Kinetics and Mechanism of Certain Acetylation Reactions with Acetamide/Oxychloride in Acetonitrile under *Vilsmeier–Haack* Conditions

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Vilsmeier–Haack (*VH*) acetylation reactions with benzaldehydes or acetophenones in MeCN followed second-order kinetics and afforded acetyl derivatives under kinetic conditions, irrespective of the nature of the oxychloride ($SOCl_2$ or $POCl_3$) used for the preparation of the *VH* reagent along with acetamide. The present finding contributes to the understanding of the nature of the reactive species of the *VH* reagent as well as of the acetylation mechanism.

Introduction. – The *Vilsmeier–Haack* reagent (VHR) is a versatile reactant in organic synthesis [1–6]. In earlier investigations, it is reported that formylation can be achieved more conveniently by the *Vilsmeier–Haack* (*VH*) reaction than by the *Reimer–Tiemann*, *Gattermann–Koch*, or *Duff*'s formylation methods [7–12]. In the recent past, several formylation, acetylation, and bromination reactions under *VH* conditions have been reported from our group and others [13–20]. For example, benzanilide (= *N*-phenylbenzamide) and *N*,*N*-dimethylaniline (= *N*,*N*-dimethylbenzenamine) react with phosphorus oxychloride (= phosphoric trichloride; $POCl_3$) to produce an unsymmetrical diaryl ketone [17]. Similarly, anthracene can be formylated exclusively at the 9-position [19]. Under *VH* conditions, formylation of 1*H*-indole [18] takes place at room temperature exclusively at C(3), to afford 1*H*-indole-3-carboxaldehyde. Since the pyrrole part is the most reactive portion of 1*H*-indole, nucleophilic substitution of the fused carbocyclic (benzene) ring can take place only after N(1), C(2), and C(3) are substituted. This was supported by the fact that at C(3) position of 1*H*-indole, electrophilic substitution is 10^{13} times faster than that of benzene.

Earlier publications from our group elaborated kinetic and mechanistic aspects of the formylation of coumarin derivatives (*i.e.*, 4*H*-1-benzopyran-4-one derivatives) [3][17] and formation of a chromen-4-one (= 4*H*-1-benzopyran-4-one) and its subsequent formylation products from 2-hydroxyacetophenone (= 1-(2-hydroxyphenyl)ethanone; 2-OHap) [3][17] under *VH* conditions in various solvent media. These studies revealed second-order kinetics with first-order in [substrate] and first-order in [VHR] reagent. The reaction rates altered nonlinearly with an increase in the dielectric constant of the medium, and the data did not fit completely well with either *Amis* or *Kirkwood*'s theories of ion–dipole- and dipole–dipole-type reactions. On the basis of kinetic and spectroscopic results, participation of the *VH* adduct and substrate

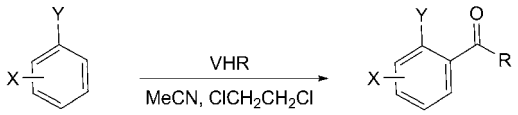
molecule in the rate-limiting step has been proposed. Encouraged by the striking features of our publications, we took up the present study on the *VH* acetylation reaction of benzaldehydes and acetophenones, in various solvent media, *viz.*, CH_2Cl_2, 1,2-dichloroethane ($ClCH_2CH_2Cl$), MeCN, and also in binary mixtures of $ClCH_2CH_2Cl$ and MeCN, to explore the kinetic features with the aim to contribute to the understanding of the mechanistic aspects. The study was also aimed at exploring the similarities and dissimilarities in the mechanistic aspects and the nature of the reactive species and also the transition state when different *VH* adducts were used as reagents for the acetylation reaction.

Experimental. – VH *Reagents.* Flasks containing acetamide dissolved in a suitable solvent (generally $ClCH_2CH_2Cl$, or MeCN) along with $SOCl_2$ and $POCl_3$ were cooled and thermally equilibrated for *ca.* 30 min at $-5°$ by keeping them in a benzene trough chilled from outside with ice and NaCl. Requisite amounts of solvent and amide were transferred into a 100 ml flask, and $POCl_3$ or $SOCl_2$ was added dropwise, at $-5°$ with constant stirring. The resultant reagent mixture was kept aside for *ca.* 1 h at to ensure complete formation of the *VH* adduct. Its concentration was checked by acid–base titrations to the bromocresol-green end point according to literature reports [3][17–19].

Kinetic Method. The method of following the kinetics of the *VH* reaction is by and large similar to that reported in our earlier reports [3][17][18]. The thermostat (*Toshniwal*, India) was adjusted to the desired reaction temp. Two different flasks, one containing a known amount of *VH* reagent (VHR) in a suitable solvent and the other with the substrate soln., were put in the thermostatic bath for *ca.* 30 min. The reaction was initiated by adding the requisite amount of substrate sol. to the flask containing the *VH* reagent, and stirring was continued until the end of the reaction. At regular time intervals, aliquots of the mixture were withdrawn into a conical flask containing *ca.* 50 ml of hot distilled H_2O; the unreacted *VH* adduct underwent hydrolysis to give a mixture of hydrochloric and sulfuric acid in the case of the acetamide/$SOCl_2$ and a mixture of hydrochloric and phosphoric acid in the case of the acetamide/$POCl_3$ reagent. The acid content was determined by titration against standard NaOH soln. to the bromocresol-green end point.

Product Analysis under Kinetic Conditions. After completion of the kinetic study of the reaction, the remaining part of the reaction mixture was refluxed for further 4 to 5 h and left aside overnight. The soln. was then poured into ice-cold water under vigorous stirring and kept aside for *ca.* 2 h. The resulting soln. was neutralized by $NaHCO_3$. The org. phase was extracted with $ClCH_2CH_2Cl$ and the extract dried ($MgSO_4$) and concentrated. The products were isolated under kinetic conditions and found to be acetyl derivatives of the substrates. The products were characterized by ^{1}H-NMR and mass spectra, which in satisfactory agreement with those of authentic samples. It is of interest to note that 2-OHap underwent cyclization followed by acetylation and afforded an acetyl chromen-4-one *i.e.*, 3-acetyl-2-methyl-4*H*-1-benzopyran-4-one, as described in earlier works [15]. However, 3-hydroxyacetophenone (=1-(3-hydroxyphenyl)ethanone; 3-OHap), and 4-hydroxyacetophenone (=1-(4-hydroxyphenyl)ethanone; 4-OHap) could not undergo cyclization but afforded the corresponding acetyl derivatives (*Scheme 1*).

