Kinetic and Theoretical Consideration of 3,4- and 3,5-Dimethoxybenzoyl Chlorides Solvolyses

Kyoung-Ho Park[*] and Dennis N. Kevill[†]

Department of Chemistry and Applied Chemistry, Hanyang University, Ansan-si, Gyeonggi-do 426-791, Korea
[*]E-mail: piroho@hanyang.ac.kr
[†]Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, Illinois 60115-2862, U.S.A.
Received June 22, 2013, Accepted July 15, 2013

The solvolysis rate constants of 3,4- (**1**) and 3,5-dimethoxybenzoyl (**2**) chlorides were measured in various pure and binary solvents at 25.0 °C, and studied by application of the extended Grunwald-Winstein (G-W) equation, kinetic solvent isotope effect in methanolysis and activation parameters. The solvolysis of **1** was interpreted as the unimolecular pathway due to a predominant resonance effect from *para*-methoxy substituent like 4-methoxybenzoyl chloride (**3**), while that of **2** was evaluated as the dual mechanism, with unimolecular or bimolecular reaction pathway according to the character of solvent systems (high electrophilic/nucleophilic) chosen, caused by the inductive effect by two *meta*-methoxy substituents, no resonance one. In the solvolyses of **1** and **2** with two –OCH$_3$ groups, the resonance effect of *para*-methoxy substituent is more important to decide the mechanism than the inductive effect with other corresponding evidences.

Key Words : Dimethoxybenzoyl chloride, Extended Grunwald-Winstein equation, Resonance effect, Kinetic solvent isotope effect, Activation parameters

Introduction

The Grunwald-Winstein (G-W) equation has usually applied[1] in order to analyze the rate constants of substrates for predicting the solvolysis mechanism. Initially, simple G-W equation (eq. 1)[2] contains only solvent ionizing power term,[3] that is, only substrates of the unimolecular pathway (S$_N$1 and E1) are analyzed well, but there are many substrates showed the deviated plots. The reason is the simple G-W equation involves only electrophilic characters of solvents. The extended G-W equation (eq. 2)[4] has two terms which are the solvent ionizing power and the nucleophilicity of solvent,[5] and the extended form is served more improved plots for many substrates.

$$\log (k/k_0) = mY + c \qquad (1)$$

$$\log (k/k_0) = lN + mY + c \qquad (2)$$

In the above equations, k and k_0 are the solvolysis rate constants of substrate in given and standard (80% ethanol) solvents, respectively. The m and l are the sensitivities toward solvent ionizing power (Y)[3] and nucleophilicity (N_T).[5] Many researchers made an efforts to develop the standard substrates of solvent ionizing power and nucleophilicity hardly. The Y scale is determined by 1-adamantyl derivatives which are hardly back side attack at the reaction center relatively, and the N_T scale is determined by *S*-methyldibenzothiophenium ion which contains neutral leaving group for substitution reactions. These two substrates were used as the standard materials of the G-W equations for the mechanism study recently.[3,5]

The kinetic study of solvolysis were used a lot of solvents, for example, ethanol (EtOH), methanol (MeOH) have the strong nucleophilc character, while 2,2,2-trifluoroethanol (TFE), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) have the strong electrophilic characters. In order to control the ionizing power and nucleophilicity of solvents, they were mixed with water (H$_2$O). Water is played the role of electrophilic part when mixed with nucleophilic solvent and nucleophilic part when mixed with electrophilic solvent. So many mixed solvents were prepared from the pure to 50% mixture of nucleophilic solvent systems by volume ratio and of electrophilic solvents systems by weight ratio. Another type of mixtures, EtOH and TFE, was also considered. EtOH and TFE are the same structural compounds and have the different properties of solvent. Additionally, the binary solvents mixed with acetone and water were prepared for studying hydrolysis, because acetone does not react with substrate in solvolysis reaction.

