Nucleophilic Substitution Reactions of Benzyl Benzenesulfonates with Benzylamine in Acetonitrile and Methanol

Ikchoon Lee*, Chul Hyun Kang, Pyoung Sam Park, and Hai Whang Lee

Department of Chemistry, Inha University, Inchon 402-751. *Received December 17, 1990*

Kinetic studies of the reactions of benzyl benzenesulfonates with benzylamines in methanol and acetonitrile have been carried out. The reaction was found to proceed by a dissociative S_N2 in MeCN but by an associative S_N2 mechanism in MeOH. The transition state was rather loose in MeCN whereas it was tight in MeOH, in contrast to a tighter TS in MeCN for the corresponding reactions with aniline. The reaction of benzylamine in MeOH was characteristic of the highly solvated nucleophile, benzylamine, compared to the normal reaction in MeCN.

Introduction

Our previous works[1,2] on the reactions of benzyl benzenesulfonates (BBS) with anilines in methanol and acetonitrile have shown that the reactions are S_N2 type but the transition state (TS) structure was found to be loose (a dissociative S_N2)[1] in MeOH whereas it was tight (an associative S_N2)[2] in MeCN. Moreover, the cross-interaction contants[3] ρ_{XZ} between the substituents in the nucleophile, i=X in Eq. (1), and the leaving group (LG), j=Z in Eq. (1), were negative

$$\log(k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \qquad (1)$$

both in MeOH[4] and in MeCN[2]; a change in the solvent and temperature from MeOH at 35.0℃ to MeCN at 20.0℃ led to no change in the pattern of the TS variation from that of the quantum mechanical (QM) model (for $\rho_{XZ}<0$).[5]

The benzylic effect[2,6] was, however, similar in the two cases, albeit the contribution of inductive effect, ρ_I, decreased leading to relative increase in the resonance to inductive ratio, $R=\rho_R/\rho_I$ in the dual substituent parameter (DSP) Eq. (2),[7] in MeCN due to a small decrease in the electrostatic interaction owing to a slightly higher dielectric constant of MeCN relative to MeOH.[8]

$$\log k = \rho_I\sigma_I + \rho_R\sigma_R + \text{constant} \qquad (2)$$

It is of interest to see the effects of changing the basicity of nucleophiles in the similar reaction on the mechanism since the strong solvation of nucleophiles is expected to have substantial influence on the mechanism.

In this work, we have investigated such a reaction of BBS with a strong base, benzylamine, in MeOH and MeCN, Eq. (3), at 20.0℃.

$$2XC_6H_4CH_2NH_2 + YC_6H_4CH_2OSO_2C_6H_4Z \xrightarrow{\text{MeOH, MeCN}} XC_6H_4CH_2NHCH_2C_6H_4Y + XC_6H_4CH_2NH_3^+ + {}^-OSO_2C_6H_4Z \qquad (3)$$

Results and Discussion

The second order rate constants, k_2, for the reactions of BBS with benzylamines in MeCN and MeOH at 20.0℃ are summarized in Tables 1 and 2. The rates are in general greater in MeCN (0.902×10^{-2} $M^{-1}s^{-1}$ for X=Y=Z=H) than in MeOH (0.285×10^{-2} $M^{-1}s^{-1}$ for X=Y=Z=H); this is in

Table 1. Second-order Rate Constants, $10^2\times k_2(l\cdot mol^{-1}s^{-1})$, for the Reactions of Benzyl Benzenesulfonates with Benzylamines in MeCN at 20.0℃

