

Solubilities and Hydrophobic Interactions in Aqueous Solutions of Monoalkylbenzene Molecules

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Solubilities of a series of monoalkylbenzene molecules in water were determined spectroscopically at several temperatures. The standard free energies of transferring these solutes from the gas into the liquid phase were calculated. From these data we have estimated the hydrophobic interaction between a methane molecule and the various alkyl residues of these solutes.

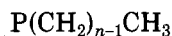
1. Introduction

In the course of our study of the problem of hydrophobic interactions (HI),¹⁻⁴ we have raised two questions the answers to which are believed to be of central importance to the understanding of the phenomenon of HI and its contribution to association processes in biological systems.

The first question is concerned with the range of the HI, as compared with the range of the direct intermolecular forces operating between the same pair of molecules (or groups in molecules). The second is concerned with both the magnitude and the range of the effect of adjacent groups on the HI between two simple molecules (or non-polar groups in molecules).

At present we know of no experimental methods for studying the first problem. This seems to be more amenable to theoretical means, and some progress in this field has recently been published.⁵

Regarding the second question we have recently³ suggested a possible experimental way for studying the effect of adjacent groups on the strength of the HI. To do so, consider the following series of homologous molecules



where we have a normal alkyl chain attached to any group P on one of its edges.

We now consider the following process. We start with the solute S_n (i.e., the group P with an alkyl radical consisting of n methylene groups) and a methane molecule at fixed positions and orientation at infinite separation from each other, within the solvent at some temperature and pressure. We then bring the methane molecule to the edge of the solute S_n , such that the new configuration is closely resembling that of the solute S_{n+1} . The total free energy change for this process is written as

$$\Delta G(n \rightarrow n+1) = \Delta U(n \rightarrow n+1) + \delta G^{HI}(n \rightarrow n+1) \quad (1.1)$$

where ΔU is the (direct) energy change (or the vacuum free energy change) for the same process and δG^{HI} is the solvent contribution to the total free energy of the process.

For the latter, we have recently suggested an approximate measure in terms of experimentally measurable quantities,⁴ namely

$$\delta G^{HI}(n \rightarrow n+1) = \Delta \mu^\circ_{n+1} - \Delta \mu^\circ_n - \Delta \mu^\circ_{CH_4} \quad (1.2)$$

where $\Delta \mu^\circ_n$ is the standard free energy of transferring the solute S_n from the gas into the liquid. If the solvent is water δG^{HI} is a measure of the so-called hydrophobic interaction (HI). In this particular study we have chosen P as the phenyl ring and investigated the dependence of

δG^{HI} on the chain length of the alkyl residue. One could easily extend the same type of measurements to study the effect of various groups P on the strength of the HI. The choice of this particular group P was made because of the experimental feasibility and convenience in measuring the concentrations of the solutes S_n ($n = 0, 1, 2, \dots, 8$) in aqueous solutions. Some aspects of the experimental work are described in the next section. Then section III presents the results obtained and their interpretation in terms of hydrophobic interactions.

The same results are also reinterpreted in terms of the "solvent-induced probabilities" of finding certain states of a hypothetical system.

2. Experimental Section

The solubilities of a series of monoalkylbenzene compounds were measured in water at several temperatures between 5 and 50 °C. All the organic solutes were from Fluka, puriss grade (benzene 99.99%, all others 99.9%), and were used without further purification. Triple distilled water was used to prepare the solutions. The solubilities were determined spectroscopically by a Perkin-Elmer Model 450 spectrophotometer in the UV region. The temperature of the solution was maintained within ± 0.2 °C in a thermostat.

The molar extinction coefficients, ϵ , were determined by different and independent measurements. First, we prepared a solution of a known concentration of the solute (which was about 0.2–0.5 of the saturation value), and for which the optical density was determined. In order to ensure that all the weighted quantity of the solute has been dissolved in the water, we have in some cases first dissolved the solute in a small quantity of ethanol or methylcyanide, which was then dissolved in 1 L of water. (We have previously found that the small quantity of the ethanol or the methylcyanide had no detectable effect on the spectra of the solutions.)