Scheme 1

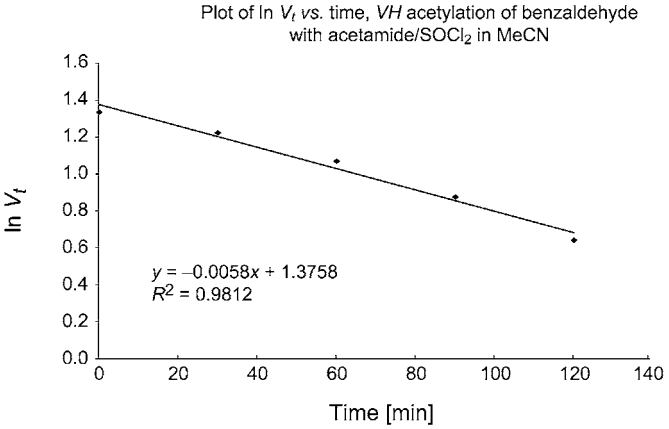


VHR = acetamide + $SOCl_2$ or $POCl_3$
Y = OH, NH_2, and NHAc
X = electron donating or withdrawing groups

Results and Discussion. – *Salient Kinetic Features: i*) When $[substrate]_0 \gg [VHR]_0$, the plots of ln V_t *vs.* time were linear with a negative slope and an intercept as shown in *Figs. 1–4*. This observation revealed first-order kinetics in [substrate], where substrate indicates aldehyde or ketone. Representative data are listed in *Tables 1* and *2*.

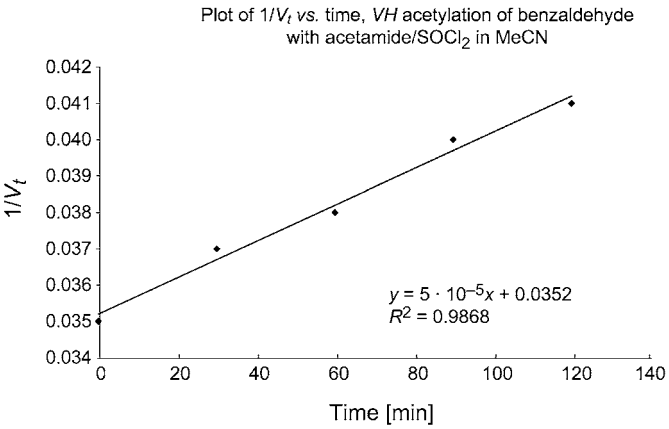
First-order plot

Time [min]	Titer [ml]	ln V_t
0	3.8	1.335
30	3.4	1.223
60	2.9	1.069
90	2.4	0.875
120	1.9	0.641



Second-order plot

Time [min]	Titer [ml]	$1/V_t$
0	28.0	0.035
30	27.0	0.037
60	26.1	0.038
90	25.0	0.040
120	24.0	0.041



Eyring's plot

1000/*T*	ln (*Nhk*/*RT*)
3.300	8.4
3.195	9.2
3.096	10.2
3.003	10.8

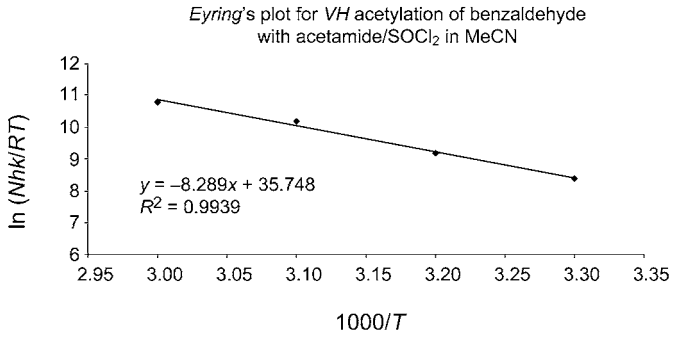
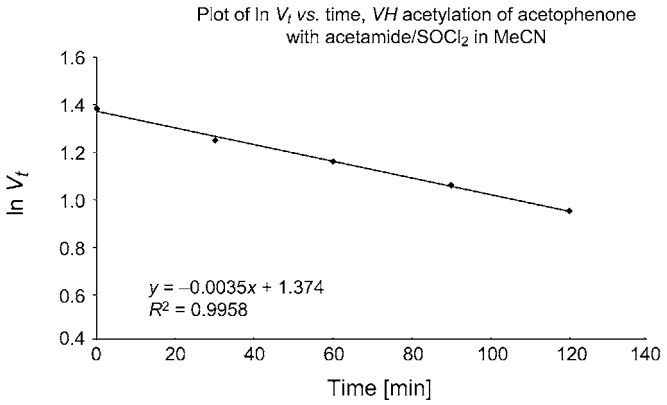


Fig. 1. *Kinetics and* Eyring*'s plots for* VH *acetylation of benzaldehyde with acetamide/$SOCl_2$ in MeCN*

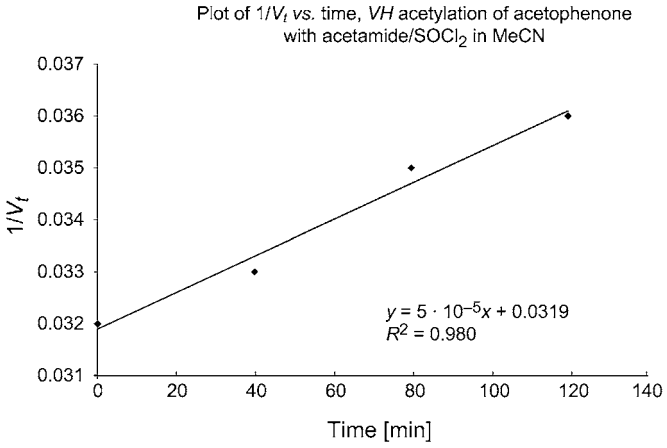
First-order plot

Time [min]	Titer [ml]	ln V_t
0	4.0	1.386
30	3.5	1.252
60	3.2	1.163
90	2.9	1.064
120	2.6	0.955



Second-order plot

Time [min]	Titer [ml]	$1/V_t$
0	31.0	0.032
30	30.0	0.033
60	28.5	0.035
90	27.6	0.036



