1-Fluoro-3,4,5-trimethylbenzene (14) and 1-fluoro-2,3,4-trimethylbenzene (15): yield 75 mg (27%) of a liquid mixture in the ratio of 1:4 **14**/**15**; we were unable to separate the two products; NMR for **14** δ(F) −128.5 (t, J = 9 Hz); NMR for **15** δ(F) −130 ppm (m). Both products were transformed with xenon difluoride in to 1,2-difluoro-3,4,5-trimethylbenzene (**16**).

Registry No. **1**, 95-93-2; **2**, 10585-06-5; **3**, 400-01-1; **4**, 3360-65-4; **5**, 85649-60-1; **6**, 319-92-6; **7**, 3360-61-0; **8**, 108-67-8; **9**, 392-61-0; **10**, 392-69-8; **11**, 3360-56-3; **12**, 52040-88-7; **13**, 526-73-8; **14**, 52547-91-8; **15**, 52547-99-6; **16**, 85649-61-2; **17**, 85649-62-3; **18**, 85649-63-4; XeF_2, 13709-36-9; HF, 7664-39-3; CF_3COOH, 76-05-1; 1,3,4-trimethylbenzene, 95-63-6.

A Simple Method for Predicting Hydration Energies of Organic Cations Derived from Protonation or Alkylation of Neutral Oxygen and Nitrogen Bases

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A simple method is presented for predicting the hydration free energies of certain organic cations on the basis of additive group contributions and an electrostatic component. Approximate hydration effects accompanying protonation or alkylation of various functional groups are tabulated and illustrated with reference to published data on benzylation of adenosine and guanosine in aqueous mixtures.

Qualitative reasoning based on the idea that charge development is facilitated in solvents of high dielectric constant and that small ions are more highly solvated than larger ones, is sometimes useful in rationalizing solvent effects on reaction rates and equilibria.[1] However, it is frequently necessary to consider specific solute–solvent interactions, particularly in polar protic solvents.[2] A good example is provided by the "anomalous" basicity order of the aliphatic amines in water.[3] Electronic factors suggest that amine basicity should increase in the order $NH_4 < MeNH_2 < Me_2NH < Me_3N$, which is indeed that observed in the gas phase and in many organic solvents.[4] However, a different order is observed in aqueous solution, which Arnett et al.[3] demonstrated was due to more effective hydration of the less highly substituted ammonium ions. They attributed this to the greater number of acidic hydrogen atoms in these ions available for hydrogen bonding to the solvent. Specific contributions to hydration energies of this kind seemed to be characteristic of ions arising from the protonation of both nitrogen and oxygen bases[5] and led Arnett, Taft, and their co-workers to propose that "the number and type of hydrogen bond which an onium ion can donate to a basic solvent is a rough first order guide to its solvation behavior".[6]

It has been known for some time that the hydration free energies of neutral organic compounds are approximately additive functions of the groups present,[7] and Hine and Mookerjee (HM) have devised a scheme for estimating them on this basis.[8] We therefore wondered whether this scheme could be extended to organic onium ions by deducing additional group contributions from the available experimental data. This should provide a semiquantitative framework for the discussion of hydration effects in chemical reactions involving organic cations in terms of the functional groups present.

A Model for Cation Hydration

Ionic hydration differs from that of neutral species by the presence of an electrostatic component, ΔG_{el}, associated with the energy of charging the cavity in the solvent in which the ion resides.[9] While numerous workers have attempted to calculate cationic hydration energies, they have focused almost exclusively on those of the metal cations.[9-11] Nevertheless some of the ideas developed should form a useful basis for the model proposed here.

It has been customary to represent the total hydration energy by eq 1, where ΔG_{ne} is the "nonelectrostatic" component, i.e., the hydration energy of the hypothetical discharged ion. This has most often been estimated by comparison with appropriate neutral analogues, the assumption being of course, that the energies of cavity formation and solvent structure making/breaking interactions are similar in species of similar size and shape, regardless of charge. Here we propose a similar idea based on eq 2

$$\Delta G^{g\rightarrow H_2O} = \Delta G_{el} + \Delta G_{ne} \qquad (1)$$

$$\Delta G_{ne} = -2.303RT \sum_{i}^{\text{group}} [\log \gamma]_i \qquad (2)$$

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(1) Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; Cornell University Press: Ithaca, New York, 1953.

(2) (a) Gordon, J. E. "The Organic Chemistry of Electrolyte Solutions"; Wiley: New York, 1975; Chapter 2. (b) Ritchie, C. D. In "Solute–Solvent Interactions"; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Chapter 4. (c) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1–32.

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(11) Important exceptions to this statement are described in papers by Aue et al.[12] and Arnett[13] in which hydration free energies of ammonium ions were discussed in terms of the Born equation. In neither work was explicit account of specific solvation attempted.

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where $[\log \gamma]_i$ are the group contributions introduced by Hine and Mookerjee.[8] For neutral molecules, $\Delta G_{\mathrm{ne}} = \Delta G^{\mathrm{g} \rightarrow \mathrm{H_2O}}$. The contribution to the hydration energy due to the uncharged skeleton of an ion is therefore identical with that of the skeleton of a comparable neutral relative.

The most well-known expression for the electrostatic free energy of an ion in a continuous medium is the Born equation[9] (eq 3), which refers to an arbitrarily distributed,

$$\Delta G_{\mathrm{el}}^{\mathrm{Born}} = -q^2e^2(1 - \epsilon_0^{-1})/2r' \tag{3}$$

centrosymmetric charge distribution q within a sphere of effective radius r' immersed in a medium of dielectric constant ϵ_0. In practice, values of r' substantially larger than the Pauling crystal radii (r^*) are necessary to reproduce the hydration energies of the alkali metal cations.[9] Adjustments to these according to eq 4 have therefore been

$$r' = r^* + \Delta \tag{4}$$

proposed. The physical significance of Δ has been variously interpreted as the distance from the surface of the ion to the center of the adjacent water dipole,[14] an increment representing the volume of void space surrounding the ion[15] and, probably most satisfactorily, as the thickness of the layer of solvent dielectric saturation.[9] The problem here is that the empirically chosen value of r' must compensate in some way for the decrease in effective dielectric constant expected close to the surface of the ion. For treatment of this problem in a more rational way, modifications of eq 3 and 4 have been suggested in which either ϵ_0 is replaced by a continuous function $\epsilon(r)$ or in which the solvent around the ion is partitioned into one or more concentric shells with intermediate values of ϵ.