The values of ϵ that were determined from the different solutions were found to agree with each other within 1%. Also the temperature dependence of ϵ was determined. The effect in the range of 5–50 °C is usually quite small. We found a decrease in ϵ of about 0.03% for an increase in temperature of 1 deg.

For the first three solutes (benzene, toluene, and ethylbenzene) the saturation concentrations were determined by two different methods. First, by direct contact of the water with excess of the solutes. In this case the two phases were stirred for about 48 h in a thermostat, and then the two phases were allowed to separate for about 24 h, and samples from the aqueous solution were taken for the spectroscopic measurements.

In the second method we have reached saturation of the solution through contact between water and the vapor of

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TABLE XI: Comparison between the Solubilities (in mol/L at $t = 25^\circ\text{C}$) of Benzene, Toluene, and Ethylbenzene Obtained from This Work and Other Sources

solute	this work	other sources	ref
benzene	2.33×10^{-2}	2.44×10^{-2}	8
		2.20×10^{-2}	9
		2.30×10^{-2}	10
		2.24×10^{-2}	11
		2.29×10^{-2}	12
toluene	6.69×10^{-3}	6.15×10^{-3}	8
		6.20×10^{-3}	13
		6.84×10^{-3}	10
ethylbenzene	2.00×10^{-3}	1.93×10^{-3}	8
		1.97×10^{-3}	10

the solute. This method has been described earlier,⁶ its main advantage being the lack of direct contact between the two liquid phases, which presumably reduces the possibility of supersaturation.⁶

Since the two methods gave almost the same results for the lower homologous molecules, we have used only the first method for the higher homologous in the series of these solutes.

We have also checked and confirmed the validity of Beer's law in these solutions up to the saturation concentrations.

The Ostwald absorption coefficients

$$\gamma_S = (\rho_S^W / \rho_S^G)_{\text{eq}} \quad (2.1)$$

were calculated from the solubilities of S in water, ρ_S^W (in mol L⁻¹), and from the vapor pressures P_S of the solutes taken from the literature⁷ and converted into molar density through $\rho_S^G = P_S / RT$.

The experimental data on all of the aqueous solutions of the alkylbenzenes are presented in Tables I-X (see paragraph at end of text regarding supplementary material). The vapor pressures P_S of the pure liquids were computed from data collected by Zwolinski and Wilhoit.⁷ From the Ostwald absorption coefficients γ_S , the standard free energies of transferring a solute from the gas into the liquid were calculated from

$$\Delta\mu^\circ_S = -RT \ln \gamma_S \quad (2.2)$$

The reproducibility of our solubility measurements was within 1%. Some comparisons between our results and the literature are made in Table XI. We feel that the accuracy of our results is sufficient to allow the processing and interpretation of these data in terms of hydrophobic interactions.

3. Results and Discussion

The values of $\Delta\mu^\circ_S$ obtained by the method described in the previous section were fitted to a polynomial of the second degree, as a function of the absolute temperatures, namely

$$\Delta\mu^\circ_S = a + bT + cT^2 \quad (3.1)$$

The coefficients a , b , and c as well as the standard deviation σ computed for each solute are given in Table XII.

The HI between a methane molecule and a solute S_n , defined in (2.2), was calculated for each case by using the smoothed values of $\Delta\mu^\circ_S$ obtained from polynomial (3.1). Also the corresponding enthalpies and entropies associated with the same process were calculated from (3.1) through

$$\delta S^{\text{HI}} = -(\partial / \partial T) \delta G^{\text{HI}} \quad (3.2)$$

$$\delta H^{\text{HI}} = \delta G^{\text{HI}} + T \delta S^{\text{HI}} \quad (3.3)$$

In all the cases we found that $|\delta G^{\text{HI}}|$ increases with the

TABLE XII: Coefficients of the Second Degree Polynomial for the Standard Free Energy of Transfer of the Solutes from the Gas into the Liquid as a Function of the Temperature, Eq 3.1

solute	a	b	c	σ^a
benzene	-7342.9	24.3	-0.009	8.34
toluene	-11705.1	49.3	-0.044	7.41
ethylbenzene	-21362.9	110.1	-0.138	16.99
<i>n</i> -propylbenzene	-17393.7	79.3	-0.079	15.70
<i>n</i> -butylbenzene	-26582.0	134.0	-0.160	16.31
<i>n</i> -pentylbenzene	-27621.6	131.6	-0.144	17.39
<i>n</i> -hexylbenzene	-28680.6	128.2	-0.127	23.79
<i>n</i> -heptylbenzene	-26489.8	101.5	-0.069	21.26
<i>n</i> -octylbenzene	-32478.7	129.6	-0.102	40.26

^a σ is the standard deviation for each of the solutes.

