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Limitations of the Linear Solvation Energy Relationships in Reversed Phase Liquid Chromatography

Won Jo Cheong* and Jang Duck Choi

Department of Chemistry, Inha University, Incheon 402-751, Korea
Received July 11, 1994

We have re-examined the linear solvation energy relationships in reversed phase liquid chromatography by considering various solutes including quite a number of compounds of strong hydrogen bond capability. We observed that solutes of strong hydrogen bond ability should be excluded in order to obtain resonable correlations between ln k' and solute polarity parameters and that inclusion of one or two such solutes causes severe distortions of correlation results. This anomaly may be due to existence of residual silanol groups in the stationary phase, that is, their specific interactions with solutes.

Introduction

Linear solvation energy comparison methods based on Kamlet/Taft polarity scales[1-5] have been known to be very useful in exploring linear solvation energy relationships (LSER) in reversed phase liquid chromatography.[6-12] The basic idea of this approach is that a distribution of a solute between two immiscible phases is governed by the cavity formation energy of the solute and by the solute-solvent interaction energies in each phase and that the solute-solvent interaction energies are the linear sum of several independent terms each of which corresponds to a characteristic solute-solvent interaction. Each interaction energy is proportional to the product of the semiempirical polarities of the solute and the solvent.

According to the LSER formalism, when applied to chromatographic retention, a logarithmic capacity factor, the solute-solvent specific property for a given chromatographic column, can be related to solute and solvent(phase) solvatochromic properties as follows[6-12]:

$$\ln k' = I + M\ (\delta_m^2 - \delta_s^2)\ V_{12}/100 + S\ (\pi^*_s - \pi^*_m) + B\ (\alpha_s - \alpha_m)\ \beta_2 + A(\beta_s - \beta_m)\ \alpha_2 \quad (1)$$

Retention in reversed phase liquid chromatography is determined by the difference in various types of solute-solvent interactions in the mobile and stationary phases. Each solute property is multiplied by a term that represents the difference in complementary solvent properties for the two phases. In Eq. (1), subscript s denotes the stationary phase, m, the mobile phase respectively, and subscript 2 designates a solute property. π^* represents a polarizability-dipolarity of a solvent(phase) or a solute, α, hydrogen bond donating acidity, and, β, hydrogen bond accepting basicity. δ is a solvent solubility parameter and $V_{1,2}/100$ is a normalized solute intrinsic volume.[13] I is the intercept of regression, and M, S, B, and A, the regression coefficients of positive value.

When a system with a fixed pair of mobile and stationary phases is considered, Eq. (1) is reduced to

$$\ln k' = I' + m\ V_{12}/100 + s\pi^*_2 + b\ \beta_2 + a\ \alpha_2 \quad (2)$$

The coefficients m, s, b, and a are determined by multiple linear regression of ln k' against the solute parameters and are measures of the difference of each specific polarity between the mobile and stationary phases. In reversed phase liquid chromatography, each polarity of the mobile phase is greater than that of the stationary phase, thus m (representing $\delta_m^2 - \delta_s^2$) is positive and s ($\pi^*_s - \pi^*_m$), b ($\alpha_s - \alpha_m$), and $a(\beta_s - \beta_s)$ are negative (See Eq. (1)).

Experimental

The retention data of solutes on a Shodex (Tokyo, Japan) C18-5B column (250×4.6 mm, 5 μ) were measured with methanol/water mixtures as eluents at various compositions.

Table 1. Solute Polarity Parameters

Solute	$V_I/100^a$	π^{*b}_2	α^c_2	β^d_2
propiophenone	0.788	0.88	0	0.49
benzylacetone	0.984	1.22	0.04	0.58
4-bromophenol	0.669	0.79	0.69	0.23
perylene	0.415	1.00	0	0.30
triphenylene	1.227	0.90	0	0.25
2,3-benzofluorene	1.222	0.76	0	0.26
2,2'-biquinoline	1.642	1.84	0	1.28
hydrocinnamonitrile	0.786	1.29	0	0.41
phenol	0.536	0.72	0.61	0.33
acetophenone	0.690	0.90	0	0.49
benzyl benzoate	1.139	1.32	0	0.50
1,3-dinitrobenzene	0.771	1.06	0	0.55
acridine	0.996	1.02	0	0.64
3-chloroaniline	0.652	0.78	0.20	0.40
aniline	0.562	0.73	0.16	0.50
3-phenyl-1-propanol	0.830	0.95	0.33	0.55
m-nitroaniline	0.702	1.15	0.39	0.46
p-nitroaniline	0.702	1.25	0.47	0.48
benzamide	0.676	0.94	0.49	0.75
N,N-dimethylbenzylamine	0.855	0.75	0	0.67
benzoic acid	0.650	0.74	0.75	0.40
3-bromophenylacetic acid	0.881	1.39	0.67	0.45
naphthalene	0.753	0.70	0	0.15
toluene	0.592	0.55	0	0.11