Solvolyses of benzoyl chloride derivatives have studied hardly for distinguish the mechanisms of simple nucleophilic substitution reactions. Earlier researchers reported that 4-methoxybenzoyl chloride (**3**)[6-11] is followed by unimolecular reaction mechanism and 4-nitrobenzoyl chloride (**4**)[12] is proceeded through bimolecular pathway. Both substrates have one substituent on *para*-position which is not involved a steric hindrance effect at the carbonyl carbon of the reaction center. Also the electron density of this sp^2-hybridized acyl carbon is very important for deciding the solvolysis pathway, because the electron density of this carbon is affected to the bond strength between the reaction center and a leaving group. The methoxy group is known to have more the resonance electron donating effect than inductive electron withdrawing effect, while the nitro group is known as an
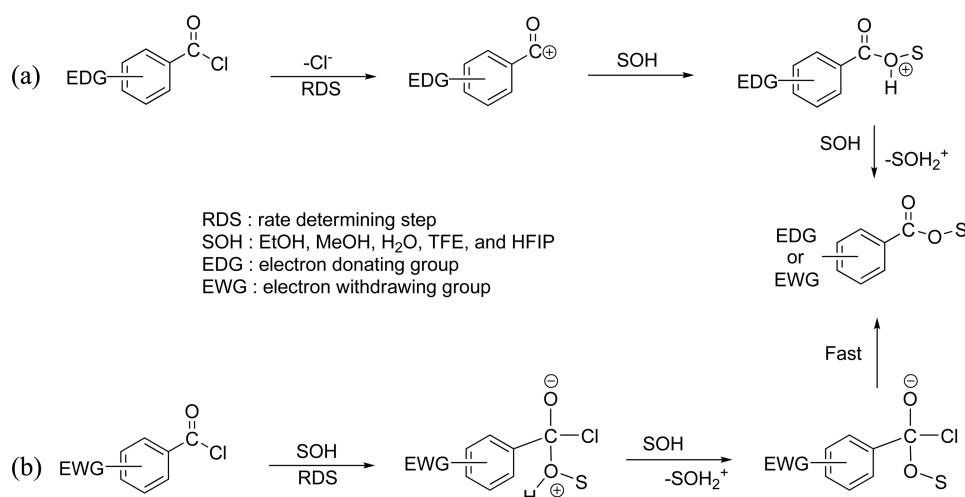
Scheme 1. Unimolecular (a) and bimolecular pathways (b) of several substituted benzoyl chloride solvolyses.

inductive and/or resonance withdrawer. Therefore, the formal substrate has the resonance effect from the *para*-methoxy substituent which increases the electron density at reaction center, and then it makes help the detachment of chlorine; **3** follows the unimolecular solvolysis mechanism.[6-11] Also the later substrate has the electron withdrawing effect from the *para*-nitro substituent which, in contrast, decreases the electron density at reaction center, it makes larger bond strength between the acyl carbon and the leaving group; **4** follows the bimolecular solvolysis mechanism.[12]
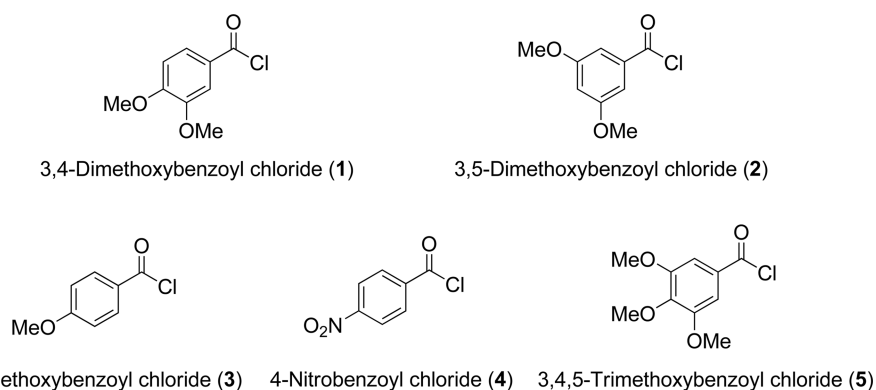
Recently our group reported the results of di- and tri-substituted benzoyl chlorides[13-15] containing the effects of steric hindrance on *ortho*- position and resonance on *para*-position of benzene ring. The results were that the *ortho*-substituent can help to proceed through the unimolecular mechanism, because the steric hindrance of *ortho*-substituent, like a chlorine atom, prevent to bimolecular character at the carbonyl carbon as a reaction center, and also the resonance effect of *para*-substituent, like methoxy group, helps the unimolecular characters in solvolysis. As an extended research, this study dealt with 3,4- (**1**) and 3,5- (**2**) dimethoxybenzoyl chlorides that they have the resonance and inductive effects, but no steric hindrance by substituents.