Eyring's plot

1000/T	ln (Nhk/RT)
3.300	9.2875
3.195	9.7898
3.096	10.0800
3.003	10.6119

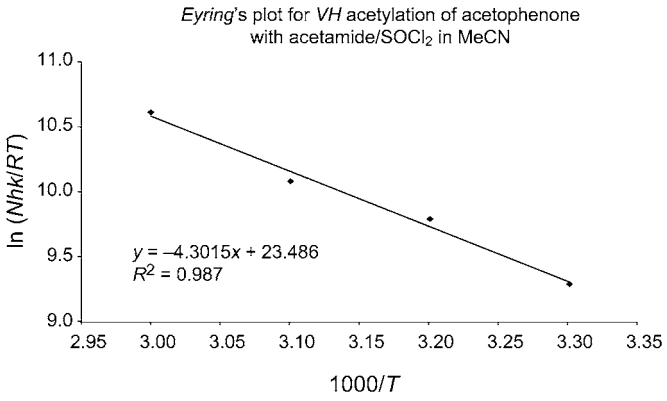
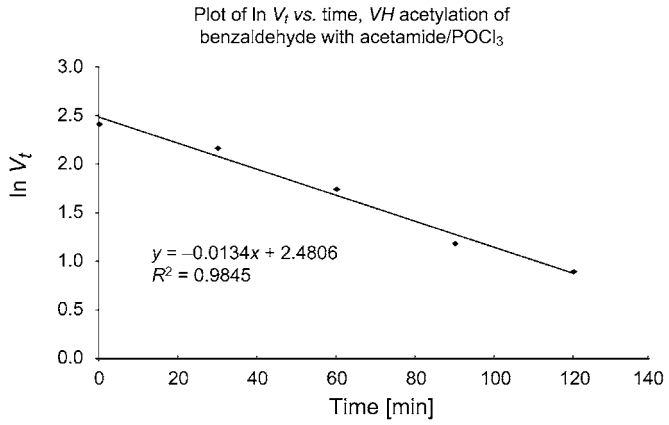


Fig. 2. *Kinetics and* Eyring*'s plots for* VH *acetylation of acetophenone with acetamide/$SOCl_2$ in MeCN*

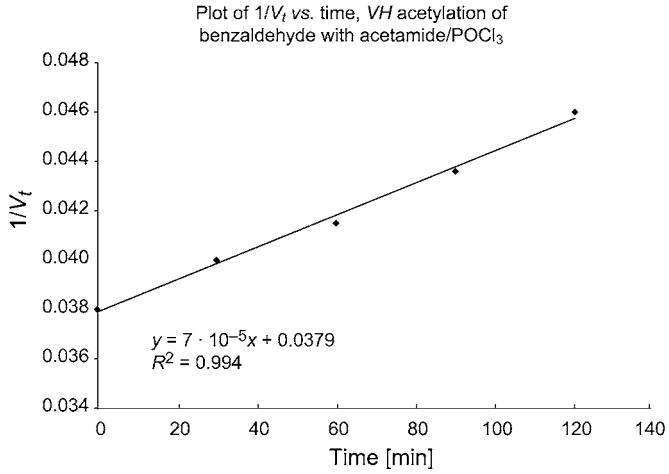
First-order plot

Time [min]	Titer [ml]	ln V_t
0	4.1	2.41
30	3.2	2.163
60	2.1	1.741
90	1.2	1.182
120	0.9	0.894



Second-order plot

Time [min]	Titer [ml]	$1/V_t$
0	26.3	0.038
30	25	0.04
60	24	0.0415
90	23	0.0436
120	21	0.046



Eyring's plot

1000/T	ln (Nhk/RT)
3.300	8.693
3.195	8.777
3.096	8.901
3.003	9.015

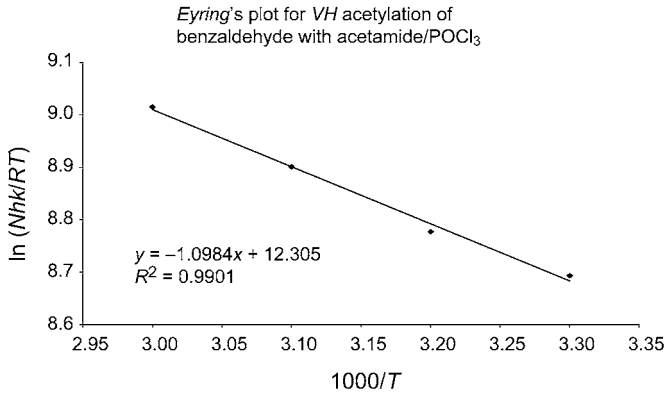
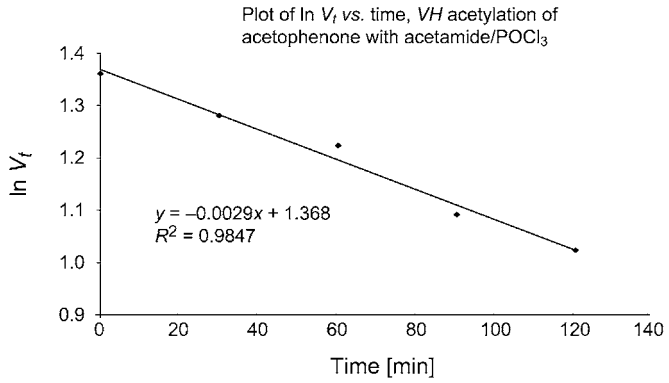


Fig. 3. *Kinetics and* Eyring*'s plots for* VH *acetylation of benzaldehyde with acetamide/$POCl_3$ in MeCN*

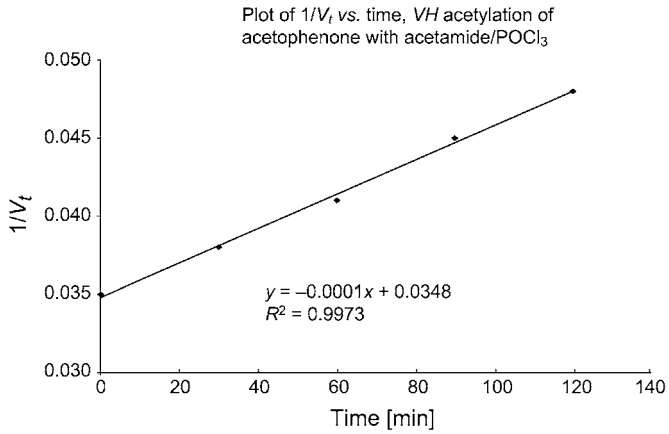
First-order plot

Time [min]	Titer [ml]	ln V_t
0	3.9	1.36
30	3.6	1.28
60	3.4	1.223
90	3.0	1.091
120	2.8	1.023



Second-order plot

Time [min]	Titer [ml]	$1/V_t$
0	28.1	0.035
30	26	0.038
60	24.2	0.041
90	22	0.045
120	20.5	0.048