A formulation of the first type (eq 5) was proposed by Glueckauf[16] (GLU) using an approximate expression for

$$\Delta G_{\mathrm{el}}^{\mathrm{GLU}} = \frac{-q^2e^2}{2r'}\left[\frac{n^2 - 1}{n^2} + \frac{\epsilon_0 - n^2}{\epsilon_0 n^2}\left(\frac{8\rho 3r' - 6\rho^2 r'^2 + r'^4}{3\rho^4}\right)\right] \tag{5}$$

$$\rho = (\beta q e/3\epsilon_0)^{1/2} \text{ for } r' < \rho \qquad \rho = r' \text{ for } r' \geq \rho$$

$\epsilon(r)$ due to Booth.[17] In this equation n is the refractive index of water, r' is given by eq 4, $\Delta = 0.55$ Å, and $\beta = 0.116T^{-1}$. In an approach of the second type, Abraham and Liszi[18] (AL) have recently obtained excellent predictions of electrostatic solvation energies for the alkali metal cations, the tetramethyl and tetraethyl ammonium ions, and various anions in a number of solvents including water by using a simplified version of a two-shell model due to Beveridge and Schnuelle.[19] This refers to a spherical cavity of radius a within a concentric sphere of radius b. Outside this sphere the dielectric constant is that of the bulk medium (ϵ_0) while within the layer of thickness ($b - a$) it is assigned a lower vaue, ϵ_{loc}. The relevant equations may be written:

$$\Delta G_{\mathrm{el}}^{\mathrm{AL}} = \frac{-q^2e^2}{2}\left[\frac{(\epsilon_a - 1)}{a\epsilon_a} + \frac{(\epsilon_b - 1)}{b\epsilon_b}\right] \tag{6}$$

where

$$\epsilon_a = \epsilon_{\mathrm{loc}}\left[1 + \frac{(1 - \epsilon_{\mathrm{loc}})(1 - \epsilon_b)a}{b\epsilon_b}\right]^{-1}$$

$$\epsilon_b = \epsilon_0/\epsilon_{\mathrm{loc}}$$

Here AL took the distance ($b - a$) to be 1.553 Å in aqueous solution and assigned $\epsilon_{\mathrm{loc}} = 2.0$ in all solvents.

To accommodate the ions studied here, none of which were spherical, we adopted the necessary, if somewhat arbitrary, expedient of employing the radii of the sphere having the same total volumes as the ions in question. How such volumes should be defined is not obvious; experimental partial molar volumes of the ions[20] are at first sight attractive, but these require uncertain corrections for electrorestriction[9,20] and intermolecular void volumes.[21] Molar volumes of neutral analogues avoid the former but not the latter problem and share the disadvantage of requiring the existence of experimental data. To make the model as general as possible, we calculated the molecular volumes directly via a three-dimensional numerical integration using the van der Waals radii of the atoms.[22-26] We assumed that one molecule of water was strongly coordinated to each polar hydrogen of the solute[6,27] and was taken to effectively increase the volume of the latter. This increment was treated as a transferable quantity obtained in a separate calculation from the corresponding van der Waals radii and appropriate hydrogen-bonded distances. For the $\mathrm{OH^+ \cdots OH_2}$ and $\mathrm{NH^+ \cdots OH_2}$ distances, we settled on 1.8 and 2.2 Å, respectively.[28] Fortunately, the magnitudes of the volume increments[33] were rather insensitive to the exact placement of the coordinated water.

The geometries of the ions themselves were calculated by using the MNDO semiempirical molecular orbital procedure.[34]

Results

With the exception of the data for $\mathrm{Me_4N}$ and $\mathrm{Et_4N}$, all experimental hydration energies were relative values taken

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(22) The molecular volume used here refers to the volume enclosed within the surface defined by the spheres of the appropriate van der Waals radii centered at the atomic nuclei. For discussion of the problems associated with the calculation and definition of molecular volumes see: Pearlman, R. S. In "Physical Chemical Properties of Drugs"; Yalkowsky, S. H., Sinkula, A. A., Valvani, S. C., Eds.; Marcel Dekker: New York, 1980; pp 321–347.

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(28) Following a suggestion by Newton and Ehrenson[29] that the $\mathrm{^+OH \cdots OH_2}$ distance in $\mathrm{H_3O^+}$ surrounded by a sufficiently large number of water molecules should be similar to that in neutral water, we took this distance for all protonated oxygen compounds to be 1.8 Å, the corresponding distance in ice.[30] Analogously, the $\mathrm{^+NH \cdots OH_2}$ distance was set equal to 2.2 Å, consistent with the observed crystal structures of the hydrates of ammonia[31] and several aliphatic amines.[32]

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Table I. Decomposition of Experimental Hydration Energies[a] of Organic Onium Ions

ion	$-\Delta G_{el}^{AL}$ [b]	$-\Delta G_{ne}$ [c]	$-\Delta G^{\circ}{}_{calcd}{}^{g\rightarrow H_2O}$	$-\Delta G^{\circ}{}_{obsd}{}^{g\rightarrow H_2O}$ [d]	error
$MeOH_2$	52.1	28.6	80.7	81.4	0.7
$EtOH_2$	49.0	28.5	77.5	76.8	−0.7
Me_2OH	51.9	16.5	68.3	69.3	1.0
Et_2OH	46.5	16.2	62.7	61.9	−0.8
MeEtOH	48.8	16.3	65.1	65.9	0.8
$(CH_2)_4OH$	47.9	17.4	65.3	64.1[e]	−1.2
$(CH_2)_5OH$	45.8	17.2	62.9	63.1[e]	0.2
$MeNH_3$	48.0	21.4	69.4	69.7	0.3
$EtNH_3$	45.8	21.2	67.0	67.0	0.0
n-PrNH_3	44.0	21.0	65.0	65.1	0.1
i-PrNH_3	44.0	20.9	64.9	64.3	−0.6
n-BuNH_3	42.4	20.8	63.2	64.7	1.5
sec-BuNH_3	42.4	20.8	63.2	63.3[f,g]	0.1
t-BuNH_3	42.4	20.8	63.2	62.0	−1.2
$C_6H_5NH_3$	41.9	22.6	64.5	65.0[g]	0.5
3-$MeC_6H_4NH_3$	40.7	22.6	63.3	62.9[f,g]	−0.4
4-$MeC_6H_4NH_3$	40.7	22.6	63.3	63.1[f,g]	−0.2
Me_2NH_2	48.0	14.7	62.7	62.8	0.1
$(CH_2)_3NH$	47.0	16.0	63.0	62.0	−0.1
$(CH_2)_4NH$	45.0	15.8	60.9	60.7	−0.2
$(CH_2)_5NH$	43.4	15.6	59.0	59.2	0.2
Et_2NH_2	44.0	14.5	58.5	58.1	−0.4
n-Pr_2NH_2	41.1	14.1	55.2	55.6	0.4
$PhMeNH_2$	41.9	16.8	*h*	58.7[f,g]	*h*
Me_3NH	48.0	8.4	56.4	55.8	−0.6
Me_2EtNH	45.8	8.3	54.1	54.3[f,g]	0.2
$MeEt_2NH$	43.9	8.1	52.0	52.5[f,g]	0.5
Et_3NH	42.4	8.0	50.4	49.9	−0.5
n-Pr_3NH	38.9	7.4	46.3	47.3[g]	1.0
$(CH_2)_4MeNH$	45.1	9.4	54.5	54.0	−0.5
$PhMe_2NH$	41.9	9.3	*h*	51.2[g]	*h*
Me_4N	48.1	4.4	52.5	52.3[i]	−0.2
Et_4N	41.1	4.0	45.1	45.3[i]	0.2