The below results were summarized the aspects of rate

constants, G-W equation analyses, activation parameters, and kinetic solvent isotope effect (KSIE) of solvolyses of **1** and **2**. Also these results were compared with the previous revealed derivatives for evidencing clearly.

Results and Discussion

The solvolysis rate constants of **1** and **2** are measured at 25.0 °C in variety solvents of nucleophilic, electrophilic and/or those two mixed systems. We used the aqueous ethanol, methanol, and acetone, also the pure ethanol and methanol as the nucleophilic solvents and used aqueous TFE and the pure TFE as the electrophilic solvents. In Table 1, there are reported the measured rate constants for **1** and **2** with standard deviations, the required nucleophilicity $(N_T)^3$ and the solvent ionizing power $(Y_{Cl})^5$ values. Also we report the KSIE values for the methanolysis of **1** and **2** in the footnote of Table 1. These rate constants were tried to analyze by simple and extended G-W equations. The results were summarized with the corresponding ones of several other benzoyl chlorides later. The activation parameters of entropies and enthalpies for both **1** and **2** as the supporting results were calculated from the rate constants measured in four selected solvents at four different temperatures. There were showed

3,4-Dimethoxybenzoyl chloride (**1**)   3,5-Dimethoxybenzoyl chloride (**2**)

4-Methoxybenzoyl chloride (**3**)   4-Nitrobenzoyl chloride (**4**)   3,4,5-Trimethoxybenzoyl chloride (**5**)

Scheme 2. Molecular structures of substituted benzoyl chlorides.

Table 1. Solvolysis rate constants of **1**[a] and **2**[b] in pure and binary solvents at 25.0 °C with the N_T and Y_{Cl} values for the solvents

Solvent[c]	**1** 10^2k (s^{-1})[d]	**2** 10^2k (s^{-1})[d]	N_T[e]	Y_{Cl}[f]
100%EtOH	0.127±0.001	0.0806±0.0003	0.37	-2.52
90%EtOH	0.672±0.022	0.193±0.001	0.16	-0.94
80%EtOH	2.35±0.01	0.279±0.001	0.00	0.00
70%EtOH	5.26±0.02	0.382±0.001	-0.20	0.78
60%EtOH	13.1±0.1	0.538±0.001	-0.38	1.38
50%EtOH	30.8±1.3	0.897±0.004	-0.58	2.02
100%MeOH	1.23±0.01[h]	0.473±0.001[i]	0.17	-1.17
90%MeOH	3.67±0.14	0.925±0.007	-0.01	-0.18
80%MeOH	9.26±0.07	1.47±0.01	-0.06	0.67
70%MeOH	22.3±0.3	2.07±0.01	-0.40	1.46
60%MeOH	52.5±0.1	2.56±0.16	-0.54	2.07
50%MeOH		1.66±0.19	-0.75	2.70
90%Acetone		0.0228±0.0004	-0.35	-2.39
80%Acetone	0.231±0.001	0.0604±0.0002	-0.37	-0.83
70%Acetone	1.11±0.02	0.115±0.001	-0.42	0.17
60%Acetone	4.25±0.04	0.208±0.001	-0.52	0.95
50%Acetone	15.6±0.01	0.405±0.001	-0.70	1.73
100%TFE	16.0±0.01	0.137±0.004	-3.93	2.81
97%TFE	19.2±0.6	0.139±0.001	-3.30	2.83
90%TFE	28.6±0.08	0.208±0.001	-2.55	2.85
80%TFE		0.348±0.004	-2.22	2.90
70%TFE		0.553±0.004	-1.98	2.96
60%TFE		0.828±0.003	-1.85	3.06
50%TFE		1.26±0.02	-1.73	3.16
80T-20E[g]	5.70±0.06	0.0611±0.0003	-1.76	1.89
60T-40E[g]	2.12±0.01	0.0470±0.0001	-0.94	0.63
40T-60E[g]	0.796±0.003	0.0567±0.0002	-0.34	-0.48
20T-80E[g]	0.315±0.001	0.0736±0.0001	0.08	-1.42

[a]Substrate concentration of 3.602×10^{-4} mol dm^{-3}. [b]Substrate concentration of 3.983×10^{-4} mol dm^{-3}. [c]Volume/volume basis at 25.0 °C, except for TFE-H$_2$O and HFIP-H$_2$O mixtures, which are on a weight/weight basis. [d]The average of all integrated specific rates from duplicate runs, with associated standard deviation. [e]Values from ref. 22. [f]Values from ref. 17. [g]T-E are 2,2,2-trifluoroethanol-ethanol mixtures. [h]Value in MeOD of (1.00 ± 0.01), and kinetic solvent isotope effect (k_{MeOH}/k_{MeOD}) of 1.23 ± 0.01. [i]Value in MeOD of (0.279 ± 0.003), and kinetic solvent isotope effect (k_{MeOH}/k_{MeOD}) of 1.70 ± 0.04.

the results of the activation parameters with the corresponding deviations for each solvent later.

