We suggest that these two types of reaction site, which we shall call "open" (lower τ) and "masked" (higher τ), are in fact present in all the labeled matrices; where, however, we have interposed a spacer between the label and its point of attachment to the solid phase, the two components of the EPR spectrum are not resolved; the rotational freedom of the label is not sensitive to the site of attachment of the spacer to the matrix.

Evidence for this contention was obtained by subjecting the ten labeled agaroses to a cycle of solvent changes: water to ethanol, from this to 1,4-dioxane and finally to *n*-heptane.[15] A progressively less polar environment is thus experienced by a label exposed to free solution. The agarose was observed to contract increasingly during the cycle, and two components were now visible in the EPR spectrum of each product in ethanol.[11] All these changes were completely reversible; that is, by addition of water at any point in the cycle one could return to spectra such as those shown in Figure 1.

These observations are in accord with a model for the structure of precipitated agarose in which separate polysaccharide strands associate,[16] probably by hydrogen bonding, giving rise to some form of tertiary structure. We propose that "open" ligand attachment sites are located on regions of single stranded, unassociated chain, and that "masked" sites are created by chain associations.

However, line shapes resembling that in Figure 1A can also arise as a result of very anisotropic rotational reorientation of a spatially isotropic distribution of spin labels.[17] Thus rapid rotation could occur about the single bonds joining a label to the polysaccharide matrix, motion perpendicular to this being more restricted.

Further investigations aimed at the elucidation and extension of this model are in progress.

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(1) See, e.g., Affinity Chromatography, P. Cuatrecasas and C. B. Anfinsen, *Annu. Rev. Biochem.*, **40**, 259 (1971).
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(6) Agarose was obtained as gifts of Sepharose 4B and CNBr-activated Sepharose 4B from Pharmacia, and as a gift from Marine Colloids, Ltd. (SKA-Me 11335).
(7) In cases where the activation was performed in the laboratory, the method of S. C. March, I. Parikh, and P. Cuatrecasas, *Anal. Biochem.*, **60**, 149 (1974), was used.
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(9) Obtained from Eastman.
(10) In the absence of a spacer, and for small *n*, the EPR spectrum of the products was sufficiently broad that the presence of noncovalently bound label, characterized by a sharp triplet, was obvious. This enabled us to design a thorough washing procedure; six washes with 10 mL of buffer to 0.1 g of product, using each buffer alternately, were generally enough.
(11) Detailed results to be published in the full paper.
(12) Calculated according to the method of T. J. Stone, T. Buckman, P. L. Nordio, and H. M. McConnell, *Proc. Natl. Acad. Sci. U.S.A.*, **54**, 1010 (1965), which assumes Lorentzian line shape and isotropic tumbling of the label. Because these conditions are not fulfilled, and because there is, for example, an estimated 20% error in the calculation for Figure 1B, and no estimate of τ has been quoted for Figure 1A, we attach only order-of-magnitude significance to the figures.
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John D. Aplin, Laurance D. Hall*
Department of Chemistry, The University of British Columbia
Vancouver, British Columbia, Canada V6T 1W5
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Gas-Phase Acidities: Alkanethiols

Sir:

The order of acidity of the simple aliphatic alcohols in the gas phase is known to be H_2O < MeOH < EtOH < *i*-PrOH < *t*-BuOH.[1-3] This order is reversed, however, upon solvation in a variety of solvents.[4-6] Calorimetry has revealed that in dimethyl sulfoxide (Me_2SO) the reversal results primarily from the effect of alkyl substituents upon the heat of solvation of the anions.[7] It appears that increasing bulk of the alkyl substituent strongly hinders solvation of the anion and leads to destabilization of the anion relative to the neutral acid, but the extensive ion-pairing of alkoxides in Me_2SO[8] makes interpretation of the calorimetric results somewhat uncertain. Ion-pairing does not occur in water, but unfortunately only the free energies of ionization, $\Delta G°_i{}^{H_2O}$, are known there. The low acidity of the alcohols seems to have prevented determination of the entropies, $\Delta S°_i{}^{H_2O}$, and the enthalpies, $\Delta H°_i{}^{H_2O}$, of ionization.

The entropies and enthalpies of ionization in water are known for the alkanethiols, the next higher group 6A acids.[9] We have, therefore, measured the acidities of several thiols in the gas phase to determine the intrinsic effect of alkyl groups on acidity and to compare gas-phase acidities with aqueous acidities where ion-pairing is absent.