Eyring's plot

1000/*T*	ln (*Nhk*/*RT*)
3.300	9.320
3.195	9.590
3.096	9.949
3.003	10.344

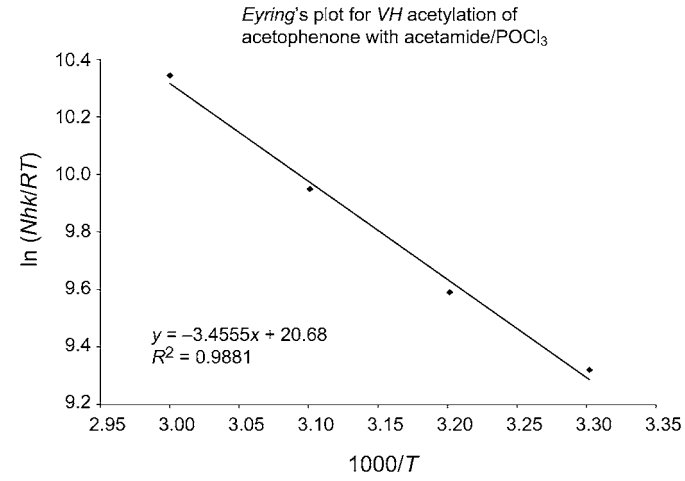


Fig. 4. *Kinetics and* Eyring*'s plots for* VH *acetylation of acetophenone with acetamide/POCl$_3$ in MeCN*

Table 1. VH *Acetylation First-Order Reactions with Acetamide/$SOCl_2$ in MeCN at 303 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	First-order rate constant (k') [s^{-1}]
PhCHO	$y = -0.0058x + 1.3758$	0.9812	9.66
2-OHC_6H_2CHO	$y = -0.0089x + 1.0604$	0.9998	14.8
4-OHC_6H_4CHO	$y = -0.0122x + 1.73$	0.9431	20.3
4-$MeOC_6H_4CHO$	$y = -0.0057x + 1.4134$	0.9897	9.5
4-ClC_6H_4CHO	$y = -0.0035x + 1.2628$	0.996	5.83
4-BrC_6H_4CHO	$y = -0.0115x + 1.701$	0.9452	19.7
4-$NO_2C_6H_4CHO$	$y = -0.0079x + 1.3532$	0.9811	13.2
(*E*)-PhCH=CHCHO	$y = -0.0063x + 1.1312$	0.9875	10.5
Acetophenone (PhCOMe; ap)	$y = -0.0036x + 1.3772$	0.997	6.0
2-OHap	$y = -0.005x + 1.1674$	0.9748	8.33
4-OHap	$y = -0.0049x + 1.013$	0.9927	8.16
4-Meap	$y = -0.0037x + 0.4554$	0.9691	6.16
3-OHap	$y = -0.0062x + 0.7558$	0.9942	10.3
4-Brap	$y = -0.006x + 1.2034$	0.9564	10.0
4-NO_2ap	$y = -0.0027x + 1.176$	0.9796	4.5

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

Table 2. VH *Acetylation First-Order Reactions with Acetamide/$POCl_3$ in MeCN at 303 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	First-order rate constant (k') [s^{-1}]
PhCHO	$y = -0.0134x + 2.4806$	0.9845	22.3
2-OHC_6H_4CHO	$y = -0.0039x + 1.2788$	0.964	6.5
4-OHC_6H_4CHO	$y = -0.0026x + 1.5162$	0.9798	4.33
4-$MeOC_6H_4CHO$	$y = -0.0045x + 1.3889$	0.9588	7.5
4-ClC_6H_4CHO	$y = -0.0023x + 1.217$	0.9762	3.83
4-BrC_6H_4CHO	$y = -0.0018x + 1.4494$	0.9708	3.0
4-$NO_2C_6H_4CHO$	$y = -0.0048x + 1.393$	0.9633	8.0
(*E*)-PhCH=CHCHO	$y = -0.004x + 1.1681$	0.9689	6.67
Acetophenone (PhCOMe; ap)	$y = -0.0029x + 1.368$	0.9847	4.83
2-OHap	$y = -0.0026x + 1.2458$	0.9928	4.33
4-OHap	$y = -0.0025x + 1.0654$	0.9674	4.16
4-Meap	$y = -0.0029x + 1.4006$	0.9704	4.83
3-OHap	$y = -0.0016x + 1.0406$	0.9628	2.67
4-Brap	$y = -0.0049x + 1.2292$	0.987	8.17
4-NO_2ap	$y = -0.0022x + 1.202$	0.9515	3.67

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

ii) Under the condition $[VHR]_0 = [substrate]_0$, plots of $[1/(a-x)]$ or $[1/V_t]$ *vs.* time were linear with a positive slope and an intercept on the ordinate indicating that the *VH* reaction follows overall second-order kinetics (*Figs. 1–4*). The second-order rate constant data are presented for certain aldehydes and ketones in *Tables 3–10*.

iii) The rate constants increased substantially with an increase in the temperature. The *Eyring* plots of ln (*Nhk*/*RT*) *vs.* 1/*T* were linear with a negative slope and an intercept (*Figs. 1–4*) as demanded by *Eyring*'s equation (*Eqn. 3*). This equation was

Table 3. VH *Acetylation Second-Order Reactions with Acetamide/$SOCl_2$ in MeCN at 303 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 5 \cdot 10^{-5}x + 0.0351$	0.9918	$6.665 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 4 \cdot 10^{-5}x + 0.0338$	0.9826	$5.332 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 20 \cdot 10^{-5}x + 0.0306$	0.9801	$26.667 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 6 \cdot 10^{-5}x + 0.0255$	0.9922	$7.998 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 6 \cdot 10^{-5}x + 0.0289$	0.9924	$7.998 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 8 \cdot 10^{-5}x + 0.0307$	0.9947	$10.664 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 5 \cdot 10^{-5}x + 0.0317$	0.9882	$6.665 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 4 \cdot 10^{-5}x + 0.0298$	0.973	$5.332 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 5 \cdot 10^{-5}x + 0.0317$	0.9882	$6.665 \cdot 10^{-5}$
2-OHap	$y = 9 \cdot 10^{-5}x + 0.0302$	0.9823	$10.664 \cdot 10^{-5}$
4-OHap	$y = 8 \cdot 10^{-5}x + 0.0306$	0.9796	$10.664 \cdot 10^{-5}$
4-Meap	$y = 5 \cdot 10^{-5}x + 0.0334$	0.982	$6.665 \cdot 10^{-5}$
3-OHap	$y = 8 \cdot 10^{-5}x + 0.0376$	0.9891	$10.664 \cdot 10^{-5}$
4-Brap	$y = 8 \cdot 10^{-5}x + 0.0306$	0.973	$10.664 \cdot 10^{-5}$
4-NO_2ap	$y = 4 \cdot 10^{-5}x + 0.0348$	0.9796	$5.332 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