Solvolysis of 3,4-Dimethoxybenzoyl Chloride (1). The kinetic study of **1** was performed at 25.0 °C by a conductivity method. The solvent range was limited in 22 solvents containing pure solvents (EtOH, MeOH, and TFE), aqueous solvents (above solvents and acetone) and EtOH-TFE mixture solvents. The small number of rate constants were measured for **1** relatively, because the rates were appreciably fast compare to **2** and 3,4,5-trimethoxybenzoyl chloride (**5**).[15] Along the previous report of our research group, the rate constants of **5** were showed slower than **3**, the reason is the tighten bond between carbonyl carbon and chloride due to two methoxy groups.[15] The substrate **1** has one *meta*-methoxy substituent, and the rate constants of **1** were obtained the reasonable results such as a middle reaction speed between **3**

and **5**. Bentley and co-workers[6-9] reported the result about **3** which is followed the unimolecular reaction dominantly due to the strong resonance behavior of *para*-positioned methoxy group on the benzene ring. Our research group reported the results of **5** which have also the dominant unimolecular solvolysis reactions in wide range of solvent systems.[15] In addition, the linear free energy relationship between **3** and **5** was showed the very good correlation meaning that the above two substrates have similar reaction mechanisms.[15]

In this study, **1** is showed that the rate constants are increased along the increase contents of water in aqueous solvents and along the increase of the TFE in EtOH-TFE mixtures. In simple comparison of reaction rates, the rate of 90% TFE is 7.8 and 43 times faster than 90% MeOH and 90% EtOH. These results are the typical phenomenon of unimolecular solvolysis pathway. For more evidences, the extended G-W equation (Eq. 2) was applied and the sensitivity toward the solvent nucleophilicity (*l*) and solvent ionizing power (*m*) were calculated 0.29 and 0.62, respectively, with a good correlation coefficient (R = 0.962), also *l/m* ratio was 0.47 (Figure 1). This value indicate that the solvolysis of **1** is followed the dissociative S$_N$2 reaction by using the category which was characterized by Kevill and co-workers previously. Also, the KSIE value, k_{MeOH}/k_{MeOD}, of **1** was 1.23 which is in the coverage of unimolecular mechanism. In addition, the activation parameters of enthalpies and entropies obtained from **1**, was 16.3-19.8 kcal/mol for $\Delta H^{\neq}$ and $-12.0\sim0.6$ cal/(mol·K) for $\Delta S^{\neq}$ in all rage of solvents. These values were not clear to distinguish the reaction mechanism, but they imply that the reaction is controlled by enthalpy; it indicated the solvolysis of **1** has the character of the unimolecular pathway. All above evidences are showed that **1** is solvolyzed by unimolecular pathway which contains more important resonance effect of *para*-methoxy group than the inductive effect of *meta*-one. The electron density of the reaction center, carbonyl carbon, is increased by these substituents, and this helps the dissociation of the leaving group, chlorine ion, from the reaction center.
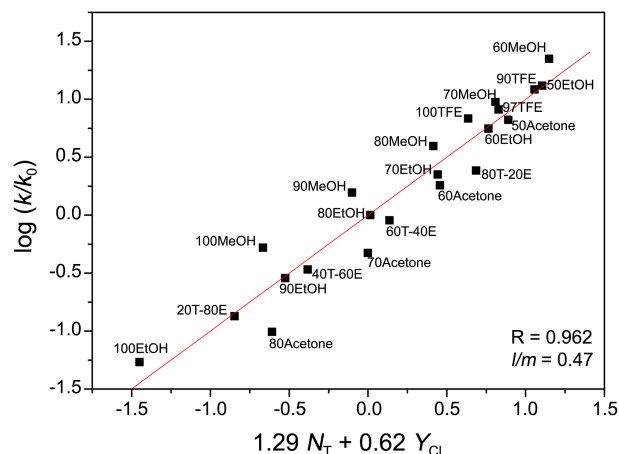

Figure 1. Plot of log (k/k_0) of **1** solvolysis at 25.0 °C from the analysis of the extended G-W equation for all pure and binary solvents.