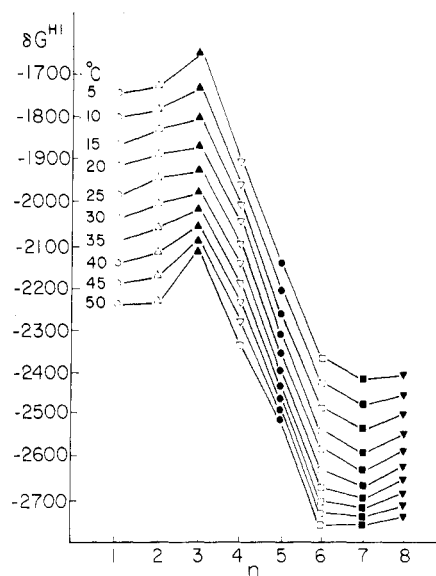


Figure 1. Values of $\delta G^{\text{HI}}(n-1 \rightarrow n)$ in cal/mol as a function of n at different temperatures as indicated next to each curve.

increase of the temperature. This is consistent with our previous finding^{3,4} that the strength of the HI increases with the temperature.

In Figure 1 we plotted $\delta G^{\text{HI}}(n-1 \rightarrow n)$ as a function of n (for $n = 1$ this corresponds to the formation of toluene from methane and benzene).

The general trends exhibited in this figure seem to indicate that for $n = 1, 2$, and 3 the values of δG^{HI} are either independent or slightly increasing with n . We believe that the main reason for this finding is the proximity of the phenyl ring, which makes the environment around the interacting methylene groups somewhat intermediate between water and a nonpolar liquid. Indeed the values of δG^{HI} for two methane molecules in water is about -2.17 kcal/mol whereas the values of δG^{HI} for $n = 1, 2$, and 3 are somewhat smaller than this figure.

For n 's between 3 and 6 there is a clear-cut increase in the strength of the HI. This is probably a result of the gradual shift of the interacting methylene groups from the phenyl ring. Finally for $n = 6, 7$, and 8 the values of δG^{HI} seem to level out at a constant value. We suspect that at $n \approx 6$ the effect of the phenyl ring becomes negligible and any further increase of the chain by a methylene group has no effect on δG^{HI} .

In Figures 2 and 3 we plot the average values δH^{HI} and δS^{HI} as a function of n . Although the error in the determination of these quantities is quite large we believe that the main trend shown in these figures is beyond the experimental error, namely, that both δH^{HI} and δS^{HI} decrease with n . This result was unexpected and in a sense it

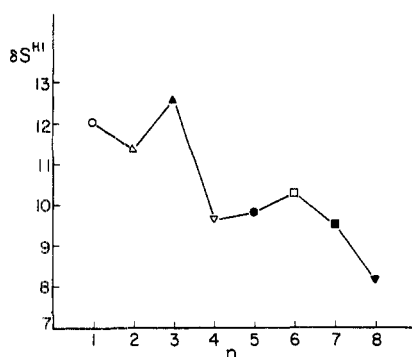


Figure 2. Average values of $\delta S^{\text{HI}}(n-1 \rightarrow n)$ in cal/(mol K) as a function of n . Computed from δG^{HI} values between 5 and 35 °C.