Table 4. VH *Acetylation Second-Order Reactions with Acetamide/$SOCl_2$ in MeCN at 313 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 0.0002x + 0.0384$	0.9833	$33.34 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 0.0001x + 0.0416$	0.9943	$16.67 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 0.0001x + 0.036$	0.9793	$16.67 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 0.00006x + 0.0378$	0.9704	$10.002 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 0.0002x + 0.0406$	0.9927	$33.34 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 0.0001x + 0.035$	0.9928	$16.67 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 0.0001x + 0.0328$	0.9987	$16.67 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 0.0002x + 0.0368$	0.9703	$33.34 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 0.0001x + 0.0458$	0.9806	$16.67 \cdot 10^{-5}$
2-OHap	$y = 0.0001x + 0.0374$	0.9935	$16.67 \cdot 10^{-5}$
4-OHap	$y = 0.0002x + 0.0344$	0.9959	$33.34 \cdot 10^{-5}$
4-Meap	$y = 0.0001x + 0.0482$	0.9985	$16.67 \cdot 10^{-5}$
3-OHap	$y = 0.00007x + 0.0408$	0.9918	$11.669 \cdot 10^{-5}$
4-Brap	$y = 0.00009x + 0.0384$	0.9494	$15.003 \cdot 10^{-5}$
4-NO_2ap	$y = 0.0001x + 0.042$	0.965	$16.67 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

obtained from *Eyring*'s theory of reaction rates. According to *Eyring*'s theory, rate constant (k) can be given by *Eqn. 1*, where the transmission coefficient (k_t) is assumed to be unity, R, N, h, and T represent the gas constant, *Avogadro* number, *Planck*'s constant, and the reaction temperature, and $\Delta S^{\#}$ and $\Delta H^{\#}$ represent the enthalpy and entropy of activation, respectively. Rearrangement of *Eqn. 1* gives *Eqn. 2*, and its

Table 5. VH *Acetylation Second-Order Reactions with Acetamide/$SOCl_2$ in MeCN at 323 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 0.0004x + 0.0386$	0.9919	$66.68 \cdot 10^{-5}$
2-OHC_6H_4HO	$y = 0.0002x + 0.0417$	0.9875	$33.34 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 0.0002x + 0.033$	0.9921	$33.34 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 0.0002x + 0.0392$	0.9925	$33.34 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 0.0003x + 0.0442$	0.9855	$51.01 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 0.0002x + 0.0348$	0.9954	$33.34 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 0.0003x + 0.0338$	0.9706	$51.01 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 0.0004x + 0.0118$	0.9945	$66.68 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 0.0002x + 0.0558$	0.9873	$33.34 \cdot 10^{-5}$
2-OHap	$y = 1 \cdot 10^{-4}x + 0.0404$	0.9689	$1.667 \cdot 10^{-5}$
4-OHap	$y = 8 \cdot 10^{-5}x + 0.0422$	0.9952	$13.336 \cdot 10^{-5}$
4-Meap	$y = 0.0002x + 0.0542$	0.9878	$33.34 \cdot 10^{-5}$
3-OHap	$y = 0.0001x + 0.0436$	0.9972	$16.67 \cdot 10^{-5}$
4-Brap	$y = 0.0002x + 0.0345$	0.991	$33.34 \cdot 10^{-5}$
4-NO_2ap	$y = 0.0003x + 0.0361$	0.9892	$51.01 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

Table 6. VH *Acetylation Second-Order Reactions with Acetamide/$SOCl_2$ in MeCN at 333 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 0.0005x + 0.0411$	0.9947	$83.35 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 0.0004x + 0.04$	0.9954	$66.68 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 0.0005x + 0.0385$	0.9891	$83.35 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 0.0006x + 0.0347$	0.9966	$100.02 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 0.0004x + 0.0493$	0.9652	$66.68 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 0.0004x + 0.0329$	0.9944	$66.68 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 0.0004x + 0.034$	0.9905	$66.68 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 0.0006x + 0.0339$	0.9925	$100.02 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 0.0004x + 0.0454$	0.9016	$66.68 \cdot 10^{-5}$
2-OHap	$y = 0.0002x + 0.0434$	0.9734	$33.34 \cdot 10^{-5}$
4-OHap	$y = 0.00009x + 0.0466$	0.9949	$15.003 \cdot 10^{-5}$
4-Meap	$y = 0.0003x + 0.0596$	0.9719	$51.01 \cdot 10^{-5}$
3-OHap	$y = 0.0003x + 0.0474$	0.9703	$51.01 \cdot 10^{-5}$
4-Brap	$y = 0.0004x + 0.0508$	0.979	$66.68 \cdot 10^{-5}$
4-NO_2ap	$y = 0.0004x + 0.0506$	0.9716	$66.68 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

natural logarithms gives *Eqn. 3*. According to *Eqn. 3* the plots of $\ln (Nhk/RT)$ *vs.* $(1/T)$ should be linear with negative slopes $(\Delta H^{\#}/R)$ and definite intercepts on the ordinate which are equal to $(\Delta S^{\#}/R)$. Such plots were realized in the present study (*Figs. 1–4*), and from the slopes and intercepts, the enthalpy and entropies of activation were evaluated. The free energy of activation ($\Delta G^{\#}$) was also calculated by the *Gibbs–Helmholtz* equation *Eqn. 4*.

Table 7. VH *Acetylation Second-Order Reactions with Acetamide/$POCl_3$ in MeCN at 303 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 7 \cdot 10^{-5}x + 0.0376$	0.9423	$11.667 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 7 \cdot 10^{-5}x + 0.0356$	0.9423	$11.667 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 9 \cdot 10^{-5}x + 0.0342$	0.9769	$15.003 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 9 \cdot 10^{-5}x + 0.0342$	0.9769	$15.003 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 9 \cdot 10^{-5}x + 0.0326$	0.9851	$15.003 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 5 \cdot 10^{-5}x + 0.0352$	0.98	$8.335 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 7 \cdot 10^{-5}x + 0.0368$	0.9918	$11.667 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 4 \cdot 10^{-5}x + 0.0318$	0.973	$6.668 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 10 \cdot 10^{-5}x + 0.0348$	0.9973	$16.67 \cdot 10^{-5}$
2-OHap	$y = 5 \cdot 10^{-5}x + 0.0336$	0.9698	$8.335 \cdot 10^{-5}$
4OHap	$y = 10 \cdot 10^{-5}x + 0.0356$	0.9972	$16.67 \cdot 10^{-5}$
4-Meap	$y = 10 \cdot 10^{-5}x + 0.0336$	0.9928	$16.67 \cdot 10^{-5}$
3-OHap	$y = 30 \cdot 10^{-5}x + 0.0384$	0.9732	$50.01 \cdot 10^{-5}$
4-Brap	$y = 9 \cdot 10^{-5}x + 0.0336$	0.9826	$15.003 \cdot 10^{-5}$
4-NO_2ap	$y = 6 \cdot 10^{-5}x + 0.0392$	0.9878	$10.002 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