Y	X Z=	p-CH$_3$	H	p-Cl	p-NO$_2$
H	p-OCH$_3$	0.653	1.24	3.31	22.9
	p-CH$_3$	0.589	1.09	2.98	20.6
	H	0.497	0.902	2.38	16.3
	p-Cl	0.351	0.645	1.68	11.5
p-Cl	p-OCH$_3$	0.631	1.18	3.24	22.6
	p-CH$_3$	0.575	1.06	2.85	20.1
	H	0.475	0.859	2.29	15.5
	p-Cl	0.330	0.604	1.57	10.8
m-Cl	p-OCH$_3$	0.519	0.894	2.32	16.5
	p-CH$_3$	0.467	0.783	2.18	14.5
	H	0.380	0.610	1.64	11.2
	p-Cl	0.262	0.443	1.12	7.55
p-NO$_2$	p-OCH$_3$	0.368	0.625	1.76	11.5
	p-CH$_3$	0.319	0.568	1.48	9.81
	H	0.253	0.430	1.12	7.14
	p-Cl	0.174	0.299	0.760	4.86

Table 2. Second-order Rate Constants, $10^3\times k_2(l\cdot mol^{-1}s^{-1})$, for the Reactions of Benzyl Benzenesulfonates with Benzylamines in MeOH at 20.0℃

Y	X Z=	p-CH$_3$	H	p-Cl	p-NO$_2$
H	p-OCH$_3$	2.24	3.43	6.59	29.6
	p-CH$_3$	2.03	3.24	6.37	28.4
	H	1.74	2.85	5.97	26.7
	p-Cl	1.38	2.41	5.22	24.7
p-Cl	p-OCH$_3$	1.81	2.74	5.92	26.4
	p-CH$_3$	1.62	2.54	5.48	24.7
	H	1.23	2.21	4.95	22.3
	p-Cl	1.01	1.90	4.36	20.8
m-Cl	p-OCH$_3$	1.21	1.98	4.08	18.4
	p-CH$_3$	0.993	1.82	3.55	17.8
	H	0.784	1.60	3.30	15.8
	p-Cl	0.590	1.34	2.83	13.9
p-NO$_2$	p-OCH$_3$	0.881	1.49	3.48	16.2
	p-CH$_3$	0.725	1.34	3.12	14.4
	H	0.548	1.05	2.48	12.4
	p-Cl	0.382	0.790	2.10	10.5

Table 3. Simple Hammett Coefficients ρ_i, in MeCN

1) ρ_X values

Z=	*p*-CH$_3$	H	*p*-Cl	*p*-NO$_2$
Y= H	−0.54	−0.57	−0.59	−0.61
p-Cl	−0.57	−0.59	−0.63	−0.65
m-Cl	−0.60	−0.62	−0.66	−0.69
p-NO$_2$	−0.65	−0.65	−0.69	−0.73

Correlation coefficient (r); 0.998±0.002

2) ρ_Y^+ values

Z=	*p*-CH$_3$	H	*p*-Cl	*p*-NO$_2$
X=*p*-OCH$_3$	−0.32	−0.37	−0.37	−0.40
p-CH$_3$	−0.35	−0.38	−0.40	−0.43
H	−0.38	−0.42	−0.43	−0.47
p-Cl	−0.39	−0.43	−0.45	−0.49

Correlation coefficient (r); 0.995±0.003

3) ρ_Z values

Y=	H	*p*-Cl	*m*-Cl	*p*-NO$_2$
X=*p*-OCH$_3$	1.63	1.64	1.60	1.59
p-CH$_3$	1.63	1.63	1.59	1.57
H	1.61	1.60	1.57	1.56
p-Cl	1.60	1.60	1.55	1.54

Correlation coefficient (r); 0.999±0.000

Table 4. Simple Hammett Coefficients ρ_i, in MeOH

1) ρ_X values

Z=	*p*-CH$_3$	H	*p*-Cl	*p*-NO$_2$
Y= H	−0.42	−0.31	−0.20	−0.16
p-Cl	−0.53	−0.32	−0.25	−0.21
m-Cl	−0.58	−0.34	−0.30	−0.25
p-NO$_2$	−0.70	−0.56	−0.45	−0.38