[a]Normalized intrinsic volume. [b]Dipolarity/polarizability. [c]Hydrogen bond donating acidity. [d]Hydrogen bond accepting basicity.

The methanol volume fractions used were 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9. Methanol and water were HPLC grade and purchased from Fisher (Pittsburg, U. S. A.). The column was placed in a water jacket and kept at 25± 0.1℃ by circulating thermostated water. All the solutes were reagent grade and obtained from Aldrich (Milwaukee, U. S. A.) and used without further purification. The used solutes were as follows: propiophenone, benzylacetone, 4-bromophenol, perylene, triphenylene, 2,3-benzofluorene, 2,2'-biquinoline, hydrocinnamonitrile, phenol, acetophenone, benzylbenzoate, 1,3-dinitrobenzene, acridine, 3-chloaniline, aniline, 3-phenyl-1-propanol, m-nitroaniline, p-nitroaniline, benzamide, N,N-dimethylbenzylamine, benzoic acid, 3-bromophenylacetic acid, naphthalene, toluene.

The HPLC system was a Samsung (Hwasung, Korea) SLC system composed of a Model SLC-100 intelligent pump, a Model SLC-200 UV/VIS variable wavelength detector, a SIC (Tokyo, Japan) Model 23B autosampler, a Model SLC-600 degasser, and a Model SLC-1000 system control & data processing unit. An 1 μl of methanol·solution of each solute was injected one by one with the autoinjector. An aliquot of 5% sodium nitrate was injected to determine the column void volume. The eluent flow rate was kept constant at 1 ml/min. The column was saturated with the eluent by flowing the eluent for 30 min. before measuring solute retentions for each eluent.

Table 2. Regression results of correlation of ln k' *vs.* solute polarity parameters for individual solute groups

Group	ϕ^a	m^b	s^b	a^b	b^b	r^c
I[d]	0.3	2.81	−1.15	−2.19	−4.62	0.789
	0.4	2.73	−1.18	−1.85	−4.30	0.798
	0.5	2.34	−1.12	−1.80	−4.00	0.870
	0.6	3.68	−1.52	−1.55	−3.54	0.859
	0.7	3.99	−1.69	−1.05	−3.24	0.947
	0.8	4.21	−1.54	−0.73	−1.29	0.898
	0.9	3.13	−1.11	−1.19	−2.12	0.968
II[e]	0.3	8.30	−2.66	−0.69	−4.83	0.990
	0.4	7.76	−2.60	−0.58	−4.39	0.993
	0.5	6.03	−2.38	−0.62	−4.05	0.992
	0.6	5.63	−2.21	−0.75	−3.79	0.992
	0.7	4.25	−1.86	−0.85	−3.19	0.996
	0.8	3.83	−1.72	−0.59	−2.34	0.996
	0.9	3.34	−1.55	−0.52	−1.81	0.994
III[f]	0.3	5.04	−2.30	−1.63	−5.12	0.919
	0.4	5.03	−2.25	−1.34	−4.68	0.933
	0.5	4.20	−2.10	−1.09	−3.93	0.967
	0.6	4.77	−1.87	−0.88	−4.02	0.987
	0.7	4.18	−1.65	−0.81	−3.45	0.994
	0.8	3.64	−1.47	−0.66	−2.77	0.994
	0.9	3.19	−1.49	−0.71	−2.12	0.986
IV[g]	0.3	6.13	−1.97	−1.21	−5.19	0.928
	0.4	5.47	−1.88	−1.13	−4.78	0.913
	0.5	4.16	−1.71	−1.03	−4.26	0.947
	0.6	5.83	−2.29	−0.70	−3.75	0.992
	0.7	4.29	−1.90	−0.82	−3.12	0.995
	0.8	3.84	−1.73	−0.59	−2.33	0.996
	0.9	3.33	−1.53	−0.54	−1.85	0.994

[a]Volume fraction of methanol in the eluent. [b]Regression coefficients based on equation (2). [c]Correlation coefficient. [d]Including 24 solutes. [e]From Group 1, excluding 2,2'-biquinoline, phenol, benzyl benzoate, acridine, N,N-dimethylbenzylamine, benzoic acid, aniline, 3-bromophenylacetic acid, 3-phenyl-1-propanol. [f]To Group 2, adding N,N-dimethylbenzylamine, 3-bromoacetic acid. [g]To Group 2, adding 3-phenyl-1-propanol.