[a] All energies in kcal mol^{-1} at 25 °C. [b] Calculated from eq 6 by using van der Waals radii recommended by Pauling.[23] [c] Calculated from eq 2 by using $[\log \gamma]_i$ values for neutral groups from ref 8 (cf. ref 40) and for charged groups from Table IV. [d] Data from ref 5 unless noted otherwise, using $\Delta G^{\circ\, g\rightarrow H_2O}(NH_4^+) = -76.7$ kcal mol^{-1}, see text. [e] Reference 37. [f] Reference 35. [g] The hydration energy of the neutral base required in the thermodynamic cycle for $\Delta G^{g\rightarrow H_2O}(BH^+)$ estimated from ref 8 (cf. ref 40). [h] Only ion containing this (charged) group thus calculated, and observed hydration energies are necessarily identical. [i] Reference 18.

from the work of Taft, Arnett, and their co-workers.[5,6,13,35–38] The relative energies were put on the absolute scale by using $\Delta G^{0g\rightarrow H_2O}(NH_4^+) = -76.7$ kcal mol^{-1} obtained by combining the recommended values of the corresponding enthalpy[2a] and entropy[9] of hydration at 298 K for the required standard state.[39] The available experimental data are collected in Tables I and II. We next attempted to deduce new contributions (values of $[\log \gamma]$) for each cationic group by least-squares fitting of the data to eq 1. We tried four different formulations of ΔG_{el} (see footnotes to Table III for definitions) with van der Waals radii suggested by Pauling,[23] those on which the CPK[24] models are based, a set designed by Bondi for the computation of molecular volumes,[25] and one due to Allinger used in empirical force field calculations.[26]

This preliminary comparison was restricted to the ions in Table I. For this group complications due to internal delocalization of the positive charge should be at a minimum. The results are summarized in Table III, which compares the standard deviations between the experimental hydration energies and those predicted from the derived onium group contributions. The best agreement was obtained by using ΔG_{el}^{AL} and the radii suggested by Pauling. However, this superiority was rather slight. All but the simple Born treatment led to deviations within the surprisingly narrow range of 0.7–0.9 kcal mol^{-1}. Never-

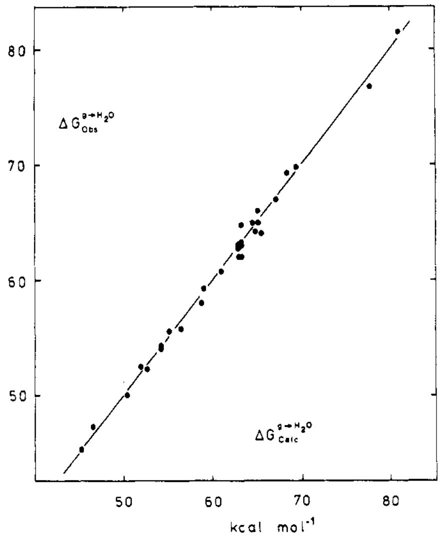

Figure 1. Comparison of "calculated" and observed hydration energies for the ions in Table I.

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(39) We have adopted the standard-state convention used by Hine and Mookerjee,[8] i.e., ΔG° (g → H_2O) = $-2.303RT \log (c_w/c_g)$, where c_w and c_g are the concentrations in the aqueous and gaseous phases expressed in mol L^{-1}. This differs from two more frequently used conventions. One refers to the transfer of 1 mol of gas at 1 atm to a solution of unit mole fraction and in the other to a solution of unit molality. Hydration energies expressed on these bases are respectively 4.25 and 1.89 kcal mol^{-1} more positive than those quoted here.

Table II. Decomposition of Experimental Hydration Energies[a] of Delocalized Ions

ion	$-\Delta G_{el}^{AL}$ [b]	$-\Delta G_{ne}$ [c]	$-\Delta G°_{calcd}{}^{g\to H_2O}$	$-\Delta G°_{obsd}{}^{g\to H_2O}$ [d]	error
Me_2COH	50.2	16.4	66.6	66.9	0.3
$(CH_2)_4COH$	46.6	17.3	63.9	63.3[e]	−0.6
Me-*t*-BuCOH	43.6	15.7	59.3	59.4[e]	0.1
i-Pr_2COH	42.1	15.4	57.5	55.7[e]	−1.8
c-$C_6H_{11}MeCOH$	41.7	16.6	58.3	60.3[e]	2.0
PhMeCOH	43.0	13.1	*h*	56.1[e]	*h*
c-PrMeCOH	46.4	12.5	*h*	58.9[e]	*h*
c-Pr_2COH	43.6	10.0	*h*	53.6[e]	*h*
Me(OMe)COH	48.9	14.9	63.9	63.5[e]	−0.4
Me(OEt)COH	46.5	14.7	61.2	61.6	0.4
Ph(OMe)COH	42.4	13.7	*h*	56.1[e]	*h*
c-Pr(OMe)COH	45.5	13.1	*h*	58.6[e]	*h*
$Me(NMe_2)COH$	46.0	9.4	*h*	55.4[f]	*h*
pyH	47.1	7.6	54.7	55.0	0.3
2-Me(py)H	45.2	7.4	52.6	52.5[g]	−0.1
3-Me(py)H	45.2	7.5	52.7	53.0[g]	0.3
4-Me(py)H	45.2	7.5	52.7	52.4	−0.3
4-NMe_2(py)H	42.3	10.6	52.7	~47.4[i]	~−5.5
4-OMe(py)H	44.4	7.7	52.1	~49.0[i]	~−3.1
4-Cl(py)H	45.2	7.7	52.9	~53.9[i]	~1.0
2,4-Me_2(py)H	43.5	7.3	50.8	53.3[g]	−0.5
2,5-Me_2(py)H	43.5	7.3	50.8	50.4[g]	−0.4
2,6-Me_2(py)H	43.5	7.2	50.7	49.1[g]	−1.6
3,5-Me_2(py)H	43.5	7.5	51.0	50.8[g]	−0.2
4-*t*-Bu(py)H	41.4	7.1	48.5	50.5[g]	2.0
2,6-*t*-Bu_2(py)H	36.9	6.3	43.2	43.5[g]	0.3