Pulsed ion cyclotron resonance (ICR) mass spectrometry was used to measure equilibrium constants for proton-transfer reactions between the thiols, RSH,

$$A^- + RSH = RS^- + HA \qquad (1)$$

and various reference acids, HA, using established techniques.[3,10-13] Methyl nitrite was used as the source of negative ions. Double resonance between A^- and RS^- was observed for all acid pairs measured, indicating that the reactions are fast compared to the time scale of the experiment. Multiple overlaps with different reference acids provided results which agreed to within ±0.2 kcal/mol for all acid pairs measured.

The data in Table I show the effects of alkyl groups on the relative acidity of alkanethiols and alcohols in the gas phase and in aqueous solution. The thiols are quite similar to the alcohols in substituent and solvation effects on acidity: increasing the size of the alkyl group results in increased gas-phase acidity and decreased aqueous acidity. In the gas phase the incremental change in going from Me to Et is larger for O than for S acids, but Et to *i*-Pr and *i*-Pr to *t*-Bu produces the same acidity increases for both series. In aqueous solution there is a complete inversion in the order of acidities for both the alcohol series and the alkanethiol series. This trend is analyzed for the thiols in Table II in terms of the effects of alkyl substituents on the relative enthalpy and entropy of ionization in the gas phase and in aqueous solution. In the gas phase the entropy change is very small for proton-transfer reactions such as in Table II. The numbers shown were calculated using literature values for the absolute entropies of the alkanethiol

Table I. Relative Acidities in the Gas Phase and in Aqueous Solution at 298 K[a]

Reference Reaction: $RS^- + t\text{-}BuSH = t\text{-}BuS^- + RSH$		
R	$\Delta G°_{GP}$	$\Delta G°_{H_2O}$[b,c]
Me	−4.1	1.22
Et	−2.5	0.83
n-Pr	−1.7	0.78
i-Pr	−0.8	0.49
t-Bu	(0.0)	(0.0)
H	1.7	5.75

Reference Reaction: $RO^- + t\text{-}BuOH = t\text{-}BuO^- + ROH$		
R	$\Delta G°_{GP}$[d]	$\Delta G°_{H_2O}$[e]
Me	−5.6	1.7
Et	−2.7	1.0
i-Pr	−0.8	0.3
t-Bu	(0.0)	(0.0)
H	−17.8	1.1

[a] All values are kcal/mol. [b] Reference 9. [c] M. M. Kreevoy, B. E. Eichinger, F. E. Stary, E. A. Katz, and J. H. Sellstedt, *J. Org. Chem.*, **29**, 1641 (1964). [d] Reference 3, with revision of the values for MeOH and EtOH. [e] Reference 6.

Table II. Relative Enthalpies and Entropies of Ionization of Alkanethiols in the Gas Phase and in Aqueous Solution[a]

Reference Reaction: $RS^- + t\text{-}BuSH = t\text{-}BuS^- + RSH$				
	Gas-phase[d]		Aqueous solution	
R	$\Delta H°_{GP}$	$\Delta S°_{GP}$	$\Delta H°_{H_2O}$[b]	$\Delta S°_{H_2O}$[c]
Me	−3.8	1.2	—	—
Et	−2.4	0.9	−1.1	−6.5
i-Pr	−0.9	−0.4	−0.1	−1.8
t-Bu	(0.0)	(0.0)	(0.0)	(0.0)
H	1.9	0.7	—	—

[a] Enthalpies are in kcal/mol and entropies are in eu. [b] Reference 9. [c] Calculated from $(\Delta H° - \Delta G°)/T$. [d] $\Delta H°$, ± 0.2 kcal/mol; $\Delta S°$ ± 1 eu.

Table III. Gas Phase Thermochemical Data for the Alkanethiols and Alcohols[a]

	$AH = H^+ + A^-$			
AH	$\Delta G°_{298}$	$\Delta H°_{298}$	DH°(A − H)[b]	EA(A)[c]
H_2S	344.7	351.1	91	53
MeSH	350.5	356.8	87	44
EtSH	348.9	355.3	88	46
n-PrSH	348.1	354.7	86	45
i-PrSH	347.2	353.9	87	47
t-BuSH	346.4	353.0	87	48
H_2O	384.0[d]	390.7	119.3[e]	42
MeOH	371.8	378.4	103.6	39
EtOH	368.9	377.5	104.3	40
i-PrOH	367.0	373.5	(104 estimate)	44
t-BuOH	366.2	372.7	104.2	45

[a] All numbers are in kcal/mol. [b] RSH, ref 16, ±1 kcal/mol; ROH, S. W. Benson and R. Shaw, *Adv. Chem. Ser.*, **No. 75,** 288 (1968) ±2 kcal/mol. [c] Calculated from this work using EA(A) = DH°(A − H) − $\Delta H°_{298}$ + IP(H·) ± 3 kcal/mol. [d] Calculated using EA(OH) = 42.2 kcal/mol from H. Hotop, T. A. Patterson, and W. C. Lineberger, *J. Chem. Phys.*, **60,** 1806 (1974). [e] Reference 16.