Results and Discussion

The measured logarithmic capacity factors are correlated via multiple linear regression against solute polarity parameters. The necessary solute polarity parameters[5] are assembled in Table 1. The regression results are given in Table 2. According to Table 2, the correlations are poor when we examine all the 24 solutes (Group 1) in the regression. The correlation coefficients are less than 0.97. They become worse as the content of methanol gets lower. These results are very disappointing as we note that the reported correlation coefficients of LSER studies in RPLC are generally better than 0.99.[6-11]

As we mention before, we included quite a number of

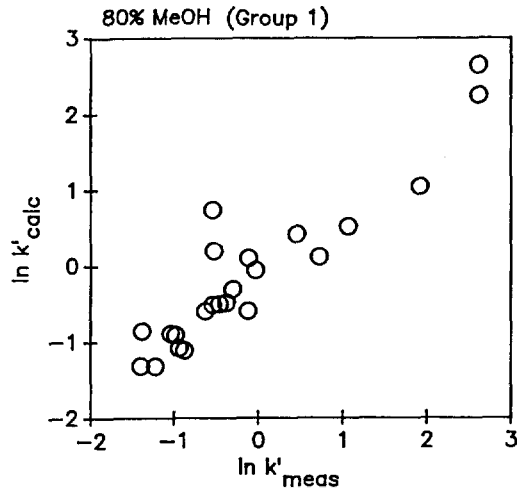

Figure 1. Correlation of calculated ln k' against measured ln k' for the retention data of Group 1 solutes collected in the eluent composed of 80 volume% methanol and 20% water.

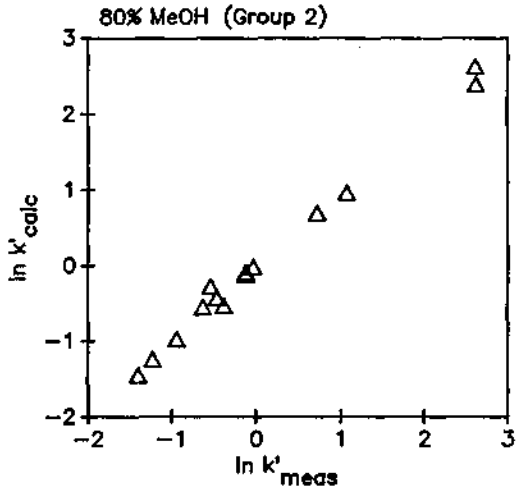

Figure 2. Correlation of calculated ln k' against measured ln k' for the retention data of Group 2 solutes (excluding solutes of strong hydrogen bond ability) collected in the eluent composed of 80 volume % methanol and 20% water.

solutes of very strong hydrogen bond ability which we suspect to cause strong specific interactions with residual silanol groups in the stationary phase. Distribution of the silanol groups is heterogeneous, and polarity contribution of the silanol groups is not simply additive to the overall stationary phase polarity. Such specific interactions are difficult to incorporate in the LSER formalism and are subject to future studies.

If we exclude definite outlier solutes from the regression, the correlations become remarkably improved. The removed solutes are mostly ones of very strong hydrogen bond ability: 2,2'-biquinoline, phenol, acridine, benzoic acid, aniline, N,N-dimethylbenzylamine, 3-bromophenylacetic acid, 3-phenyl-1-propanol, and benzyl benzoate. The deviation of benzyl benzoate is not clear to explain, but we suspect that the structural peculiarity of the solute yields its different retention behavior. Benzyl benzoate is composed of two phenyl rings separated by a flexible junction capable of free rotation, which is clearly different from features of other solutes. The solute group without the above outlier solutes, called Group 2, gives much improved correlations. All the correlation coefficients are better than 0.99 (See Table 1).