Correlation coefficient (r); 0.995±0.006

2) ρ_Y^+ values

Z=	*p*-CH$_3$	H	*p*-Cl	*p*-NO$_2$
X=*p*-OCH$_3$	−0.51	−0.44	−0.36	−0.34
p-CH$_3$	−0.56	−0.47	−0.40	−0.37
H	−0.61	−0.53	−0.48	−0.42
p-Cl	−0.69	−0.60	−0.50	−0.47

Correlation coefficient (r); 0.975±0.013

3) ρ_Z values

Y=	H	*p*-Cl	*m*-Cl	*p*-NO$_2$
X=*p*-OCH$_3$	1.19	1.24	1.25	1.34
p-CH$_3$	1.21	1.26	1.31	1.36
H	1.25	1.32	1.35	1.42
p-Cl	1.32	1.37	1.41	1.50

Correlation coefficient (r); 0.998±0.002

contrast to the greater reactivity found in MeOH than in MeCN for the reactions of BBS with anilines.[1,2] The strong basicity of the nucleophile, benzylamine (pK_a=9.35 for X=H at 25.0℃)[9] appears to be the main cause of this reactivity order reversal. Our calorimetric measurements[10] have shown that the heats of solution. ΔH_s, for aniline were −0.57 and 0.03 kcal/mol, whereas those for benzylamine were −2.75 and 0.44 kcal/mol respectively in MeOH and MeCN.

This suggests that benzylamine is strongly solvated in MeOH so that the desolvation energy required in the activation process[11] becomes greater than the enhanced lability of the LG due to the hydrogen bonding by MeOH in the TS.[12]

The desolvation energy in MeOH also reduces the relative reactivity of a more basic nucleophile compared to the less basic one; in MeOH the rate constant ratio of k(X=*p*-OCH$_3$)/k(X=*p*-Cl)=1.4 (for Y=Z=H) is less than that of 2.0 in MeCN due to a greater desolvation energy required for the more basic nucleophile in MeOH.

It is well known that in the protic solvent anionic nucleophiles have a reactivity order in reverse of their basicity due to the high desolvation energy required in the activation process[11]; thus typically the heats of hydration at 25.0℃ are (−113.3), −81.3, −77.9 and −64.1 kcal/mol for (F$^-$), Cl$^-$, Br$^-$ and I$^-$, respectively[13] and the nucleophilic reactivity toward the benzylic center in water increases in the order (F$^-$)<Cl$^-$<Br$^-$<I$^-$ as expected from the decreasing desolvation energy.[14] In this respect, aniline nucleophile (pK_a=4.60 for X=H at 25.0℃)[15] will require very much less desolvation energy in the rate determining step so that the rate is faster in MeOH due to an enhanced lability of the LG by the electrophilic assistance of MeOH.

This interpretation is supported by the solvent isotope effect, k(CH$_3$OH)/k(CH$_3$OD)=0.976, found for the reaction of BBS (with Y=Z=H) with benzylamine (with X=H) at 20.0℃. Since the O−H zero-point stretching vibration will be at a higher level than the O−D zero point level, solvation of benzylamine by hydrogen bonding, in which the O−H and O−D bonds must stretch,[16] will be stronger with CH$_3$OH so that a greater desolvation energy will be needed and hence the rate in CH$_3$OH will be slower than that in CH$_3$OD.

The reactivity trends in both solvents are in line with those expected for a typical S_N2 reaction[17]; the rate increases with a stronger nucleophile (X=*p*-OCH$_3$) and with a better LG (Z=*p*-NO$_2$). The rate decreases, however, with a more electron-withdrawing group (EWG) in the substrate (Y=*p*-NO$_2$), which suggests that positive charge developes at the benzylic carbon in the TS.[18]

The simple Hammett coefficients, ρ_i, are summarized in Tables 3 and 4. The magnitudes of ρ_X and ρ_Z are somewhat greater in MeCN, suggesting that the degrees of bond-formation and bond-cleavage are slightly greater in MeCN than in MeOH. This conclusion is, however, misleading since the simple Hammett constants ρ_i can at most serve as a relative measure of bond length involved in the activation process within a particular family of closely related reactions.[19] In this case, comparison of the ρ_i values in MeOH and MeCN may not be justified since the efficiency of charge transmission between reaction centers R_i and R_j (i, j=X, Y or Z) in bond formation and cleavage may differ for different solvent systems (vide infra).