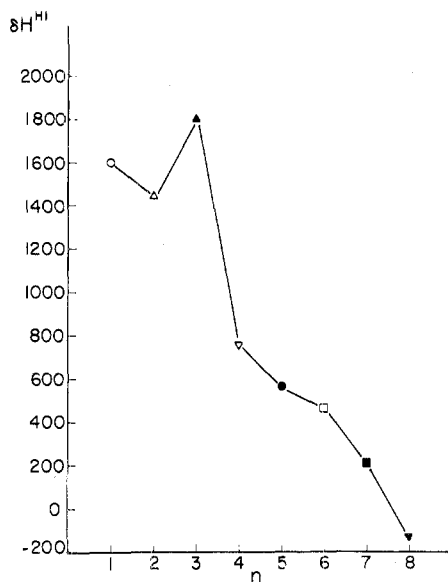


Figure 3. Values of $\delta H^{\text{HI}}(n-1 \rightarrow n)$ in cal/mol as a function of n . Computed from $\delta H^{\text{HI}} = \delta G^{\text{HI}} + T\delta S^{\text{HI}}$ at 20 °C.

contradicts our conclusion based on Figure 1. The reason is the following. The enthalpy and the entropy of the HI between two methane molecules in water are about 1.6 kcal/mol and 12 eu, respectively. We expected to find that the values of δH^{HI} and δS^{HI} for small n should have been smaller than the above cited figures, because of the proximity of the phenyl ring. As n increases, we expected that δH^{HI} and δS^{HI} would approach the values close to those in pure water. The experimental observation is in fact the opposite, and we have no rationalization for this finding.

We now turn to suggest a different interpretation of the results reported in Figure 1.

Consider the following system: water, at a given temperature and pressure, having eight solute molecules at fixed positions and orientations and at infinite separation from each other. Suppose that the methyl groups on the toluene molecule on the left-hand side of the first row of Figure 4 can be exchanged with any one of the hydrogens on the terminal methyl groups of the other molecules in the row. Any of these exchanges produces a new state of the system, and altogether we can produce eight states which are depicted by the eight rows in Figure 4.

In this system we may ask what is the probability of finding the system in one of these eight states? The relative probabilities of the j and i states are given by

$$P(j)/P(i) = \exp[-\Delta G(i \rightarrow j)/kT] = \frac{\exp[-\Delta U(i \rightarrow j)/kT] \exp[-\delta G^{\text{HI}}(i \rightarrow j)/kT]}{\exp[-\delta G^{\text{HI}}(i \rightarrow j)/kT]} \quad (3.4)$$

where $\Delta U(i \rightarrow j)$ is the direct (or the vacuum) energy change

State	1	2	3	4	5	6	7	8
1	CH_3/Ph	CH_3/Ph	$\text{C}_2\text{H}_5/\text{Ph}$	$\text{C}_3\text{H}_7/\text{Ph}$	$\text{C}_4\text{H}_9/\text{Ph}$	$\text{C}_5\text{H}_{11}/\text{Ph}$	$\text{C}_6\text{H}_{13}/\text{Ph}$	$\text{C}_7\text{H}_{15}/\text{Ph}$
2	H/Ph	$\text{CH}_2\text{CH}_3/\text{Ph}$	$\text{C}_2\text{H}_5/\text{Ph}$	"	"	"	"	"
3	"	CH_3/Ph	$\text{C}_2\text{H}_4\text{CH}_3/\text{Ph}$	$\text{C}_3\text{H}_7/\text{Ph}$	"	"	"	"
4	"	"	$\text{C}_2\text{H}_5/\text{Ph}$	$\text{C}_3\text{H}_6\text{CH}_3/\text{Ph}$	$\text{C}_4\text{H}_9/\text{Ph}$	"	"	"
5	"	"	"	$\text{C}_3\text{H}_7/\text{Ph}$	$\text{C}_4\text{H}_8\text{CH}_3/\text{Ph}$	$\text{C}_5\text{H}_{11}/\text{Ph}$	"	"
6	"	"	"	"	$\text{C}_4\text{H}_9/\text{Ph}$	$\text{C}_5\text{H}_{10}\text{CH}_3/\text{Ph}$	$\text{C}_6\text{H}_{13}/\text{Ph}$	"
7	"	"	"	"	"	$\text{C}_5\text{H}_{11}/\text{Ph}$	$\text{C}_6\text{H}_{12}\text{CH}_3/\text{Ph}$	$\text{C}_7\text{H}_{15}/\text{Ph}$
8	"	"	"	"	"	"	$\text{C}_6\text{H}_{13}/\text{Ph}$	$\text{C}_7\text{H}_{14}\text{CH}_3/\text{Ph}$

Ph =

Figure 4. Eight states of a system of a solvent with eight solute molecules at fixed positions and orientations and at infinite separation from each other.