Table 2. Rate constants for the solvolyses of **1** and **2** at various temperatures and the calculated activation parameters

Solvent (%)[a]	Temp (°C)	**1**			Temp (°C)	**2**		
		$10^2 k$ (s^{-1})[b]	$\Delta H^{\neq}_{298}$[c]	$\Delta S^{\neq}_{298}$[c]		$10^2 k$ (s^{-1})[b]	$\Delta H^{\neq}_{298}$[c]	$\Delta S^{\neq}_{298}$[c]
100MeOH	10.0	0.244±0.004			25.0	0.473±0.001[d]	13.2±0.2	-24.8±0.6
	15.0	0.435±0.003			30.0	0.706±0.003		
	20.0	0.733±0.001			35.0	1.03±0.01		
	25.0	1.23±0.01[d]	17.4±0.2	-8.8±0.6	40.0	1.45±0.01		
100EtOH	20.0	0.0746±0.0001			25.0	0.0806±0.0003[d]	14.4±0.1	-24.3±0.2
	25.0	0.127±0.001[d]	17.8±0.1	-12.0±0.4	30.0	0.123±0.001		
	35.0	0.354±0.005			35.0	0.185±0.001		
	45.0	0.892±0.016			40.0	0.271±0.001		
80EtOH	10.0	0.383±0.006			25.0	0.279±0.001[d]	14.3±0.2	-22.3±0.7
	15.0	0.711±0.002			30.0	0.427±0.006		
	20.0	1.36±0.07			35.0	0.642±0.004		
	25.0	2.35±0.01[d]	19.8±0.6	0.6±1.2	40.0	0.926±0.001		
90TFE	10.0[e]	6.39±0.28			25.0[f]	0.348±0.004[d]	17.6±0.2	-10.8±0.6
or	15.0[e]	11.4±0.4			30.0[f]	0.583±0.001		
80TFE	20.0[e]	19.5±0.1			35.0[f]	0.958±0.001		
	25.0[e]	28.6±0.8[d]	16.3±0.9	-6.3±4.2	40.0[f]	1.51±0.01		

[a,b]See footnotes in Table 1. [c]enthalpies ($\Delta H^{\neq}$, kcal mol^{-1}) and entropies ($\Delta S^{\neq}$, cal mol^{-1}K^{-1}) with associated standard error. [d]From Table 1. [e]Binary solvent is 90%TFE. [f]Binary solvent is 80%TFE.

Solvolysis of 3,5-Dimethoxybenzoyl Chloride (2): The solvolysis of **2** was studied by the same above method and at the same temperature. The solvolysis rates of **2** were showed relatively slower than **1**, because **2** has no *para*-methoxy group which has the resonance effect and can support to proceed through unimolecular pathway. So substrate **2** has only an inductive effect of two *meta*-methoxy groups, these would not help the solvolysis efficiently. In general rate comparison of **2** in the same composition solvent systems, the rate in 90%TFE is a little faster than in EtOH (1.1 folds), but slower than in MeOH (4.4 folds). This phenomenon is interpreted that the solvolysis of **2** has more bimolecular and less unimolecular characters than **1**. The application of the extended G-W equation showed 0.49 of *l* value and 0.40 of *m* value respectively with a little poor correlation coefficient