Since it is safe to compare the ρ_i values within a solvent

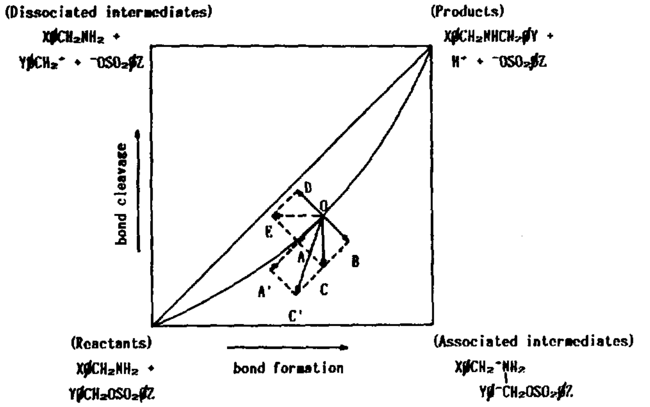

Figure 1. The PES diagram for an associated S_N2 reaction.

Table 5. Cross-Interaction Constants, ρ_{ij}, for Reactions; $2XC_6H_4CH_2NH_2+YC_6H_4CH_2OSO_2C_6H_4Z \longrightarrow XC_6H_4CH_2NHCH_2C_6H_4Y+XC_6H_4CH_2{}^+NH_3+{}^-OSO_2C_6H_4Z$ in MeCN and MeOH

1) ρ_{XY} values

Solvent	Z=*p*-CH$_3$	H	*p*-Cl	*p*-NO$_2$
MeCN	−0.14	−0.15	−0.16	−0.18
	(0.996)	(0.997)	(0.996)	(0.997)
MeOH	−0.36	−0.32	−0.29	−0.26
	(0.981)	(0.990)	(0.970)	(0.974)

2) ρ_{YZ} values

Solvent	X=*p*-OCH$_3$	*p*-CH$_3$	H	*p*-Cl
MeCN	−0.069	−0.079	−0.083	−0.092
	(0.999)	(0.999)	(0.999)	(0.999)
MeOH	0.17	0.18	0.19	0.21
	(0.997)	(0.996)	(0.996)	(0.995)

3) ρ_{XZ} values

Solvent	Y=H	*p*-Cl	*m*-Cl	*p*-NO$_2$
MeCN	−0.068	−0.088	−0.093	−0.11
	(0.999)	(0.999)	(0.999)	(0.999)
MeOH	0.26	0.28	0.30	0.34
	(0.999)	(0.998)	(0.997)	(0.997)

system, we can conclude that bond formation ($|\rho_X|$) decreases in MeOH but increases MeCN with a better LG (Z=*p*-NO$_2$) and increases with a more EWG in the substrate (Y=*p*-NO$_2$) in both solvents alike. In contrast, bond cleavage decreases in MeOH but increases in MeCN with a stronger nucleophile and it decreases in MeCN whereas it increases in MeOH with a more EWG in the substrate (Y=*p*-NO$_2$). These effects of the nucleophile (σ_X) and the LG (σ_Z) on the TS variation in MeOH are in accord with those predicted by the PES diagram,[20] Figure 1, for an associated S_N2 reaction.