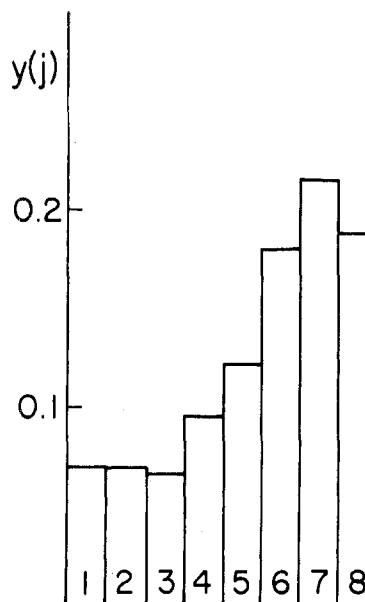


Figure 5. Values of $y(j)$ computed from eq 3.5 and 3.6 at 20 °C.

involved in the exchange reaction that leads from state i to state j .

The solvent contribution to the relative probabilities of state j and 1 is given by

$$\frac{y(j)}{y(1)} = \exp[-\beta \delta G^{\text{HI}}(1 \rightarrow j)/kT] = \frac{\exp[-\Delta \mu_j^\circ/kT] \exp[-\Delta \mu_0^\circ/kT]}{\exp[-\Delta \mu_1^\circ/kT] \exp[-\Delta \mu_{j-1}^\circ/kT]} = \frac{\gamma_j \gamma_0}{\gamma_{j-1} \gamma_1} \quad (3.5)$$

where γ_j is the Ostwald absorption coefficient of the solute j [note that $j = 0$ correspond to benzene and $j = 8$ to octylbenzene]. The result (eq 3.5) is quite obvious if we recognize the fact that the transition from state 1 to j involves the formation of the solutes S_j and S_0 from the pair of solutes S_{j-1} and S_1 . This scheme is a straightforward generalization of a simpler one described earlier.¹⁴ The values of $y(j)$ may be given direct probability meaning in a system of these eight states in which the direct interactions $U(i \rightarrow j)$ are "switched off", so that only the solvent properties determine the relative probabilities of the various states. We also normalize the sum

$$\sum_{j=1}^8 y(j) = 1 \quad (3.6)$$

so that from each experimentally determinable ratio (eq

3.5) we can solve to obtain the values of $\gamma(j)$. The results obtained in this way are shown graphically in Figure 5. We see that the relative probability of the methyl group to attach to the various alkyl groups is almost constant for $n = 1, 2$, and 3 and then increase for the higher values of n , reaching an almost constant value for $n = 6, 7$, and 8.

In Tables IX and X we report the solubility data for cumene (CU) and for *tert*-butylbenzene (TBB). The reason for making these measurements was to use the data to study the question of nonadditivity of the HI. More specifically, suppose we view the TBB as formed by toluene (TO) and three methane (ME) residues.

If the HI (i.e., the indirect part of the potential of average force between the four residues) was pairwise additive, we should have expected an equality of the form

$$\delta G^{\text{HI}}(\text{TO}, \text{ME}, \text{ME}, \text{ME}) = 3\delta G^{\text{HI}}(\text{TO}, \text{ME}) + 3\delta G^{\text{HI}}(\text{ME}, \text{ME}) \quad (3.7)$$

where the HI among the four particles is the sum of the six pairs of the HI between the six interacting pairs of particles. Unfortunately, we cannot estimate the extent of validity of a relation of the form (3.7). Though $\delta G^{\text{HI}}(\text{TO}, \text{ME})$ may be estimated by a similar approximation used in this paper, we have no information on the magnitude of $\delta G^{\text{HI}}(\text{ME}, \text{ME})$, i.e., the HI between two methylene groups at the configuration of a TBB molecule.