(R = 0.812), also *l*/*m* ratio was 1.22. Most points were showed deviated in the plot of the extended G-W analysis. In this case, analysis is tried in two different solvent systems, the nucleophilic and electrophilic solvents separately. The substrate, **2** was analyzed and obtained the results that sensitivities were 1.27 for *l* value and 0.49 for *m* value (Figure 2) in 17 nucleophilic solvent systems and 0.47 for *l* value and 0.73 for *m* value (Figure 3) in 8 electrophilic solvent systems (except for 100%TFE, 20%TFE-80%EtOH, and 40%TFE-60%EtOH), respectively. The correlation coefficients for both cases were increased to 0.904 and 0.959, and the values of *l*/*m* ratio were 2.58 in nucleophilic and 0.64 in electrophilic solvents, respectively. In case of the electrophilic solvents, three omitted points were still deviated; they can be considered middle of between unimolecular and
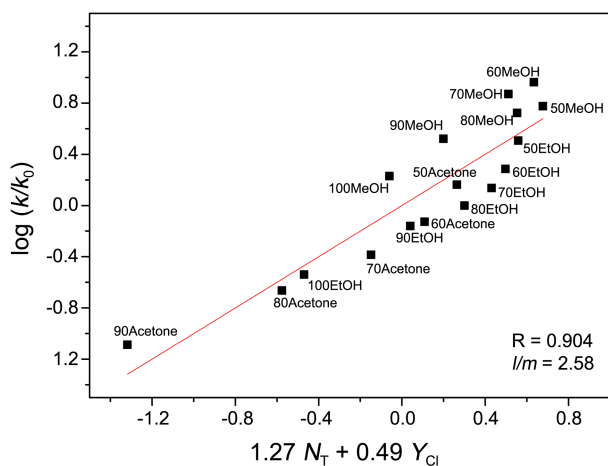

Figure 2. Plot of log (k/k_0) of **2** solvolysis at 25.0 °C from the analysis of the extended G-W equation for all nucleophilic pure and binary solvents.
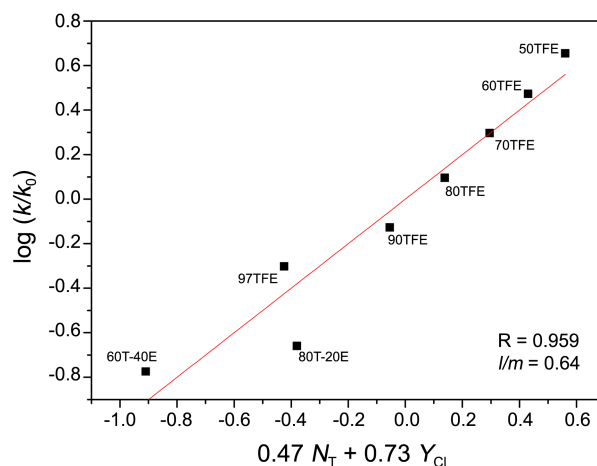

Figure 3. Plot of log (k/k_0) of **2** solvolysis at 25.0 °C from the analysis of the extended G-W equation for electrophilic binary solvents.

Table 3. Correlation on the Solvolysis Rate Constants of Several Derivatives of Benzoyl Chloride Using the Extended Grunwald-Winstein Equation

Subst. (Temp, °C)	n	l	m	c	R	l/m
1 (25.0 °C)	22	0.29±0.06	0.62±0.05	0.01±0.05	0.962	0.47
2 (25.0 °C)	17	1.27±0.29	0.49±0.06	0.30±0.09	0.897	2.59
	8	0.47±0.11	0.73±0.09	-0.92±0.21	0.959	0.64
3 (25.0 °C)[a]	37	0.31±0.05	0.81±0.02	0.08±0.06	0.989	0.38
	40	0.30±0.04	0.83±0.02	0.04±0.05	0.988	0.36
	37	0.29±0.03	0.87±0.02	-0.08±0.05	0.993	0.33
5 (25.0 °C)[b]	31	0.32±0.05	0.54±0.04	0.09±0.05	0.960	0.59
	27	0.34±0.04	0.59±0.03	-0.02±0.05	0.975	0.58

[a]From ref 12. [b]From ref. 15.

bimolecular characters. These results mean that the solvolysis of **2** is dominat by a bimolecular pathway in the former case, in contrast, by a unimolecular pathway in latter case.

The KSIE value, 1.70 for **2** shows a strong support with the above results, which is the typical phenomenon of the bimolecular pathway. Also the obtained activation parameters of **2**, could be interpreted by two different characters along the solvents. In the nucleophilic solvents (100%MeOH, 100%EtOH, and 80%EtOH), they were determined 13.2-14.4 kcal/mol for $\Delta H^{\neq}$ and -24.8 ~ -22.3 cal/(molK) for $\Delta S^{\neq}$, these results contain the bimolecular character, while in the electrophilic solvents (80%TFE), they were obtained 17.6 kcal/mol for $\Delta H^{\neq}$ and -10.8 cal/(molK) for $\Delta S^{\neq}$, which is the unimolecular character. In summary, 3,5-dichlorobenzoyl chloride (**2**) has only inductive effect by two *ortho*-methoxy substituents, so it showed the increase of the bimolecular character.