If one or two outlier solutes are added to Group 2 solutes, one can observe severe distortions of the LSER regression. For example, when we apply the LSER to Group 3, we obtain much worse correlation coefficients than those of Group 2 (Table 2). Group 3 is composed of Group 2 solutes and two excessive outlier solutes-a strong base (N,N-dimethylbenzylamine), and a strong acid (3-bromophenylacetic acid). Degradation of correlation is more severe for eluents of lower methanol content (higher water content). Group 4 is defined to be composed of Group 2 solutes and a strong hydrogen bond donor solutes, 3-phenyl-1-propanol. As we can see in Table 2, considerable degradation of LSER correlation is again observed for Group 4.

Effects of inclusion of solutes of strong hydrogen bond ability on LSER regression are illustrated comparatively in Figure 1 and Figure 2. The correlation of experimental ln k' measured in the eluent of 80 vol% methanol against computed ln k' based on the LSER regression for Group 1 is shown in Figure 1, and the corresponding correlation for Group 2, in Figure 2.

We have shown that the regression coefficient s reflects the difference in π^* between the stationary and mobile phases, b, the difference in α, and a, the difference in β. If we assume that each polarity of the stationary phase is invariable with respect to mobile phase composition, then we can expect that s is linearly correlated with mobile phase π^*, b, with mobile phase α, and a, with mobile phase β. We examine variations of s, b, and a with respect to mobile phase composition in comparison with corresponding variations of mobile phase π^*[14], α,[14-15] and β[16] in Figure 3, 4, and 5.

We assume that the regression coefficients determined for Group 2 are the most dependable in chemical sense and under this assumption we compare the regression results among different groups. First we will justify consistency of regression coefficients of Group 2 with general chemical sense. Coefficient m corresponds to the cohesive energy density (square of solubility parameter) of the mobile phase minus the cohesive energy density of the stationary phase. We can expect that m will increase as water content in the mobile phase increases (methanol content decreases). The cavity term is dominant in reversed phase liquid chromatography, and a magnitude of coefficient m is usally larger than that of any other regression coefficient.[6-12] As we can see in Table 2, the m trend of Group 2 follows the common chemical senses very well. Coefficient s represents π^* of the stationary phase minus π^* of the mobile phase. As the mobile phase π^* is larger than the stationary phase π^* and the mobile phase π^* will decrease as methanol content increases, we can expect that s is negative and that its magnitude will decrease with methanol content in the mobile phase. The s trend of Group 2 is consistent with the expectations.

The b trend of Group 2 is also consistent with general chemical senses. Coefficient b reflects the stationary phase α minus the mobile phase α and is expected to be of negative value and its magnitude will decrease with methanol content

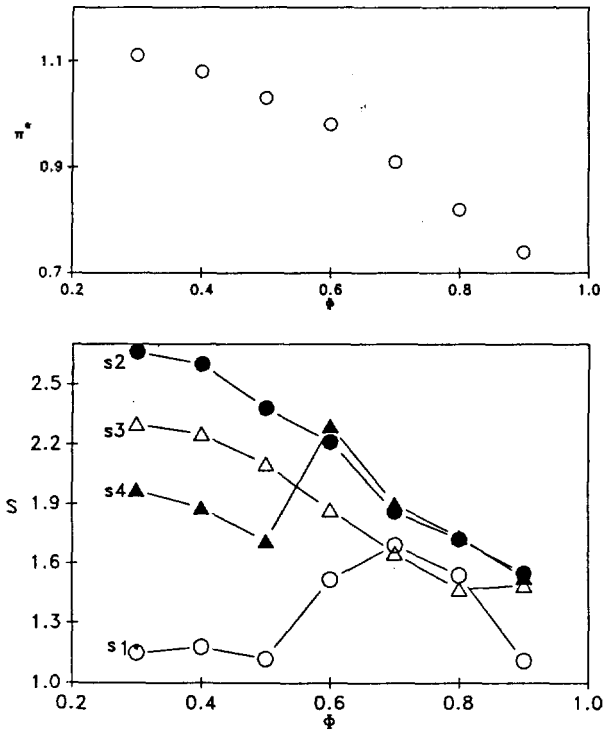

Figure 3. Comparison of variation trend of mobile phase π* with respect to methanol composition (ϕ) with those of regression coefficient s for each solute group. s1: Group 1, s2: Group 2, s3: Group 3, s4: Group 4.