Table 8. VH *Acetylation Second-Order Reactions with Acetamide/$POCl_3$ in MeCN at 313 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 6 \cdot 10^{-5}x + 0.0395$	0.9925	$10.001 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 6 \cdot 10^{-5}x + 0.038$	0.9897	$10.001 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 20 \cdot 10^{-5}x + 0.0362$	0.9888	$33.34 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 8 \cdot 10^{-5}x + 0.0284$	0.9796	$13.336 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 5 \cdot 10^{-5}x + 0.0352$	0.9868	$8.335 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 10 \cdot 10^{-5}x + 0.036$	0.9695	$16.67 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 7 \cdot 10^{-5}x + 0.0408$	0.9918	$11.669 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 10 \cdot 10^{-5}x + 0.0342$	0.9698	$1.667 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 10 \cdot 10^{-5}x + 0.0358$	0.9678	$16.67 \cdot 10^{-5}$
2-OHap	$y = 20 \cdot 10^{-5}x + 0.0491$	0.994	$33.34 \cdot 10^{-5}$
4-OHap	$y = 6 \cdot 10^{-5}x + 0.0396$	0.9633	$10.002 \cdot 10^{-5}$
4-Meap	$y = 6 \cdot 10^{-5}x + 0.0376$	0.951	$10.002 \cdot 10^{-5}$
3-OHap	$y = 8 \cdot 10^{-5}x + 0.045$	0.9944	$13.336 \cdot 10^{-5}$
4-Brap	$y = 5 \cdot 10^{-5}x + 0.0362$	0.9881	$8.335 \cdot 10^{-5}$
4-NO_2ap	$y = 7 \cdot 10^{-5}x + 0.0408$	0.9804	$11.669 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

$$k = (k_t)\ (RT/Nh)\ \exp\ (-\Delta H^{\#}/RT)\ (\Delta S^{\#}/R) \quad (1)$$

$$(Nhk/RT) = \exp\ (-\Delta H^{\#}/RT)\ (\Delta S^{\#}/R) \quad (2)$$

$$\ln\ (Nhk/RT) = -\ (\Delta H^{\#}/RT) + (\Delta S^{\#}/R) \quad (3)$$

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#} \quad (4)$$

Table 9. VH *Acetylation Second-Order Reactions with Acetamide/$POCl_3$ in MeCN at 323 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 0.00007x + 0.0428$	0.9918	$11.669 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 0.00007x + 0.0408$	0.9918	$11.669 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 0.0003x + 0.04$	0.9894	$51.01 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 0.0002x + 0.032$	0.9826	$33.34 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 0.00009x + 0.0394$	0.9746	$15.003 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 0.0002x + 0.0384$	0.9832	$33.34 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 0.0001x + 0.0382$	0.975	$16.67 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 0.0001x + 0.039$	0.9578	$16.67 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 0.0002x + 0.0378$	0.9796	$33.34 \cdot 10^{-5}$
2-OHap	$y = 0.0003x + 0.0559$	0.9903	$51.01 \cdot 10^{-5}$
4-OHap	$y = 0.00009x + 0.0468$	0.9746	$15.003 \cdot 10^{-5}$
4-Meap	$y = 0.00008x + 0.0406$	0.973	$13.336 \cdot 10^{-5}$
3-OHap	$y = 0.0002x + 0.0487$	0.9865	$33.34 \cdot 10^{-5}$
4-Brap	$y = 0.0001x + 0.039$	0.9738	$16.67 \cdot 10^{-5}$
4-NO_2ap	$y = 0.0002x + 0.0438$	0.9741	$33.34 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

Table 10. VH *Acetylation Second-Order Reactions with Acetamide/$POCl_3$ in MeCN at 333 K*

Substrate	Rate equation[a])	Correlation coefficient (R^2)	Second-order rate constant (k'') [M^{-1} s^{-1}]
PhCHO	$y = 0.0001x + 0.0494$	0.9689	$16.67 \cdot 10^{-5}$
2-OHC_6H_4CHO	$y = 0.00009x + 0.0468$	0.9746	$15.003 \cdot 10^{-5}$
4-OHC_6H_4CHO	$y = 0.0004x + 0.0488$	0.9998	$66.68 \cdot 10^{-5}$
4-$MeOC_6H_4CHO$	$y = 0.0003x + 0.037$	0.9857	$51.01 \cdot 10^{-5}$
4-ClC_6H_4CHO	$y = 0.0002x + 0.0464$	0.9972	$33.34 \cdot 10^{-5}$
4-BrC_6H_4CHO	$y = 0.0003x + 0.0576$	0.9985	$51.01 \cdot 10^{-5}$
4-$NO_2C_6H_4CHO$	$y = 0.0002x + 0.048$	0.9774	$33.34 \cdot 10^{-5}$
(*E*)-PhCH=CHCHO	$y = 0.0002x + 0.0422$	0.9985	$33.34 \cdot 10^{-5}$
Acetophenone (PhCOMe; ap)	$y = 0.0003x + 0.0461$	0.9954	$51.01 \cdot 10^{-5}$
2-OHap	$y = 0.0004x + 0.0605$	0.9888	$66.68 \cdot 10^{-5}$
4-OHap	$y = 0.0003x + 0.0498$	0.968	$51.01 \cdot 10^{-5}$
4-Meap	$y = 0.0002x + 0.0432$	0.966	$33.34 \cdot 10^{-5}$
3-OHap	$y = 0.0003x + 0.0498$	0.982	$51.01 \cdot 10^{-5}$
4-Brap	$y = 0.0002x + 0.0451$	0.9795	$33.34 \cdot 10^{-5}$
4-NO_2ap	$y = 0.0003x + 0.0492$	0.9672	$51.01 \cdot 10^{-5}$

[a]) $y = mx + c$ with $y = \ln V_t$ or $\ln (a - x)$ and $x =$ time [min].

These activation parameters are presented in *Tables 11 – 14* for all the substrates studied in the described *VH* reaction.