A stronger nucleophile and a better LG will lead to an earlier TS with a lesser degree of bond-cleavage (O→C) and bond-making (O→E), respectively in MeOH solvent systems.[21] On the other hand the TS variation in MeCN is consistent with the predictions by the quantum mechanical (QM) model.[5] The negative sign of $\rho_Y{}^+$ suggests that the reaction center, C_α, becomes electron deficient *i.e.*, more positively charged in the TS.[18]

We have subjected the rate constants k_2 in Tables 1 and 2 to the multiple regression analysis[22] using Eq. (1), where i, j=X, Y or Z, and obtained cross-interaction constants[3] ρ_{ij} as shown in Table 5. The ρ_{XZ} values are positive in MeOH whereas it is negative in MeCN so that the TS variation should be in accord with that predicted by the PES model,[20] as we have seen above with the simple Hammett coefficients ρ_X and ρ_Z in MeOH, but it should be consistent with the predictions of the QM model in MeCN.

Inspection of Table 5 reveals that the magnitudes of the cross-interaction constants, ρ_{XY}, ρ_{YZ} and ρ_{XZ}, are smaller in MeCN indicating the TS is looser in MeCN than in MeOH. The magnitude of ρ_{XY} and hence the degree of bond formation decreases with a better LG in MeOH whereas it increases in MeCN, as we have already noted above with a decrease in $|\rho_X|$ in MeOH and an increase in MeCN. The magnitude of ρ_{YZ}, decreases with a stronger nucleophile in MeCN correctly reflecting a increase in bond cleavage with a stronger nucleophile. In contrast however the ρ_{YZ} values also decreases with a stronger nucleophile in MeOH, which may be due to a stronger solvation of a stronger nucleophile in MeOH leading to a greater degree of bond breaking.[23] The magnitudes of cross-interaction constants indicate that the degree of bond formation is less in MeCN than in MeOH whereas it is similar to that for a typical dissociative S_N2 reaction in MeOH (taking an extra CH$_2$ group in benzylamine into consideration $|\rho_{XY}|$ in MeOH is equivalent to *ca.* 0.70).[24] On the other hand the degree of bond breaking is relatively large ($|\rho_{YZ}|$ is relatively small) in MeCN but it is small ($|\rho_{YZ}|$ is large) in MeOH. Overall the TS is quite tight in MeOH (ρ_{XZ}, is large) whereas it is relatively loose (ρ_{XZ} is small) in MeCN. The tight TS in MeOH is again a result of bulky solvated nucleophile causing steric hindrance;[25] a sterically hindered TS exhibits a higher barrier with a tighter TS in accordance with the Hammond postulate.[21] In MeCN the degree of bond formation is less but bond breaking is greater than those in the corresponding reactions with aniline.[2] In an associative S_N2 reaction we found that the Hammond effect[21a] (OA) is normally greater than the anti-Hammond effect[21b] (OB) so that the TS will shift to C′ instead of C with a stronger nucleophile leading to an earlier TS.[26] In MeOH, however, bond formation is similar but bond breaking is much less than that for a dissociative S_N2 reaction. A greater degree of bond formation in MeOH indicated by the larger $|\rho_{XY}|$ value is at variance with a greater degree of bond formation in MeCN implied by the relatively larger $|\rho_X|$ value. This shows the unreliability of using simple Hammett coefficients, ρ_i, as a measure of the bond tightness in the TS.[25]

The analysis of our rate data by the DSP equation, (2),[7] showed that the ratio of resonance to inductive coefficients, $R=\rho_R/\rho_I$, is always greater in MeCN than in MeOH. This is mainly due to a decrease in ρ_I in MeCN owing to a decrease in the electrostatic interaction[8] by a slightly greater dielectric constant of MeCN compared to that of MeOH. The ratio, R, was greater than one in MeCN for all four DSP equations used, *i.e.*, Talf,[27] Swain-Lupton (S-L)[28], Yukawa-Tsuno-Jencks