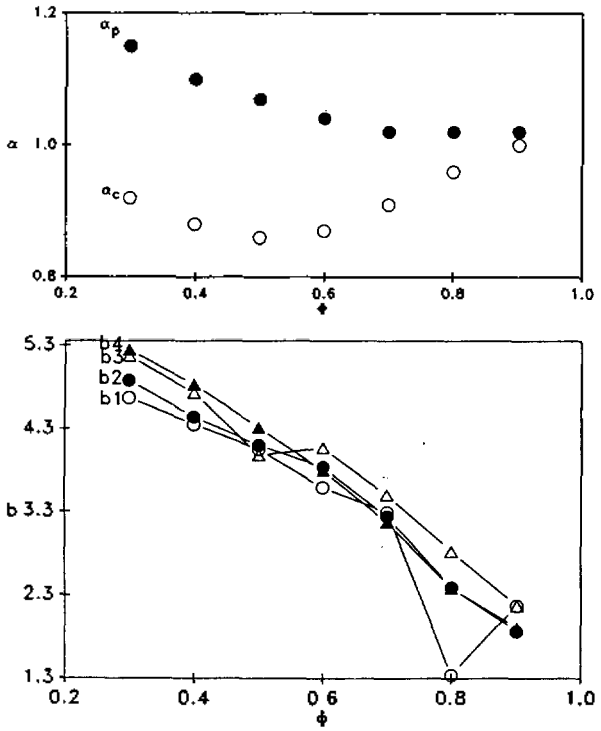

Figure 5. Comparison of variation trend of mobile phase α with respect to methanol composition (ϕ) with those of regression coefficient b for each solute group. b1: Group 1, b2: Group 2, b3: Group 3, a4: Group 4.

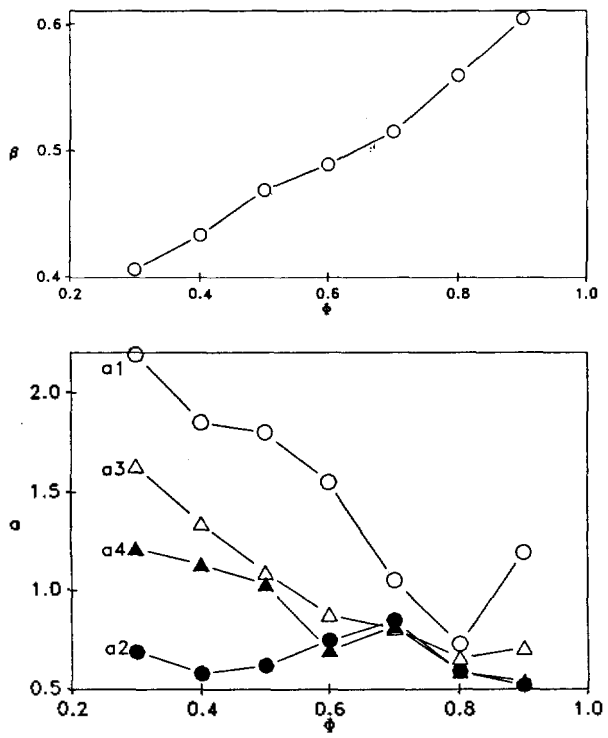

Figure 4. Comparison of variation trend of mobile phase β with respect to methanol composition (ϕ) with those of regression coefficient a for each solute group. a1: Group 1, a2: Group 2, a3: Group 3, a4: Group 4.

in the mobile phase since the hydrogen bond acidity of water is larger than that of methanol. Its contribution to LSER will be quite heavy but less heavier than that of m[6-12]. All these expectations are well fulfilled as is observed in Table 2.

Examination of the trend of coefficient a for Group 2 reveals that its variation with mobile phase composition is irregular and that its general magnitude is smaller than those of other regression coefficients. It means that there is not much difference in β between the stationary and mobile phases and that the difference, if any, does not change much. β of water (0.18) is much smaller than β of methanol (0.93).[1] β values of stationary phases in reversed phase liquid chromatography have not been yet reported. A recent study[15] showed that the basicidity of silica is much less than that of alumina while the acidity of silica is much higher than that of alumina. A stationary phase of reversed phase liquid chromatography is reasonably assumed to be composed of hydrophobic C18 ligands, sorbed mobile phase molecules, and accessible silica surface (residual silanol groups). The less polar component (methanol) in the mobile phase is preferentially sorbed in the stationary phase and sorption of water also occurs but is minimized.[17-23] Since a considerable amount of methanol of high β (0.93) is sorbed in the stationary phase for the composition range studied here ($0.3 \leq \phi \geq 0.9$), the β of the stationary phase will be at least higher than that of pure water (0.18). The β of the stationary phase will increase with methanol content in the mobile phase as more methanol is sorbed in the stationary phase. The β of the mobile phase also increases moderately with methanol