Formation of the VH *Adduct and Its Reactive Species.* Reaction kinetics is one of the most-efficient tools to propose a mechanism for a chemical reaction. However, it is essential to know the nature of the reactive species that are present in the reaction

Table 11. *Temperature-Dependent Rate Constants and Activation Parameters for* VH *Acetylation Reactions of Benzaldehydes with Acetamide/$SOCl_2$ in MeCN*

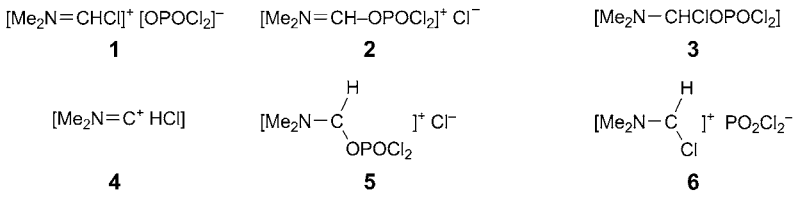
Substrate	Temp. [K]	10^5 k'' [M^{-1} s^{-1}]	Equation	R^2	$\Delta H^{\#}$ [kJ mol^{-1}]	$\Delta S^{\#}$ [J K^{-1} mol^{-1}]	$-\Delta G^{\#}$ [kJ mol^{-1}]
PhCHO	303	6.67	$y = -8.3612x + 35.98$	0.996	69.5	299	21.1
	313	33.3					
	323	66.7					
	333	83.3					
2-OHC_6H_4CHO	303	5.33	$y = -9.6606x + 39.96$	0.952	80.3	332	20.3
	313	10.0					
	323	51.0					
	333	83.4					
4-OHC_6H_4CHO	303	26.7	$y = -4.7202x + 24.89$	0.963	39.2	207	23.5
	313	16.7					
	323	33.3					
	333	83.4					
4-$MeOC_6H_4CHO$	303	8.00	$y = -8.4946x + 36.33$	0.922	70.6	302	20.9
	313	10.0					
	323	33.3					
	333	100.0					
4-ClC_6H_4CHO	303	8.00	$y = -6.5764x + 30.65$	0.863	54.7	254	22.4
	313	33.3					
	323	51.0					
	333	66.7					
4-BrC_6H_4CHO	303	10.7	$y = -6.0175x + 28.62$	0.987	50.0	238	22.1
	313	16.7					
	323	33.3					
	333	66.7					
4-$NO_2C_6H_4CHO$	303	6.67	$y = -7.8124x + 34.26$	0.960	64.9	249	21.4
	313	16.7					
	323	51.0					
	333	66.7					
(*E*)-PhOH=CHCHO	303	9.33	$y = -8.0657x + 35.53$	0.966	67.1	295	22.4
	313	33.3					
	323	66.7					
	333	100					

mixture during the course of study. On the basis of elemental analysis [1], it was indicated that 1 mol-equiv. of oxychloride $POCl_3$ reacts with 1 mol-equiv. of the amide to form the *VH* adduct. Different opinions prevail for the formulation of the reactive *VH* adduct species [4][5][21][22]. IR-Spectroscopic studies of *Arnold* and *Holy*, electronic spectroscopic and ^{31}P-NMR spectroscopic studies of *Marino*, *Martin*, and several others [4][5][21][22], together with the kinetic studies reported from our laboratory [3][17][18] on *VH* adducts have revealed that a number of covalent, ionic, and ion-pair species of *VH*-adducts **1**–**6** could exist in solution as shown by the formulae derived from *N*,*N*-dimethylformamide (DMF) and $POCl_3$ as a specific example.

Mechanism of Acetylation Reactions Involving Acetamid Oxychloride ($POCl_3$ or $SOCl_2$) *Adduct.* Acetamide is a *Lewis* base, which is analogous to DMF and forms a *VH*

Table 12. *Temperature-Dependent Rate Constants for* VH *Acetylation Reactions of Acetophenones with Acetamide/$SOCl_2$ in MeCN*

Substrate	Temp. [K]	10^5 k'' [M^{-1} s^{-1}]	Equation	R^2	$\Delta H^{\#}$ [kJ mol^{-1}]	$\Delta S^{\#}$ [J K^{-1} mol^{-1}]	$-\Delta G^{\#}$ [kJ mol^{-1}]
Acetophenone	303	26.667	$y=-4.3015x+23.486$	0.987	35.8	195	23.4
	313	16.67					
	323	33.34					
	333	66.68					
2-OHap	303	13.33	$y=-9.9888x+40.072$	0.9803	83.1	333	17.9
	313	16.67					
	323	1.667					
	333	33.34					
4-OHap	303	1.33	$y=-10.534x+41.712$	0.9838	87.6	346	17.5
	313	33.34					
	323	13.336					
	333	15.003					
4-Meap	303	13.33	$y=-4.4329x+23.626$	0.9566	36.9	196	21.7
	313	16.67					
	323	33.34					
	333	51.01					
3-OHap	303	7.998	$y=-6.0002x+28.256$	0.9667	49.9	235	21.3
	313	11.669					
	323	16.67					
	333	51.01					
4-Brap	303	13.33	$y=-5.1491x+26.017$	0.9862	42.9	216	22.7
	313	15.003					
	323	33.34					
	333	66.68					
4-NO_2ap	303	13.33	$y=-5.5054x+27.212$	0.9659	45.8	226	22.8
	313	16.67					
	323	51.01					
	333	66.68					



adduct due to the interaction with the oxychloride. In view of this, the reaction mechanism operating acetamide/$POCl_3$ may not differ much from that with DMF/$POCl_3$. It is, therefore, reasonable to consider a similar type of reactive species in the present work. Accordingly, species could be written as **7**–**10**.

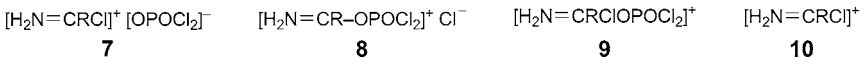


Table 13. *Temperature-Dependent Rate Constants for VH Acetylation Reactions with Acetamide/$POCl_3$ in MeCN*

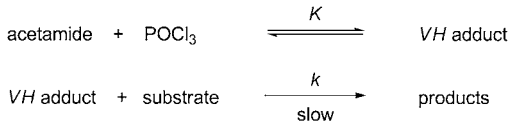
Substrate	Temp. [K]	10^5 k'' [M^{-1} s^{-1}]	Equation	R^2	$\Delta H^{\#}$ [kJ mol^{-1}]	$\Delta S^{\#}$ [J K^{-1} mol^{-1}]	$-\Delta G^{\#}$ [kJ mol^{-1}]
C_6H_4CHO	303	11.7	$y = -1.7205x + 14.32$	0.885	14.3	119	21.8
	313	10.0					
	323	11.7					
	333	16.7					
2-OHC_6H_4CHO	303	11.7	$y = -1.5972x + 13.89$	0.976	13.3	115	21.7
	313	10.0					
	323	11.7					
	333	15.0					
4-OHC_6H_4CHO	303	15.0	$y = -4.7202x + 24.89$	0.963	39.7	206	23.0
	313	33.3					
	323	51.0					
	333	66.7					
4-$MeOC_6H_4CHO$	303	15.0	$y = -3.2121x + 19.68$	0.993	26.7	163	22.9
	313	13.3					
	323	33.3					
	333	51.0					
4-ClC_6H_4CHO	303	15.0	$y = -4.3499x + 22.93$	0.980	36.2	190	21.6
	313	8.34					
	323	15.0					
	333	33.3					
4-Br C_6H_4CHO	303	8.34	$y = -6.5789x + 29.74$	0.989	54.7	247	20.2
	313	16.7					
	323	33.3					
	333	51.0					
4-$NO_2C_6H_4CHO$	303	11.7	$y = -5.0112x + 24.97$	0.997	41.7	207	21.2
	313	11.7					
	323	16.7					
	333	33.3					
(*E*)-PhCH=CHCHO	303	6.67	$y = -10.015x + 40.25$	0.957	83.3	334	18.1
	313	1.67					
	323	16.7					
	333	33.3					