[a-e,h] Table I. [f] $\Delta G°\ {}^{g\to H_2O}(B)$ from ref 42. [g] Reference 36. [i] Approximate data, not included in regression analysis. Data from ref 38 with $\Delta G°\ {}^{g\to H_2O}(B)$ estimated to be approximately equal to the corresponding 2-substituted derivatives.[36,41] For 4-Me_2Npy a further estimate of the difference between this and 4-NH_2py was necessary.[8,40]

Table III. Standard Deviations in Calculated Ion Hydration Energies[a] by Various Methods

method for ΔG_{el}	source of van der Waals radii[b] ref 23	ref 24	ref 25	ref 26
AL[c]	0.69	0.71	0.72	0.71
GLU[d]	0.70	0.71	0.72	0.72
LPS[e]	0.81	0.73	0.85	0.85
BORN[f]	1.20	1.54	1.02	1.13

[a] In kcal mol^{-1} for 31 data points (24 degrees of freedom). Experimental values from Table I; calculated values from eq 1. [b] Total volumes enclosed by the van der Waals spheres were calculated (including the coordinated water) and used to calculate the equivalent radii r_{VDW}. [c] Equation 6 with $a = r_{VDW}$. [d] Equation 5 with $r' = r_{VDW} + 0.55$. [e] Equation 3 with $r' = r_{VDW} + 0.85$. [f] Equation 3 with $r' = r_{VDW}$.

Table IV. Derived Cationic Group Contributions to Hydration Energies

group	*n*[a]	log γ ± sd[b]
$OH_2^+(C)$	2	21.6 ± 0.7
$OH^+(C)_2$	5	13.3 ± 0.7
$COH^+(C)_2$	5	13.3 ± 1.0
$COH^+(C)(C_{Ar})$	1	10.5
$COH^+(C)(C_{cp})$[c]	1	9.8
$COH^+(C_{cp})_2$[c]	1	7.5
$CO_2H^+(C)_2$	2	12.2 ± 0.4
$CO_2H^+(C)(C_{Ar})$[c,d]	1	10.9
$CO_2H^+(C)(C_{cp})$[c,d]	1	10.3
$COHN^+(C)_3$	1	8.7
$NH_3^+(C)$	7	16.3 ± 0.6
$NH_3^+(C_{Ar})$	3	16.6 ± 0.3
$NH_2^+(C)_2$	6	12.0 ± 0.2
$NH_2^+(C)(C_{Ar})$	1	12.9
$NH^+(C)_3$	6	7.8 ± 0.4
$NH^+(C)_2(C_{Ar})$	1	8.0
$N^+(C)_4$	2	5.7 ± 0.1
$N_{Ar}H^+(C_{Ar})_2$	10	5.0 ± 0.7
$O^+(C)_3$		~3.7[e]
$CO^+(C)_3$		~5.6[e]
$CO^+(C)_2(C_{Ar})$[d]		~4.0[e]
$CO_2^+(C)_3$		~4.5[e]
$CO_2^+(C)_2(C_{Ar})$[d]		~4.4[e]
$N_{Ar}^+(C)(C_{Ar})$		~0.7[e]

[a] Number of data points used to calculate [log γ]. [b] Standard deviation: $[[(n-1)^{1/2}]\Sigma^n(\Delta G_{calcd} - \Delta G_{obsd})^2]^{1/2}$. [c] C_{cp} refers to the cyclopropyl substituent. [d] Last-named substituent is bonded to carbon, e.g., $[CO_2H^+(C)(C_{Ar})]$ refers to the protonated carboxy group in alkylbenzoates. [e] Estimated data, see text.

theless we prefer the treatment based on ΔG_{el}^{AL} since the latter appears to be somewhat better founded,[19] has already been exploited in a related context,[18] and seems to offer the best promise of extention to other solvents.[18] The components of the hydration energies implied by this scheme are included in Tables I and II.[40] The new group contributions are collected in Table IV together with some additional values estimated below. A plot of calculated vs. observed hydration energies for the ions in Table I (except Me_2NHPh and $MeNH_2Ph$, which were the only members in each class) is shown in Figure 1.

We also carried out a limited investigation of other expressions for ΔG_{ne} in combination with ΔG_{el}^{AL}. Thus, replacement of the contributions not associated with the onium groups in eq 2 by a single term deduced from the correlation of rare-gas hydration energies[18] led to standard deviations inferior to those in Table III by 0.1–0.4 kcal mol^{-1} (depending on the source of the van der Waals radii). Use of data computed from scaled particle theory[43] with

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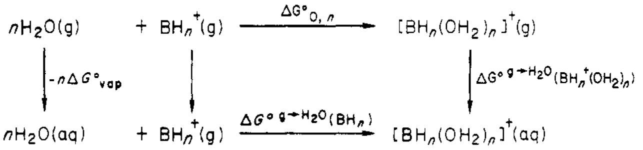
(40) Values of [log γ] for neutral groups not tabulated in ref 8 were deduced from experimental hydration energies as follows: $[C_{ar}(N)(C_{ar})_2]$ = −0.55 from aniline;[41] $[CON(C)_3]$ = 8.13 from $MeCONMe_2$;[42] $[CH(N)(C)_2]$ = 0.28 from *i*-$PrNH_2$[5] and *i*-Pr_2NH;[13] $[C(N)(C)_3]$ = 0.87 for *t*-$BuNH_2$.[5] The following equivalences were assumed: $[NH_2(C)] = [NH_2(C_{ar})]$; $[NH(C)_2] = [NH(C)(C_{ar})]$; $[N(C)_3] = [N(C)(C_{ar})_2]$; $[C(C)_4] = [C(C)_3(CO)]$; $[CH(C)_3] = [CH(C)_2(CO)]$.

(41) Cullis, P. M.; Wolfenden, R. *Biochemistry* 1981, *20*, 3024–3028.

(42) Wolfenden, R. *Biochemistry* 1978, *17*, 201–204.