content. Note that other polarities decrease with methanol content. Considering the above features, we can expect that the mobile phase β is a little higher than the stationary phase β and that the difference will grow a little with methanol content in the mobile phase. The *a* trend of Group 2 does not satisfy the expectations. It fluctuates a little. Nevertheless, the deviation of Group 2 *a* trend from the expectation is minimum compared to those of other solute groups. For Group 1, 3, and 4, the magnitude of *a* decreases considerably as the methanol content in the mobile phase increases, which is definitely against chemical senses.

Let us turn to other solute groups in examining *m*, *s*, *a*, and *b* trends. Inclusion of solutes of strong hydrogen bond ability clearly perturbs LSER correlations. The trends of regression coefficients for Group 1 are clearly inconsistent with chemical sense; *m* and *s* fluctuate with respect to mobile phase composition, the magnitudes of *m* are much smaller than those of Group 2, and the width of variation of coefficient *a* expands with a decreasing trend with methanol content in the mobile phase. Addition of one or two solutes of strong hydrogen bond ability to Group 2 does not yield trends that are seriously inconsistent with chemical senses, but there are some perturbations in LSER correlation anyway. Regression coefficients change in a parellel fashion to those of Group 2, and magnitudes of coefficient *a*, opposing to chemical sense, increase as methanol content in the mobile phase decreases.

In the following discussion, *s*, *a*, and *b* mean their absolute magnitudes (*s*,*a*, and *b* are of negative values in RPLC). In Figure 3, the upper plot shows the variation of π^* with ϕ (volume fraction of methanol in the eluent) and the lower plots, the variations of regression coefficient *s* for individual solute groups. The variation trend of *s* for Group 1 does not match with that of the mobile phase π^* at all, and the *s* trend for Group 2 matches best with the mobile phase π^* trend. The variation of mobile phase β (upper plot) with ϕ and the variations of coefficient *a* (lower plots) for individual solute groups are compared in Figure 4. We note that the *a* trend for any solute group does not reasonably match with the β trend. We can note that inclusion of solutes of strong hydrogen bond ability causes severe anomalies in the LSER correlations, especially in the interaction where the solute acts as a hydrogen bond donor, and the solvent, as a hydrogen bond acceptor. We also note that excluding solutes of strong hydrogen bond ability yields reduction of such interaction (smaller magnitudes and fluctuation of coefficient *a*). We believe that an improved solute group would give more reasonable results regarding coefficient *a*. Such study is under way.

The variation of mobile phase α (upper plots) with ϕ and the variations of coefficient *b* (lower plots) for individual solute groups are compared in Figure 5. Two sets of values are reported in the literature: α_P (by Park *et al.*)[15] and α_C (by Cheong *et al.*).[14] The α_C values were determined by use of the well known linear relationship among solvent π^*, α, and E_T and they observed a peculiar minimum in the plot of α *vs.* ϕ as is shown in Figure 5. They suspected that such phenomenon is due to specific interactions of the E_T indicator with the solvent and that the α values are erroneous. The E_T indicator [4-(2,4,6-triphenylpyridinium)-2,6-diphenyl phenoxide] is of zwitterion character. Park *et al.*[15] employed a new indicator without zwitterion character to determine α values of aqueous methanol solutions and obtained a monotonically varying trend of α with respect to methanol composition. Figure 5 reveals that *b* trends of all solute groups are generally identical and that α_P correlates with *b* better than α_C even though the correlation between *b* and α_P is also imperfect. Thus our results lead to the conclusion that α values determined by Park *et al.*[15] are more reliable.

Conclusion

Inclusion of quite a number of solutes of strong hydrogen bond ability in the LSER study of reversed phase liquid chromatography severely perturbs usual LSER correlations and yields anomalous trends of regression coefficients, especially coefficient *a* that represents the difference in β between the stationary and mobile phases. Exclusion of such solutes gives reasonable regression results consistent with chemical senses. The different retention behaviors of such solutes may be attributed to specific interactions between the solutes and the heterogeneous residual silanol groups in the stationary phase.

