studies.
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Production of Antibiotics by Biotransformation of 2,4,6/3,5-Pentahydroxycyclohexanone and 2,4/3,5-Tetrahydroxycyclohexanone by a Deoxystreptamine-Negative Mutant of *Micromonospora purpurea*

Sir:

Shier et al.[1] devised a technique for producing semisynthetic aminoglycoside antibiotics by isolating mutants of aminoglycoside producing organisms that are capable of producing antibiotic only when supplied with an exogenous source of 2-deoxystreptamine (**1**) or other suitable aminocyclitol. Several other groups[2-7] have since prepared new aminoglycoside antibiotics by this technique.

A deoxystreptamine-negative mutant of *Micromonospora purpurea*, the organism that produces the gentamicin C complex (**2**)[8] of antibiotics, has been produced and isolated in our laboratories. This mutant organism produces the gentamicin C complex (**2**) of antibiotics when a growing culture is supplemented with 2-deoxystreptamine. It also produces a new 2-hydroxygentamicin C complex (**3**)[9] when supplemented with streptamine (**4**).

When this mutant of *M. purpurea* is supplemented with 2,4,6/3,5-pentahydroxycyclohexanone (**5**, *scyllo-ms*-inosose) the same 2-hydroxygentamicin complex (**3**) is produced, along with streptamine (**4**). The isolation of streptamine (**4**) suggests that the mutant organism is capable of the biotransformation shown in Scheme I (X = OH). Acid hydrolysis of the antibiotic mixture obtained from **5** supplementation also afforded streptamine (**4**). **5** was prepared from *myo*-inositol (**7**) by microbiological oxidation of the axial hydroxyl group using *Acetobacter suboxydans*.[10]

myo-Inositol (**7**) was not incorporated by this mutant[11] although it is a precursor of **5** in the suggested biosynthesis of streptidine,[12] (a bisamidine derivative of streptamine) found in streptomycin, by *Streptomyces griseus*.

The C_1 (**3a**) and C_2 (**3b**) components[9] were separated from both supplementation experiments (thick layer chromatography, silica gel Brinkmann PF 254; 1.0 mm × 40 × 20 cm plates, lower phase of a $CHCl_3$:MeOH:concentrated NH_3; 1:1:1 system) and the products were compared by TLC, NMR, MS, and elemental analysis of their H_2SO_4 salts. 2-Hydroxygentamicin C (**3a**): mp 119–123 °C; ^{1}H NMR (D_2O) δ 5.87, 5.60 (anomeric H, 2 H) 5.22 (exchangeable H, 12 H) 3.15, 3.09 (NCH_3, 6 H) 2.9–4.8 (CHO, CHN, CH_2O, 13 H) 1.9–2.6 (CH_2CH_2, 4 H) 1.72 ppm (CH_3C, CH_3CH, 6 H); MS, (M^+) 493 fragments *m/e* 436, 376, 366, 338, 335, 320, 160, 157;[13] $[\alpha]^{25}{}_D$ +128.5° (0.2% H_2O) Anal. Calcd for

Scheme I