neutrals and an isoelectronic approximation[15] for the anion which equates the absolute entropy of RS^- with that for the corresponding alkyl chloride. It is important to note that the relative enthalpies of ionization are of comparable magnitude and in the same direction for both the gas-phase and aqueous solution. Thus, the main factor which causes the inverted acidity order of the alkanethiols is the entropy of ionization in aqueous solution. The data for $\Delta S°_{H_2O}$ in Table II show that in aqueous solution there is an increase in the entropy for the reaction $RS^- + H^+ = RSH$ as the size of the alkyl group is increased. This trend can be explained by either a relative increase in the entropy of solvated RSH or a relative decrease in the entropy of solvated RS^- with increasing size. Data on the entropy of solvation of the neutral thiols are required to distinguish between these two possibilities. Lacking these data, it appears more reasonable that the entropy of solvation of the neutrals is the controlling factor not only in the entropy of ionization but also in the relative aqueous acidities.

The gas-phase equilibrium experiments provide a measure only of relative acidities, but an absolute scale can be constructed by anchoring the relative measurements to certain well-established points. Hydrogen sulfide was used as the anchor point for the thiols. The heterolytic bond dissociation energy, $\Delta H°_{298}$, for H_2S was calculated using the following thermodynamic cycle:

$$H_2S = H\cdot + \cdot SH \quad \Delta H°_{298} = DH°(HS\text{-}H)$$

$$H\cdot + \cdot SH = H^+ + SH^- \qquad \Delta H°_{298} \cong \Delta H°_0 = IP(H) - EA(SH)$$

$$H_2S = H^+ + SH^- \qquad \Delta H°_{298} = DH°(HS\text{-}H) - EA(SH) + IP(H)$$

The enthalpy change for the electron transfer reaction at 298 K is approximately the same as at 0 K since ΔC_p for the reaction is expected to be quite small. The absolute gas-phase acidity of H_2S, $\Delta G°_{298}$ for the heterolytic bond dissociation, is obtained from $\Delta H°_{298}$ by subtracting $T\Delta S°$, where $\Delta S° = S°(SH^-) + S°(H^+) - S°(H_2S)$. The absolute entropy of SH^- is taken within the accuracy of the isoelectronic approximation[15] to be the same as $S°$(HCl). Using DH°(HS-H) = 91 ± 1 kcal/mol,[16] EA(SH) = 53.5 ± 0.2 kcal/mol,[17] IP(H) = 313.6 kcal/mol,[18] $S°(H_2S)$ = 49.15 eu,[18] $S°(H^+)$ = 26.0 eu,[18] and $S°(SH^-) \cong S°$(HCl) = 44.64 eu,[18] the gas-phase acidity of H_2S is calculated to be $\Delta G°_{298}$ = 344.7 ± 2 kcal/mol.

Table III was constructed in this way by referencing the relative gas phase acidities of the alkanethiols to H_2S and the alcohols to HF. By assuming literature values for the various bond strengths, electron affinities of RO· and RS· radicals can be calculated. As has been pointed out previously, the EA(RO·) values are in good agreement with electron photodetachment thresholds.[3,19] To our knowledge, these are the first reported values for the electron affinities of the RS· radicals. It is apparent that the relative gas-phase acidities of alkanethiols, H_2S, and the alcohols are controlled by the electron affinities of the radicals, with the bond energies nearly constant in each series. Water is an anomalous result in these two series because its gas-phase acidity relative to the alcohols is controlled by the unusually large HO-H bond dissociation energy.

Enthalpies of ionization of the thiols in solution are much smaller than in the gas phase. For example, $\Delta H°_{298}$ is 20.5 kcal/mol for the reaction $EtSH + H_2O = EtS^- + H_3O^+$ in aqueous solution,[9] whereas in the gas phase $\Delta H°_{298}$ is computed to be 185.3 kcal/mol using the following thermodynamic cycle:

$$EtSH = EtS^- + H^+ \quad \Delta H°_{298} = 355.3 \text{ kcal/mol}$$

$$H^+ + H_2O = H_3O^+ \qquad \Delta H°_{298} = -PA(H_2O) = -170 \text{ kcal/mol}^{20}$$

$$EtSH + H_2O = EtS^- + H_3O^+ \quad \Delta H°_{298} = 185.3 \text{ kcal/mol}$$

This is a reasonable result and can be attributed primarily to stabilization of the ionic products by solvation.