Therefore we addressed ourselves to a different question, which may be referred to as a *conditional* additivity. Namely, suppose we view the toluene residue as a fixed field of force. We now look at the (conditional and indirect) work required to bring three methane molecules to the final configuration near the toluene residue. This work may be symbolically denoted by $\delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2, \text{ME}_3/\text{TO})$. The question we now ask is to what extent this *conditional* (and indirect) work is pairwise additive in the sense that it fulfills the equality

$$\delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2, \text{ME}_3/\text{TO}) = \delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2/\text{TO}) + \delta G^{\text{HI}}(\text{ME}_1, \text{ME}_3/\text{TO}) + \delta G^{\text{HI}}(\text{ME}_2, \text{ME}_3/\text{TO}) = 3\delta G^{\text{HI}}(\text{ME}, \text{ME}/\text{TO}) \quad (3.8)$$

The validity of the additivity of form (3.8) may be studied by the same type of approximation used throughout the paper. Thus we estimate

$$\delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2, \text{ME}_3/\text{TO}) = \Delta\mu^{\circ}_{\text{TBB}} - \Delta\mu^{\circ}_{\text{TO}} - 3\Delta\mu^{\circ}_{\text{ME}} = -5.01 \text{ kcal/mol}$$

$$\delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2/\text{TO}) = \Delta\mu^{\circ}_{\text{CU}} - \Delta\mu^{\circ}_{\text{TO}} - 2\Delta\mu^{\circ}_{\text{ME}} = -3.61 \text{ kcal/mol}$$

Clearly such an additivity does not exist. We may define the extent of nonadditivity by the difference

$$\Delta\delta G^{\text{HI}} = \delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2, \text{ME}_3/\text{TO}) - 3\delta G^{\text{HI}}(\text{ME}_1, \text{ME}_2/\text{TO}) = -5.01 + 3 \times 3.61 = +5.82 \text{ kcal/mol} \quad (3.9)$$

Thus we conclude that the nonadditivity of the (conditional) hydrophobic interaction is *positive* and quite large, i.e., it is of the order of magnitude of the HI itself. It is interesting to note that by using cyclopropane as the final configuration of three methylene groups we have recently found¹⁵ that the nonadditivity of the HI is

$$\Delta\delta G^{\text{HI}} = \delta G_3^{\text{HI}}(\text{cyclopropane}) - 3\delta G_2^{\text{HI}}(\text{ethane}) = 2.99 \text{ kcal/mol} \quad (3.10)$$

TABLE XIII

	"reaction"	δG^{HI} cal/mol (25 °C)
I	$\text{C}-\text{C} + \text{C} \longrightarrow \text{C}-\text{C}-\text{C}$	-1851
I'	$\text{Ph}-\text{C} + \text{C} \longrightarrow \text{Ph}-\text{C}-\text{C}$	-1942
II	$\text{C}-\text{C}-\text{C} \longrightarrow \begin{array}{c} \text{C} \\ \\ \text{C}-\text{C}-\text{C} \end{array}$	-1688
II'	$\text{Ph}-\text{C}-\text{C} + \text{C} \longrightarrow \begin{array}{c} \text{C} \\ \\ \text{Ph}-\text{C}-\text{C} \end{array}$	-1952
III	$\begin{array}{c} \text{C} \\ \\ \text{C}-\text{C}-\text{C} \end{array} + \text{C} \longrightarrow \begin{array}{c} \text{C} \\ \\ \text{C}-\text{C}-\text{C} \\ \\ \text{C} \end{array}$	-1639
III'	$\begin{array}{c} \text{C} \\ \\ \text{Ph}-\text{C}-\text{C} \end{array} + \text{C} \longrightarrow \begin{array}{c} \text{C} \\ \\ \text{Ph}-\text{C}-\text{C} \\ \\ \text{C} \end{array}$	-1768

which again is large and positive, in agreement with the above findings. In both cases the results indicate that the work required to bring a third methylene group close to a pair of methylene groups at their final configuration is much less than the work that would have been predicted on the basis of pairwise additivity.

Finally, we present in Table XIII the HI associated with the successive processes (I, II, and III) of bringing methane molecules to form *tert*-butylbenzene from toluene. These figures are compared with the corresponding figures of similar consecutive steps where the phenyl ring is replaced by a methyl radical (processes I', II', and III' in Table XIII). The general trend seems to indicate that attachment of the third methane molecule involves weaker HI than the first one. This is consistent with the view that the surroundings of the two interacting groups shift from essentially aqueous to a more nonpolar one, when passing from the first to the third process.

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Supplementary Material Available: Tables I–X containing the experimental data (10 pages). Ordering information is available on any current masthead page.

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