Finally, in order to find out the linear free energy relationships (LFER), the results of **1** and **2** by the analysis of the extended G-W equation, were compared with those of the previously reported benzoyl chloride derivatives, and there were summarized in Table 3. Substrates of **3** and **5** were reported that they are mainly followed by unimolecular pathway (ionization) due to the resonance effect of *para*-methoxy substituent.[6-9,15] The *l/m* ratio of **1** in all range of solvents was 0.47, it is the similar value of **3** and **5**, which means that the solvolysis reaction pathway of **1** containing *para*-methoxy substituent, is consistent with the results of **3** and **5**. In case of **2**, the *l/m* ratio was 2.59 in 17 nucleophilic solvents and was 0.64 in 8 electrophilic solvents, respectively. This substrate is explained to be involved two different mechanisms along the solvent systems. The reaction mechanism in electrophilic solvents is same aspect of **1**, but the one in nucleophilic solvents is a typical associative S_N2 pathway.

Conclusions

The reaction mechanisms of 3,4-dimethoxybenzoyl chloride (**1**) and 3,5-dimethoxybenzoyl chloride (**2**) were confirmed by the all above experimental and theoretical results. The *para*-methoxy substituent containing the electron donating ability (resonance effect) is the key role to be

decided in the solvolysis of **1** for all range of solvents, which is confirmed to follow the unimolecular pathway involving the ionization as a rate-determining step. Several results of the extended Grunwlad-Winstein (G-W) equation analysis, the kinetic solvent isotope effect (KSIE), and parameters of activation were supported correspondently. Also **2** with two *meta*-methoxy and no *para*-methoxy substituents was concluded to follow the dual solvolysis mechanisms; the bimolecular pathway is dominant in only nucleophilic solvents and the unimolecular pathway is dominant in electrophilic solvents (except 3 solvents). Two *meta*-methoxy groups of **2** have the inductive effect and no resonance effect, it helps to increase the electron density a little at carbonyl carbon (the bimolecular character). In conclusion, the existence of *para*-methoxy substituent is the important role for deciding the solvolysis mechanism of these two substrates.

Experimentals

Substrates, 3,4-dimethoxybenzoyl chloride (**1**, 98%) and 3,5-dimethoxybenzoyl chlorides (**2**, 97%) were obtained from the company of Sigma-Aldrich and used without further purification. All solvents were purified by using the ways described previously.[16] The methods to obtain the first-order solvolysis rate[13] and to calculate the rate constants[13,17] were also were the same, there were used for the previous studies.

References

1. Kevill, D. N.; D'Souza, M. J. *J. Chem. Res.* **2008**, 61.
2. Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846.
3. Bentley, T. W.; Llewellyn, G. *Prog. Phys. Org. Chem.* **1990**, *17*, 121.
4. Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700.
5. Kevill, D. N. *In Advances in Quantitative Structure-Property Relationships*; Charton, M., Ed.; JAI Press: Greenwich, CT, **1996**, *1*, 81-115.
6. Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc. Perkin Trans. 2* **1985**, 983.
7. Bentley, T. W.; Harris, H. C. *J. Chem. Soc. Perkin Trans. 2* **1986**, 619.

8. Bentley, T. W.; Koo, I. S. *J. Chem. Soc. Perkin Trans. 2* **1989**, 1385.

9. Bentley, T. W.; Shim, C. S. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1659.

10. Liu, K.-T.; Chen, H.-I. *J. Chem. Soc. Perkin Trans. 2* **2000**, 893.

11. Bentley, T. W.; Harris, H. C. *Int. J. Mol. Sci.* **2011**, *12*, 4805.

12. Kevill, D. N.; D'Souza, M. J. *J. Phys. Org. Chem*. **2002**, *15*, 881.

13. Park, K.-H.; Kevill, D. N. *J. Phys. Org. Chem*. **2012**, *25*, 2.

14. Park, K.-H.; Kevill, D. N. *J. Phys. Org. Chem*. **2012**, *25*, 267.

15. Park, K.-H.; Kevill, D. N. *J. Chem. Res.* **2011**, 647.

16. Kevill, D. N.; Anderson, S. W. *J. Org. Chem.* **1991**, *56*, 1845.

17. Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834.