This work demonstrates that a wealth of thermochemical data results from quantitative pulsed ICR studies of gas phase reactions and that combination of the gas phase data with solution phase thermochemical data can reveal new insights into the process of solvation. We are currently involved in measuring the gas phase acidities of a wide variety of Brönsted acids.

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John E. Bartmess, Robert T. McIver, Jr.*
Department of Chemistry, University of California
Irvine, California 92717

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Organic Synthesis Involving Multipolymer Reactions. Polymeric Trityllithium[1,2]

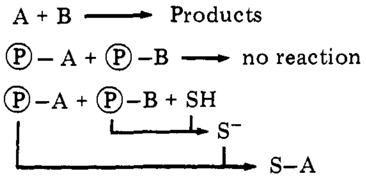
Sir:

The use of polymeric reagents in general organic synthesis has greatly increased in recent years due to a number of distinct advantages these reagents possess over analogous, soluble, low molecular weight reagents. The major advantages are insolubilization and immobilization of the polymer-attached reagent and the possibility of influencing reaction paths by specially tailored polymeric carriers. Several recent articles review this subject exhaustively.[3-5]

The use of more than a single polymeric reagent in reactions, either simultaneously or consecutively, has been rather limited to date. We have demonstrated the usefulness in certain reactions of attaching two reagents to the same polymer.[6] An ingenious method for detection of highly reactive intermediates has been developed, using two polymeric reagents simultaneously.[7] In another study two homogeneous catalysts were attached both to two mixed polymer batches and to the same batch for effecting consecutive catalytic reactions.[8]

We have shown previously that two reagents possessing high reactivity toward each other are rendered completely inactive by their attachment to two insoluble polymer batches, respectively.[6] In this communication we report on the use of this effect in selective synthetic reactions ("multipolymer reactions"), in which two or more polymeric reagents react indirectly through the mediation of a soluble "messenger" reagent. When the polymers are mixed in a common vessel we term the process a "wolf and lamb" reaction.[9] In such reactions both kinetic factors and equilibrium conditions are expected to differ from those prevailing in conventional reactions in solution, or in reactions utilizing a single polymeric reagent. This is due to the unique possibility of imposing close spacial proximity on two reagents highly reactive toward each other.

Scheme I



Ⓟ = insoluble polymer
A, B, SH = soluble reagents
S^- = reactive anion

When the polymers are placed in different, interconnected vessels a "chemical cascade" is formed. Such a system is expected to substantially improve handling convenience and speed of multi-step syntheses, leading possibly to automation of such processes. Some of these advantages are illustrated by the experiments described below.

"Wolf and Lamb" Reactions. A general scheme of the reactions studied is shown in Scheme I.

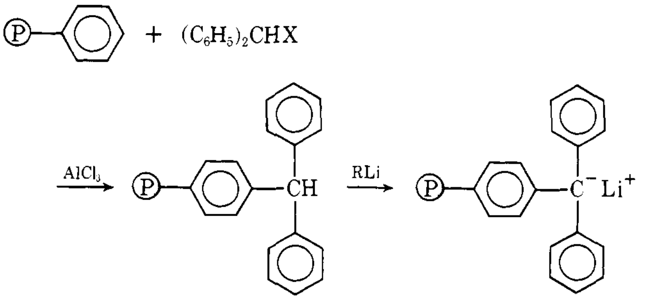
SH denotes a compound with acidic protons. Ⓟ-B is a polymeric base converting SH into its conjugate base S^-, which then reacts with an electrophilic polymer Ⓟ-A to yield the product S-A. In similar reactions in solution, S-A is often obtained in low yield because of side reactions of S^- or of S-A.

Previously, it was shown that, by immobilization of a carbon acid on a polymer, the extent of side reactions such as self-condensations and proton exchange with the products may be diminished.[10] It is shown below that the effect of such competing reactions may be eliminated also by the simultaneous use of two polymeric reagents and a soluble carbon acid.

A novel polymeric reagent, polymeric trityllithium (I), was synthesized for these reactions. It was prepared by Friedel-Crafts alkylation of polystyrene[11] by benzhydrol or benzhydryl chloride,[12] followed by reaction of the resulting polymeric triphenylmethane with methyllithium or *n*-butyllithium in THF or in 1,2-dimethoxyethane, as shown in Scheme II.

Loadings of up to 2.3 mmol/g of triphenylmethane moieties were indicated by increase in weight. This agreed well with a loading of 2.2 mmol/g of trityl anion as measured by

Scheme II



I

X = Cl, OH
R = CH_3, n-C_4H_9