(Y-T-J)[29] and Afanas'ev equations.[30] The ratio was, however, smaller than one in MeOH for the Taft and Y-T-J equations. Thus the relative importance of the benzylic effect[2,6] is always greater in MeCN; this is consistent with a looser TS based on with the cross-interaction constants in MeCN since a looser TS will necessarily have a greater positive charge development at the benzylic carbon in the TS leading to a greater resonance interaction with the substituents in the substrate ring. There was no definite trend in the R values with respect to the variations in the substituents in the nucleophile (σ_X) and LG (σ_Z). This means that although the benzylic effect is operative in the reactions with benzylamine, the importance is reduced to a much less level compared to that in the reactions with aniline. This is true since with aniline a direct conjugation of aniline ring with the substrate[6a,31] is possible through the partial bond forming in the TS, which can be ruled out for benzylamine with an intervening CH_2 group.

Experimental

Materials and kinetic proceduces are as described in previous reports.[1,2] Deuterated methanol, CH_3OD, was used as purchased from Aldrich Chem. Co. (99% content of deuterium in the hydroxylic D). Rates k_1 were determined at four different benzylamine concentrations [BA] and the k_2 value was obtained by a slope of the plot of k_1 vs [BA]. The k_2 values were 2.85 and 2.92×10^{-3} $M^{-1}s^{-1}$ with CH_3OH and CH_3OD respectively, giving $k_H/k_D=0.976$.

Acknowledgement. We thank the Ministry of Education and the Korea Science and Engineering Foundation for support of this work.