(43) Pierotti, R. *Chem. Rev.* 1976, *76*, 717–726. Morel-Desrosiers, N.; Morel, J.-P. *Can. J. Chem.* 1981, *59*, 1–7.

Scheme I. Thermodynamic Cycle for Analysis of Cation Hydration Energies



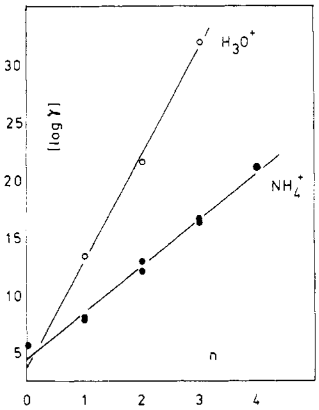


Figure 2. Correlations between [log γ] and the number of specific hydration sites for ammonium (●) and oxonium (○) ions. The slopes and intercepts are 4.0, 4.6 (ammonium ions) and 9.4, 3.6 (oxonium ions).

the parameters of Sen[44] in the same way led to results inferior to those in Table III by 0.7–0.9 kcal mol^{-1}.

Treatment of ϵ_{loc} in eq 6 as a disposable parameter with the Pauling radii led to a value of 2.04, virtually identical with that suggested by AL.[18]

Discussion

As a prescription for estimating hydration energies, this procedure (eq 1,2,6) seems to work quite well. For 90% of the ions listed in Table I the hydration energies are correctly reproduced to ±1.0 kcal mol^{-1} and 68% to within 0.5 kcal mol^{-1} of the experimental values.

We found that the calculated molecular volumes could be represented with excellent precision by the sums of individual group contributions (cf. ref 25). These, together with tables for calculating ΔG_{el}^{AL} from the resulting volumes have been provided as supplementary data.

The approximate meaning of the terms appearing in the present model may be fruitfully discussed with reference to Scheme I and eq 7. The first term on the right-hand

$$\Delta G^{\circ\, g\rightarrow H_2O}(BH_n^+) = \Delta G^\circ_{0,n} + n\Delta G_{vap}^\circ + \Delta G^{\circ\, g\rightarrow H_2O}(B^+H_n(OH_2)_n) \quad (7)$$

side of this equation refers to the free energy of the gas-phase addition of n water molecules to the ion.[45] The first two terms therefore describe the removal of n molecules of liquid water from the body of the solvent to form the gaseous hydrate complex while the last refers to the hydration of this complex. Thus the quantities $\Delta G^\circ_{0,n}$ + $n\Delta G_{vap}^\circ$ describe specific hydration effects of just the kind expected to contribute to the [log γ] values of charged groups carrying one or more hydrogen atoms. Also contributing to the latter are cavity-forming and other terms as well as the accumulation of imperfections in the model and uncertainties in the experimental data, especially in the absolute hydration energy of the ammonium ion. It should be possible to identify those components associated with specific hydration effects in ammonium and oxonium ions from the correlations involving the number of hydrogen-bonding sites in them (Figure 2). The intercepts of these correlation lines presumably correspond to those components of [log γ] that are *not* associated with specific hydration (hydrogen bonding). The relevant comparisons are then between $-2.303RT$([log γ] $- B_N$) and $-2.303RT$([log γ] $- B_O$) (where B_N and B_O are the corresponding intercepts for ammonium and oxonium ions) and the experimental values of $\Delta G_{0,n}^\circ + n\Delta G_{vap}^\circ$. In the few cases in which this was possible (Table V), the correspondence is strikingly close, especially since the experimental values may involve uncertainties of several kilocalories per mole.[46]

Table V. Analysis of Derived Cationic Group Contributions[a-c]

ion	$\Delta G^\circ_{0,n} + n\Delta G_{vap}^\circ$	$-2.303RT$([log γ] $- B$)
$EtOH_2^+$	−23.9[d]	−24.6
Me_2OH^+	−13.1[e]	−13.2
$MeNH_3^+$	−17.1[f]	−16.0
$EtNH_3^+$	−14.6[f]	−16.0
Me_3NH	−6.1[g]	−4.4

[a] Energies in kcal mol^{-1} $\Delta G^\circ_{0,n}$ values given in the original literature for the 1-atm standard state have been corrected for the process at constant volume by adding $-RT\ln(1 + n)$. [b] ΔG_{vap}° = 1.97 kcal mol^{-1}: "Handbook of Chemistry and Physics", 60th ed.; CRC Press: Boca Raton, FL, 1979. [c] B_N = 4.7; B_O = 3.6. [d] Reference 25. [e] Hiraoka, K.; Grimsrud, E. P.; Kebarle, P. *J. Am. Chem. Soc.* **1974**, *96*, 3359-3364. [f] Reference 46. [g] Private communication from P. Kebarle cited in ref 12.

Unfortunately, the number of charged-group contributions that can be deduced from the currently available data is rather small even if we include those defined by a single experimental measurement. However, we can roughly estimate [$O^+(C)_3$] to be ~3.6 from the intercept of the correlation line for oxonium ions. From the foregoing discussion, the same quantity could be estimated in a different way by subtracting the experimental value of $\Delta G_{0,1}^\circ(Me_2O) + n\Delta G_{vap}^\circ$ from $-2.303RT$[$OH^+(C)_2$], which leads (cf. Table IV) to [$O^+(C)_3$] ~3.7. By analogous treatment of the gas-phase experimental data for pyridine,[47] we estimate [$N_{Ar}(C)(C_{Ar})_2$] to be ~0.7. While the energies of the gas-phase hydration processes ($\Delta G_{0,1}$) are not available for other singly protonated oxygen cations, these should[37] be approximately 0.6 times the corresponding attachment energies of acetonitrile. Further [log γ] values estimated on this basis are included in Table IV.

Hydration Effects on Proton and Alkyl-Group Transfer: Benzylation of Adenosine and Guanosine. The relationship between this method of estimating ionic hydration energies and the Hine and Mookerjee scheme greatly simplifies discussion of hydration energies in certain proton and alkyl transfer reactions. As an example, Scheme II shows the estimation of hydration energies, $\delta_{aq}\Delta G^\circ$ (i.e., $\Delta G_{gas}^\circ - \Delta G_{aq}^{\circ 5}$) of three processes involving benzyl chloride corresponding to the first steps in the bimolecular reactions. Application of eq 2 to reactants and products (except Cl^-) leads to cancellation of all [log γ] terms except those of the functional group being modified and its immediate neighbors. Moreover, the latter tend to be fairly small, the former being primarily responsible for the different hydration effects in these processes. Thus Arnett's[6] "rough first order guide to solvation behavior..." (cf. introduction) finds quantitative expression in the difference between the contributions of the modified and

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[44] Sen, U. *J. Am. Chem. Soc.* **1979**, *101*, 2531-2534.