Acknowledgment. This work was supported by the Korea Science and Engineering Foundation and 93 Inha University Fund.

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Reaction of Diisobutylaluminum Hydride-Dimethyl Sulfide Complex with Selected Organic Compounds Containing Representative Functional Groups. Comparison of the Reducing Characteristics of Diisobutylaluminum Hydride and Its Dimethyl Sulfide Complex

Jin Soon Cha*, Min Kyu Jeong, Oh Oun Kwon, Keung Dong Lee, and Hyung Soo Lee†

Department of Chemistry, Yeungnam University, Kyongsan 712-749, Korea
†Department of Chemistry Education, Hyosung Women's University, Kyongsan 713-900, Korea
Received July 11, 1994

The approximate rate and stoichiometry of the reaction of excess diisobutylaluminum hydride-dimethyl sulfide complex (DIBAH-SMe_2) with organic compounds containing representative functional group under standardized conditions (toluene, 0 ℃) were examined in order to define the reducing characterstics of the reagent and to compare the reducing power with DIBAH itself. In general, the reducing action of the complex is similar to that of DIBAH. However, the reducing power of the complex is weaker than that of DIBAH. All of the active hydrogen compounds including alcohols, amines, and thiols evolve hydrogen slowly. Aldehydes and ketones are reduced readily and quantitatively to give the corresponding alcohols. However, DIBAH-SMe_2 reduces carboxylic acids at a faster rate than DIBAH alone to the corresponding alcohols with a partial evolution of hydrogen. Similarly, acid chlorides, esters, and epoxides are readily reduced to the corresponding alcohols, but the reduction rate is much slower than that of DIBAH alone. Both primary aliphatic and aromatic amides examined evolve 1 equiv of hydrogen rapidly and are reduced slowly to the amines. Tertiary amides readily utilize 2 equiv of hydride for reduction. Nitriles consume 1 equiv of hydride rapidly but further hydride uptake is quite slow. Nitro compounds, azobenzene, and azoxybenzene are reduced moderately. Cyclohexanone oxime liberates *ca.* 0.8 equiv of hydrogen rapidly and is reduced to the N-hydroxylamine stage. Phenyl isocyanate is rapidly reduced to the imine stage, but further hydride uptake is quite sluggish. Pyridine reacts at a moderate rate with an uptake of one hydride in 48 h, while pyridine N-oxide reacts rapidly with consumption of 2 equiv of hydride for reduction in 6h. Similarly, disulfides and sulfoxide are readily reduced, whereas sulfide, sulfone, and sulfonic acid are inert to this reagent under these reaction conditions.

Introduction

Diisobutylaluminum hydride (DIBAH) has secured its position as a common reducing agent in organic synthesis,[1] especially for conversion of ester function to aldehyde. However, most of the reduction data available are for preparative purposes; they do not show any systematic reducing characteristics toward the general organic compounds. In 1985, Yoon and Gyoung carried out a systematic study of DIBAH in toluene at 0 ℃.[2] Such an investigation has enlarged the scope of its applicability as a reducing agent.

Last year, we prepared a solution of aluminum hydride-triethylamine complex (AlH_3-NEt_3) in THF and examined its reducing characteristics systematically.[3] The aluminum hydride solution in THF is slowly destroyed at room temperature, but the complex is absolutely stable in THF at that temperature. In general, the reducing action of the complex is very similar to that observed previously for aluminum hydride itself. However, the mildness of the complex improves the selectivity of aluminum hydride itself.

It seemed of interest to investigate the reducing characteristics of DIBAH complexed with a suitable Lewis base, and compare its reducing action with DIBAH itself, in analogy to the case of aluminum hydride. DIBAH and triethylamine does not form a stable complex. Finally, we prepared a solution of diisobutylaluminum hydride-dimethyl sulfide (DIBAH-SMe_2) complex in toluene and examined the reducing charateristics of the complex toward common organic functionalities under the identical conditions, adopted previously in the study of DIBAH itself, for direct comparison.

Results and Discussion

Preparation of a Solution of Diisobutylaluminum Hydride-Dimethyl Sulfide (DIBAH-SMe_2) in Tolune. A solution of DIBAH-SMe_2 in toluene was prepared by ad-