References

1. (a) I. Lee, S. C. Sohn, C. H. Kang, and Y. J. Oh, *J. Chem. Soc., Perkin Trans. 2,* 1631 (1986); (b) I. Lee, S. C. Sohn, Y. J. Oh, and B. C. Lee, *Tetrahedron*, **42**, 4713 (1986); (c) I. Lee, W. H. Lee, S. C. Sohn, and C. S. Kim, *Tetrahedron* **41**, 2635 (1985).
2. I. Lee, W. H. Lee, and H. J. Jung, Bull. Inst. Basic Sci., Inha Univ., **12**, 69 (1991).
3. I. Lee, *Chem. Soc. Rev.*, **19**, 317 (1990).
4. I. Lee and S. C. Sohn, *J. Chem. Soc. Chem. Commun.*, 1056 (1986).
5. (a) A. Pross and S. S. Shaik, *J. Am. Chem. Soc.*, **103**, 3702 (1981); (b) I. Lee and C. H. Song, *Bull. Korean Chem. Soc.*, **7**, 186 (1986); (c) D. J. Mitchel, H. B. Schlegel, S. S. Shaik, and S. Wolfe, *Can. J. Chem.*, **63**, 1642 (1985); (d) I. Lee, C. S. Shim, S. Y. Chung, and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2,* 975 (1988).
6. (a) I. Lee, *Bull. Korean Chem. Soc.*, **11**, 260 (1990); (b) I. Lee, J. K. Cho, and C. K. Kim, *Bull. Korean Chem. Soc.*, **12**, 182 (1991); (c) J. F. King and G. T. Y. Tsang, *J. Chem. Soc., Chem. Commun.*, 1131 (1979); (d) J. I. Lynas-Gray and C. J. M. Sterling, *J. Chem. Soc., Chem. Commun.*, 483 (1984); (e) D. Kost and K. Aviram, *J. Am. Chem. Soc.*, **108**, 2006 (1986); (f) T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, **111**, 7900 (1989).
7. (a) J. Toulle and M. El-Alaoui, *J. Org. Chem.*, **50**, 4928 (1985); (b) M. C. Spanjer, C. L. de Ligny, H. C. Van Houwelingen, and J. M. Weesie, *J. Chem. Soc., Perkin Trans. 2,* 1401 (1985); (c) D. A. R. Happer, *J. Chem. Soc., Perkin Trans. 2,* 1673 (1984); (d) D. A. R. Happer, *J. Chem. Soc., Perkin Trans. 2,* 694 (1979); (e) H. Zollinger, *J. Org. Chem.*, **55**, 3846 (1990).
8. J. Niwa, *Bull. Chem. Soc. Japan,* **62**, 226 (1989).
9. J. A. Dean, "Handbook of Organic Chemistry", 13th ed., Mcgraw-Hill, New York, Section 5, 1987.
10. I. Lee, C. H. Kang, B-S. Lee, and H. W. Lee, *Bull. Korean Chem. Soc.*, **6**, 546 (1990).
11. M. J. S. Dewar and D. M. Storch, *J. Chem. Soc., Perkin Trans. 2,* 877 (1989).
12. I. A. Koppel and V. A. Palm, "Advances in Linear Free Energy Relationship", Ed. by N. B. Champman and J. Shorter, Plenum Press, London, Chap. 5, 1972.
13. J. E. Gordon, "The Organic Chemistry of Electrolyte Solutions", Wiley, New York, p. 192, 1975.
14. J. E. Gordon, "The Organic Chemistry of Electrolyte Solution", Wiley, New York, p. 300, 1975.
15. E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1963).
16. L. Melander and W. H. Saunders, "Reaction Rates of Isotopic Molecules", Wiley, New York, Chap. 7, 1980.
17. T. H. Lowry and K. S. Richardson, "Mechanism and Theory in Organic Chemistry", 2nd ed., Haper and Row, New York, Chap. 4, 1981.
18. L. P. Hammett, "Physical Organic Chemistry", 2nd ed, McGraw-Hill, Tokyo, Chep. 11, 1970.
19. (a) K. C. Westaway and Z. Waszczylo, *Can. J. Chem.*, **60**, 2500 (1982); (b) K. C. Westaway and S. F. Ali, *Can. J. Chem.*, **57**, 1354 (1979).
20. (a) E. R. Thronton, *J. Am. Chem. Soc.*, **89**, 2915 (1967); (b) M. A. More O'Ferrall, *J. Chem. Soc. B,* 274 (1970); (c) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972); (d) J. C. Harris and J. L. Kurz, *J. Am. Chem. Soc.*, **92**, 349 (1970).
21. (a) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955); (b) T. H. Lowry and K. S. Richardson, "Mechanism and Theory in Organic Chemistry" 2nd ed., Happer and Row, New York, Chap. 2, 1981.
22. J. Shorter, "Correlation Analysis of Organic Reactivity", Research Studies Press, Chichester, Chap. 2, 1982.
23. A solvated bulky nucleophilic will approach closer toward the reaction center pushing the LG farther away.
24. I. Lee, C. S. Shim, S. Y. Chung, H. Y. Kim, and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2,* 1919 (1988).
25. (a) I. Lee, K. W. Rhyu, H. W. Lee, and C. S. Shim, *J. Phys. Org. Chem.*, **3**, 751 (1990); (b) I. Lee, H. K. Kang, and H. W. Lee, *J. Am. Chem. Soc.*, **109**, 7472 (1987); (c) D. J. McLennan and A. Pross, *J. Chem. Soc., Perkin Trans. 2,* 2981 (1984); (d) W. P. Jencks, *Chem. Rev.*, **85**, 511 (1985).
26. I. Lee, C. S. Shim, S. Y. Chung, and H. W. Lee, *J. Chem. Soc., Perkin Trans. 2,* 975 (1988).
27. (a) R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959); (b) R. W. Taft, S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959); (c) M. Carton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).
28. (a) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968) The DSP used in the calculation were the modified values by Hansch *et al.*; (b) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J.*

Med. Chem., **16**, 1207 (1973).
29. (a) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **101**, 3288 (1979); (b) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 8238 (1977).
30. I. B. Afanas'ev, *J. Am. Soc., Perkin Trans 2*, 1589 (1984).
31. I. Lee and S. C. Sohn, *Bull. Korean Chem. Soc.*, 7, 321 (1986).