[45] Kebarle, P. *Annu. Rev. Phys. Chem.* **1977**, *28*, 445-476.

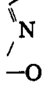
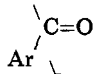
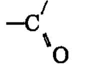
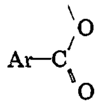
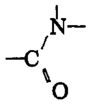
[46] Lau, Y. K.; Kebarle, P. *Can. J. Chem.* **1981**, *59*, 151-155.

[47] Davidson, W. R.; Sunner, J.; Kebarle, P. *J. Am. Chem. Soc.* **1979**, *101*, 1675-1680.

Scheme II. Estimation of Hydration Effects in Some Reactions of Benzyl Chloride

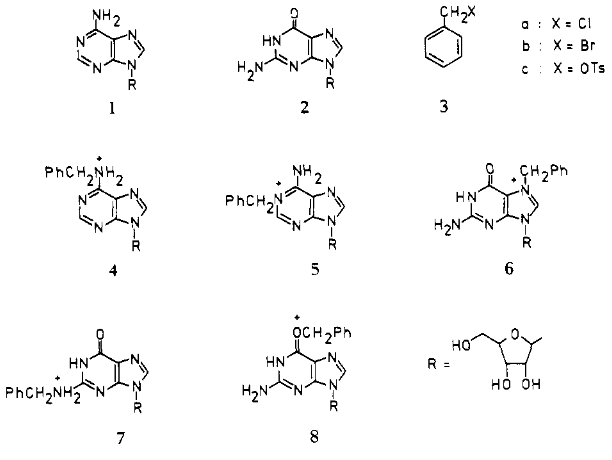
reaction	product reactant $-2.303RT(\sum_i[\log\gamma]i - \sum_i[\log\gamma]i)$	ΔG_{el}	+ $\Delta G^{g\rightarrow H_2O}(Cl^-)$	= $\delta_{aq}\Delta G°$
$C_6H_5CH_2Cl + MeNH_2 \longrightarrow C_6H_5CH_2\overset{+}{N}H_2Me + Cl^-$	$\underbrace{[\overset{+}{N}H_2(C)_2] - [NH_2(C)]}_{-10.7} + \underbrace{[CH_2(C)(N)] - [CH_2Cl(C)]}_{1.5}$	-40.8	-77.7	-127.7
$C_6H_5CH_2Cl + Me_2O \longrightarrow C_6H_5CH_2\overset{+}{O}Me_2 + Cl^-$	$\underbrace{[\overset{+}{O}(C)_3] - [O(C)_2]}_{\sim -1.1} + \underbrace{[CH_2(O)(C)] - [CH_2Cl(C)]}_{0.0}$	-42.2	-77.7	-121.0
$C_6H_5CH_2Cl + H_2O \longrightarrow C_6H_5CH_2\overset{+}{O}H_2 + Cl^-$	$\underbrace{[O\overset{+}{H_2}(C)] - [H_2O]}_{-27.5} + \underbrace{[CH_2(O)(C)] - [CH_2Cl(C)]}_{0.0}$	-42.2	-77.7	-147.4

Table VI. Approximate Hydration Energy Changes Accompanying Protonation or Alkylation of Functional Groups[a]

group	protonation	alkylation
$-NH_2$	−16.6	−10.7
>NH	−10.4	−5.0
⋗N	−5.3	−2.1
	−2.2	~3.2
—OH	−23.2	−12.1
>O	−14.1	~−1.1
>C=O	−12.6	~−2.1
	−8.5	~0.4
	−11.8	~−1.0
	−9.4	~−0.5
	−6.8	

[a] kcal mol⁻¹ from data in Table IV and ref 8.

Chart I



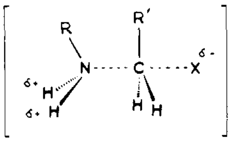


Figure 3. Charge development at the amine hydrogens accompany displacement of the leaving group X.

unmodified functional groups. Numerical values for a variety of these are collected in Table VI for proton and alkyl transfer.

With certain assumptions these ideas can be used to rationalize hydration effects on regioselective alkylation or aralkylation. An example is provided by the benzylation of adenosine (**1**, Chart I) and guanosine (**2**). Moschel, Hudgins, and Dipple[48] found that the ratio of N^6- to 1-benzylation of adenosine (**1**) by **3a–c** in buffered aqueous ethanol or aqueous DMF increased with the amount of water in the solvent. We assume that in a given solvent mixture the initial products are **4** and **5** and are formed irreversibly.[49] On this basis, the relative rates of the processes leading to them therefore determine the ratios of isolable products. According to our simple treatment, hydration effects contribute some 13 kcal mol⁻¹ (Table VI) more to the exothermicity of processes leading to **4** compared to **5**. The operation of a parallel effect in the corresponding transition states would then completely account for the experimental result. The same authors found that increasing the water content in aqueous ethanolic mixtures led to an increase in ratio of N^2- to 7-benzylation of guanosine and a parallel but smaller effect for the O^6- to 7-benzylation ratio.[50] Unfortunately, appropriate data are not avilable for us to deduce hydration parameters for the imidazole sp^2 nitrogen. However, if we assume that these will be similar to those for the pyridine nitrogen, the experimental results can be rationalized in exactly the same way via initial formation of **6–8** (cf. Table VI).

Treatment of complex polyfunctional molecules in terms of their isolated groups obviously ignores many factors that may be significant. However, it is our hope that the present treatment will at least form a convenient starting point for consideration of the more subtle effects associated with intersubstituent interactions. We shall take this up again briefly in the following section.

The parallel between hydration effects on the free energies and the rates of formation of, e.g., **6–8** is of course based on the idea that charge development in the transition states parallels that in the products. For example, partial transfer of charge from the amino group (cf. Figure 3) increases the polarity of the NH bonds and therefore

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[48] Moschel, R. C.; Hudgins, W. R.; Dipple, A. *J. Org. Chem.* **1979**, *44*, 3324–3328.

[49] More complex behavior is expected for highly stabilized aralkyl substituents where subsequent loss of the latter can occur. Cf.: Dipple, A.; Moschel, R. C.; Hudgins, W. R. *Drug Metab. Rev.* **1982**, *13*, 249–268.

[50] The logarithms of the relative yields of N^2- to 7- and O^6- to 7-benzylation of guanosine tabulated in ref 48 were directly proportional to the mole fractions of water in the solvent mixtures. For example, linear regression analysis of the data for N^2-benzylation in aqueous ethanol gave the following proportionality factors: **3a**, 4.75; **3b**, 4.71; **3c**; 2.54; and for O^6-benzylation: **3b**, 3.2; **3c**, 1.86. All correlation coefficients were ≥0.99.

the strengths of the hydrogen bonds from the solvent to them. Thus the better the leaving group X, the "earlier" or less product-like the transition state is expected to be,[51] and the smaller therefore the development of charge and associated hydration effect. Consistent with this reasoning is the observation that hydration the N^2:7 and O^6:7 benzylation ratios of guanine by **3c** were found to be about one-half those involving the inferior halide leaving groups (**3a** and **3b**).[50]

Interactions between Polar Groups. For neutral species in which more than one polar functional group was *present,* HM *found errors in calculated hydration energies,* requiring them to introduce a set of "distant polar interaction".[8] These corrections ranged from −9.6 to 1.5 kcal mol^{-1} although most fell in the range ±1.5 kcal mol^{-1} and were, on the whole, readily comprehensible in hydrogen-bonding terms. Analogous, and probably larger, polar interactions must be expected to apply to contributions involving charged groups. Unfortunately there are virtually no data available for evaluations of these.

Arnett and co-workers have studied the hydration of substituted pyridines and pyridinium ions in considerable detail.[6,13,36] Most of their work relevant to the present question, however, has focused on hydration *enthalpies* rather than energies. Here they found[6] that substitution of the pyridine nucleus by electron-withdrawing groups led to more negative, and by electron-releasing groups more positive, hydration enthalpies. This was very reasonably attributed to substituent-induced changes in the capacity of the pyridinium ion to participate in hydrogen bonding to the solvent.[6] Arnett and Chawla[36] also considered the hydration *energies* of some of these compounds but unfortunately none carrying strongly electron-attracting or -donating groups. In Table II we have therefore included *estimates (see footnote h)* for several such compounds. Although rather crude, these should be sufficient to indicate the approximate magnitudes and directions of the effects. For the substituents 4-NMe_2, 4-OMe, 4-Me, and 4-Cl, our estimates of $\Delta G^{\circ\, g \rightarrow H_2O}$ were less negative than those calculated from the model by ~6, ~3, −0.3, and ~−1 kcal mol^{-1}, respectively. These are of about the magnitude expected for the mutual modification of the hydrogen-bonding capacities of the pyridinium and substituent groups. Thus, according to the analysis of Scheme I (cf. eq 7), the hydration energies of 4-substituted pyridinium ions should be less negative than those given by the model by the corresponding energies of eq 8. From the gas-phase

$$\mathrm{XpyH^+ + pyH^+\cdots OH_2 \rightleftarrows XpyH^+\cdots OH_2 + pyH^+} \quad (8)$$

data of Kebarle,[47] these are 2.7, 1.4, 0.7 and −0.1 kcal mol^{-1}, respectively. Additionally, hydrogen bonding to either the dimethylamino or methoxy groups must be greatly reduced relative to that in the corresponding benzene derivatives. This follows from the unfavorable orientation of the solvent water molecule in the electrostatic field of the ion that would be required. If hydrogen bonding to these substituents is abolished altogether, the hydration energies of 4-dimethylamino and 4-methoxypyridinium should be less negative by a further ~3.7 and ~0.4 kcal mol^{-1} (by comparison with hydrocarbon analogues[8]), yielding total estimates of ~6 and ~2 kcal mol^{-1}, respectively and ~1 kcal mol^{-1} for 4-methylpyridinium. The almost quantitative agreement between the polar interactions estimated in this way and the corresponding quantities in the final column of Table II is probably fortuitous but does suggest that these arguments are at least qualitatively reasonable.

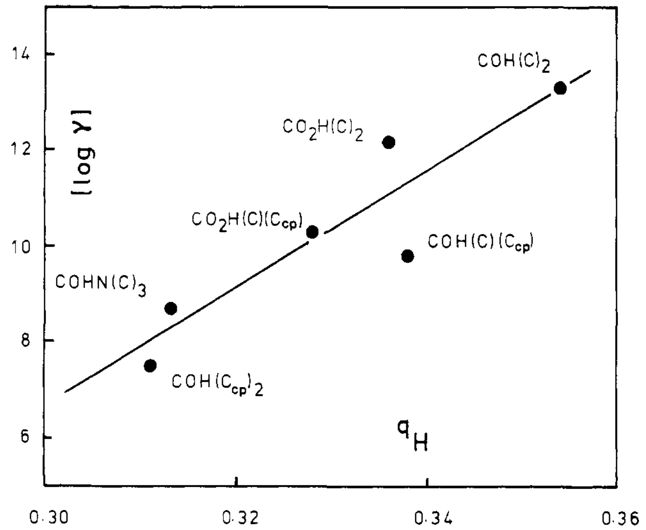

Figure 4. Relationship between [log γ] and the protonic charge, q_H (STO-3G) for carbonyl groups.

Although they lack the structural homogeneity of the pyridinium ions, the hydration energies of differently substituted protonated carbonyl compounds vary in a broadly analogous manner. Taft has noted that internal charge delocalization from the protonic site strongly reduces solvation.[37] When two groups share a common atom the distant polar interactions are automatically taken into account.[8] This is reflected in the large variation in the magnitudes of the carbonyl group contributions listed in Table IV. In general, groups that reduce the protonic charge lead to smaller [log γ] values. Although no precise correlation would be expected,[52] the latter are approximately correlated with the protonic charge given by an STO-3G Mulliken population analysis of the corresponding methyl compounds[53] (Figure 4). On the other hand the estimated [log γ] values of the fully alkylated carbonyl groups vary by considerably less. The positions of the cyclopropyl-containing groups in Figure 3 are noteworthy, reflecting the marked ability of this substituent to stabilize an adjacent positive charge.[54] Indeed it was necessary to introduce a separate group contribution for this substituent.

Summary

A simple method for estimating cationic hydration energies has been described. This involves a scheme of additive group contributions, analogous to that described by Hine and Mookerjee[8] for neutral species, together with an estimate of the electrostatic free energy of charging the cavity in the solvent containing the ion. The size of the latter was deduced from the van der Waals radii of the constituent atoms including one molecule of water assumed to be strongly bound to each hydrogen atom of the charged group. The ability to reproduce the experimental results was rather insensitive to the particular choice of van der Waals radii or to the expression used to calculate the electrostatic term. Marginally superior results were ob-

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(51) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper & Row: New York, 1976; pp 102–103; pp 245–250.