Electrostatic Interaction Between Oligopeptides and Phosphate Residues by Determination of Absolute Raman Intensities

Kye-Taek Lim

Department of Animal Science, Chonnam National University, Kwangju 500-757

Received December 27, 1990

The changed isotropic absolute Raman intensities of the phosphate residue in the complexes of positive charge oligopeptides, lys-lys, arg-arg, lys-aromat-lys, negative charge diethyl phosphoric acid (DEP) and polyriboadenylic acid{poly(rA)} were reported and discussed. Our measurements showed that the absolute intensities of phosphate stretch vibration in complexes were different according to the reaction partners. Due to the partial electrical charge and molecular structure of oligopeptides for the complex formation lysine can interact more strongly than arginine when the reaction partners have short chain and no steric hindrance. Owing to these reasons the intensity of phosphate stretching vibration is very sensitive according to the circumstance of reaction. From our results we could suggest that we can discriminate any one of the the lysine and arginine in the complicated biological molecule during interaction between nucleotides and proteins. The activity of reaction of two basical oligopeptides is not quite similar for complex formation in aqueous solution. The activity of dipeptides depends upon the structure of molecule and environment for complex formation. Aromatic ring contributes to electrostatic interaction in complexes. The amount of the absolute intensity for pure stacking interaction is smaller than electrostatic interaction in macromolecular complexes.

Introduction

There is a vast interest in protein-nucleotide interaction because of the widespread importance of these interactions for, *e.g.*, gene expression, transcription, and other processes. On the molecular basis, the forces involved in the complexing process between protein and nucleic acid are commonly divided into

i) electrostatic interaction of positive charge on the protein by the negative charge of the nucleic acid back bone;

ii) dispersive forces originating from the interaction of aromatic side chains of the protein with the bases inside of the nucleic acid helix;

iii) formation of hydrogen bonds and other[1]. The knowledge of prefered mechanisms and sites of docking between proteins and DNA or RNA is one of the fundamental problems in molecular biology, therefore all kinds of physical probing have been used, such as; UV and ORD[2], NMR[3], X-ray analysis[4] and Raman spectroscopy[5]. An advantage of Raman spectroscopy might be, that molecular properties can be studied in aqueous solution and at conditions almost physiological. In macromolecules, these vibrations are usually highly localized on small numbers of atoms within specific groups such as the peptide bond, C-O stretches, C-H stretches or bends, C-S vibrations of cysteins and S-S vibration of cystines just to name some. A shift of the Raman band position, which corresponds to the frequency of the vibration, is a measure of the change of binding forces within the characteristic group of atoms involved in the observed vibration. It needs usually strong complexation or molecular rearrangement to express major shifts of frequencies. The intensity of a Raman band depends on the change of polarizability during the corresponding vibration. Intermolecular interactions, especially those of coulombic nature, cause changes of the polarity of the molecule and hence also effect the polarizability. This can be observed on intensity changes of the Raman bands, which are consequently a very sensitive probe of intermolecular interaction giving at the same time information about the site of the interaction because of the local character of the oscillators. In this paper, we want to concentrate only on electrostatic interaction and we used simple model systems for this purpose. We assembled the data of the intensities of symmetric phosphate stretch vibration in various complexes.

Experimental

Chemicals and Their Origine. Diethylphosphoric acid (DEP)/Eastmann Kodak; the dipeptides, lys-lys. 2HCl 0.5 H_2O and arg-arg. 3HAc/Serva; the potassium salt of polyriboadenylic acid (poly(rA)) (lyophil, "reinst", homopolymer) /Boehringer Mannheim FRG; lys-tyr-lys.2 formate, lys-phe-lys. acetate (research grad)/Serva; These chemicals were used without further purification.

Sample Preparation. Solutions were prepared with 0.05 mol/*l* NaCl in CO_2 free water. DEP solutions were kept at pH 11.5 by addition of NaOH in order to have DEP in the anionic form. Sample concentrations were adjusted to,