(52) An analogous correlation of excellent precision has however been reported for the structurally more homogeneous pyridinium ions.[47]

(53) Single SCF calculations at the MNDO geometries using the GAUSSIAN 77 program package: DeFrees, D. J.; Levi, B. A.; Pollack, S. K.; Hoit, R. F.; Blurock, N.; Pietro, W. J.; Hehre, W. J., to be submitted for publication in the Quantum Chemical Program Exchange. We are most grateful to Professor Hehre for making his program available to us prior to publication.

(54) Wolf, J. F.; Harch, P. G.; Taft, R. W.; Hehre, W. J. *J. Am. Chem. Soc.* **1975**, *97*, 2902–2904.

tained by using radii suggested by Pauling[23] together with a simplification of Beveridge and Schnuelle's[19] concentric shell model of electrostatic hydration suggested by Abraham and Liszi.[18] This was also considered to be the most intellectually satisfactory procedure and was adopted throughout.

The magnitudes of the derived ionic-group contributions were largely comprehensible in terms of specific hydrogen-bonding interactions to the solvent. From these data approximate hydration energy changes accompanying protonation or alkylation of certain functional groups were tabulated and applied to the rationalization of solvent effects on product ratios in the benzylation of adenosine and guanosine.

Interactions between functional groups in the same molecule can lead to significant modifications in hydration behavior explicable in terms of parallel modification of the strengths of hydrogen bonding to the solvent.

Acknowledgment. We thank the National Institutes of Health for financial support for this research though Contract CP 85628, Grant No. CA 23712 (to J.D.S.), and Grant No. CA 30475 (to G.P.F.).

Registry No. 1, 58-61-7; **2**, 118-00-3; **3a**, 100-44-7; **3b**, 100-39-0; 3c, 1024-41-5; **4**, 85649-98-5; **5**, 85649-98-5; **6**, 71171-61-4; **7**, 85649-99-6; 8, 85650-00-6; $MeOH_2$, 17836-08-7; $EtOH_2$, 18639-79-7; Me_2OH, 17009-82-4; Et_2OH, 17009-83-5; MeEtOH, 52067-06-8; $(CH_2)_4OH$, 27659-93-4; $(CH_2)_5OH$, 27659-94-5; $MeNH_3$, 17000-00-9; $EtNH_3$, 16999-99-8; *n*-$PrNH_3$, 17033-39-5; *i*-$PrNH_3$, 16999-98-7; $BuNH_3$, 16999-97-6; *sec*-$BuNH_3$, 34755-45-8; *t*-$BuNH_3$, 22534-19-6; $C_6H_5NH_3$, 17032-11-0; 3-$MeC_6H_4NH_3$, 18971-81-8; 4-$MeC_6H_4NH_3$, 17112-11-7; Me_2NH_2, 17000-01-0; $(CH_2)_3NH_2$, 66203-35-8; $(CH_2)_4NH_2$, 55526-39-1; $(CH_2)_5NH_2$, 17523-59-0; Et_2NH_2, 19497-23-5; Pr_2NH_2, 29384-47-2; $PhMeNH_2$, 17456-49-4; Me_3NH, 16962-53-1; Me_2EtNH, 71467-09-9; $MeEt_2NH$, 85649-95-2; Et_3NH, 17440-81-2; Pr_3NH, 50985-90-5; $(CH_2)_4MeNH$, 66203-36-9; $PhMe_2NH$, 17835-98-2; Me_4N, 51-92-3; Et_4N, 66-40-0; Me_2COH, 43022-03-3; $(CH_2)_4COH$, 64725-64-0; *t*-BuMeCOH, 68706-39-8; *i*-Pr_2COH, 18639-86-6; *c*-$C_6H_{11}MeCOH$, 75031-99-1; PhMeCOH, 39922-13-9; *c*-PrMeCOH, 70058-20-7; *c*-Pr_2COH, 70058-21-8; Me(OMe)COH, 39014-36-3; Me(OEt)COH, 39014-41-0; Ph(OMe)COH, 59137-82-5; *c*-Pr(OMe)COH, 85649-96-3; $Me(NMe_2)COH$, 52754-55-9; PyH, 16969-45-2; 2-Me(py)H, 16969-46-3; 3-Me(py)H, 17203-41-7; 4-Me(py)H, 16950-21-3; 4-NMe_2(py)H, 55277-36-6; 4-OMe(py)H, 33613-95-5; 4-Cl(py)H, 37449-65-3; 2,4-Me_2(py)H, 17126-11-3; 2,5-Me_2(py)H, 64343-93-7; 2,6-Me_2(py)H, 17033-11-3; 2,5-Me_2(py)H, 19495-57-9; 4-*t*-Bu(py)H, 40569-37-7; 2,6-*t*-Bu_2(py)H, 62907-61-3; $MeNH_2$, 74-89-5; Me_2O, 115-10-6; H_2O, 7732-18-5.

Supplementary Material Available: Tables for calculating molecular volumes and electrostatic hydration free energies (9 pages). Ordering information is given on any current masthead page.

Deuterium and Tritium Labeling with the Zinc–Sodium Iodide Method

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Primary and secondary hydroxyl groups can be replaced by deuterium or tritium when the corresponding sulfonate esters are reduced with zinc, sodium iodide, and deuterium or tritium oxide in 1,2-dimethoxyethane. The method tolerates a variety of other reducible functionalities, namely, α,β-enone, ketone, and ester. The labeling can be conducted with a high regiospecificity in the presence of enolizable hydrogens. The method is less satisfactory for a stereospecific replacement of secondary hydroxyl groups, yielding mixtures of stereoisomers and olefins as byproducts. The distribution of the stereoisomers depends on the rate of configurational inversion in the intermediary iodides arising by displacement of the original tosyloxy group. Deuterium NMR spectra and their use in the configurational assignment are discussed.

The reductive removal of the hydroxyl group is a standard method of deuterium labeling.[1] The hydroxyl to be removed is first converted to an activated form (a sulfonate ester, halide, or thiocarbonate) and then reduced with a suitable reagent, e.g., $LiAl^2H_4$,[1,2] NaB^2H_3CN,[3] $Li(C_2H_5)_3B^2H$,[4] $(n\text{-}C_4H_9)_3Sn^2H$,[5] $Zn\text{–}Cu/^2H_2O$,[6] Li/THF-*t*-$C_4H_9O^2H$,[7,8] or Zn/CH_3COO^2H.[9,10] While the reduction utilizing metal deuterides can be conducted with a high regio- and stereospecificity, the cost may become prohibitive when scaling up the preparation. Especially tritium introduction may pose a problem, for the corresponding

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