This aspect, coupled with the observed linearity of the plot log $k(POCl_3)$ *vs.* log $k(SOCl_2)$ indicates that a similar type of mechanism is operative in both $POCl_3$ and $SOCl_2$ systems. Earlier studies from our laboratory [13] also revealed that the cationic species $[Me_2N–CHCl]^+$ of the *VH* adduct was electrophilically more reactive than the ion-pair intermediate of the *VH* adduct, the relatively higher rates in $ClCH_2CH_2Cl$ medium than those of MeCN medium could be reasonably explained. For the reactions which occur in other media, a dipole–dipole-type mechanism has been proposed [13]. In any case, the mechanism could be generally given in the steps shown by *Eqn. 5*.

Products of the reaction were separated by TLC and analyzed by spectroscopy according to literature procedures. Acetyl derivatives were found to be the products irrespective of the nature of the *VH* reagent used, as shown by the similar IR spectra of

Table 14. *Temperature-Dependent Rate Constants and Activation Parameters for* VH *Acetylation Reactions of Acetophenones with Acetamide/$POCl_3$ in MeCN*

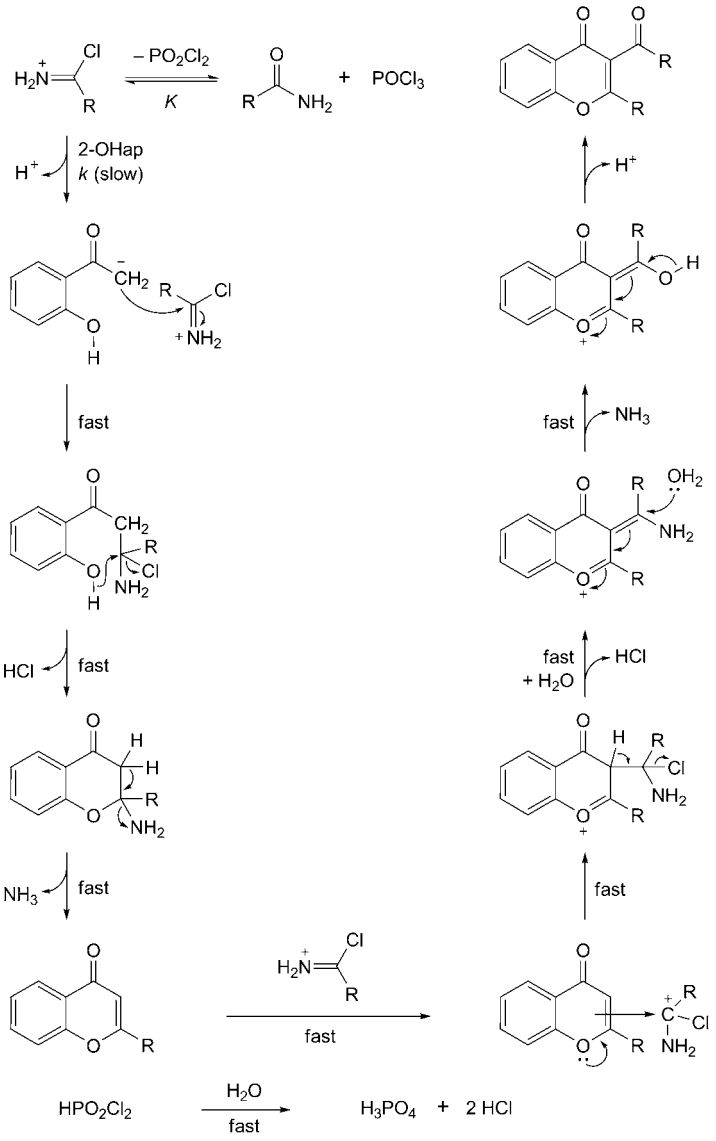
Substrate	Temp. [K]	10^5 k'' [M^{-1} s^{-1}]	Equation	R^2	$\Delta H^{\#}$ [kJ mol^{-1}]	$\Delta S^{\#}$ [J K^{-1} mol^{-1}]	$-\Delta G^{\#}$ [kJ mol^{-1}]
Acetophenone	303	16.67	$y=-3.5422x+20.979$	0.9872	29.5	174	23.5
	313	16.67					
	323	33.34					
	333	51.01					
2-OHap	303	8.335	$y=-6.6718x+30.642$	0.9999	55.5	254	21.7
	313	33.34					
	323	51.01					
	333	66.68					
4-OHap	303	16.67	$y=-4.9302x+24.959$	0.9764	41.0	207	21.9
	313	10.002					
	323	15.003					
	333	51.01					
4-Meap	303	16.67	$y=-3.944x+21.734$	0.9801	32.8	180	22.0
	313	10.002					
	323	13.336					
	333	33.34					
3-OHap	303	50.01	$y=-4.5269x+24.096$	0.9671	37.6	200	23.1
	313	13.336					
	323	33.34					
	333	51.01					
4-Brap	303	15.003	$y=-5.9996x+28.226$	0.9521	49.9	235	21.2
	313	8.335					
	323	16.07					
	333	33.34					
4-NO_2ap	303	10.002	$y=-5.3942x+26.602$	0.9699	44.9	221	22.2
	313	11.669					
	323	33.34					
	333	51.01					



(5)

the isolated products. For the above scheme (*Eqn. 5*), the rate law *Eqn. 6* comes out. This rate law explains second-order kinetics with a first-order dependence on [substrate] and also on [*VH* adduct], showing the consistency of the proposed mechanism. It is of interest to note that 2-OHap underwent cyclization followed by acetylation to afford an acetylchromen-4-one, *i.e.*, 3-acetyl-2-methyl-4*H*-1-benzopyran-4-one, as outlined in the mechanism of *Scheme 2*. However, 3-OHap and 4-OHap cannot undergo cyclization and, therefore, afforded acetyl derivatives (*cf. Scheme 1*); the corresponding mechanistic path is exemplified in *Scheme 3*.

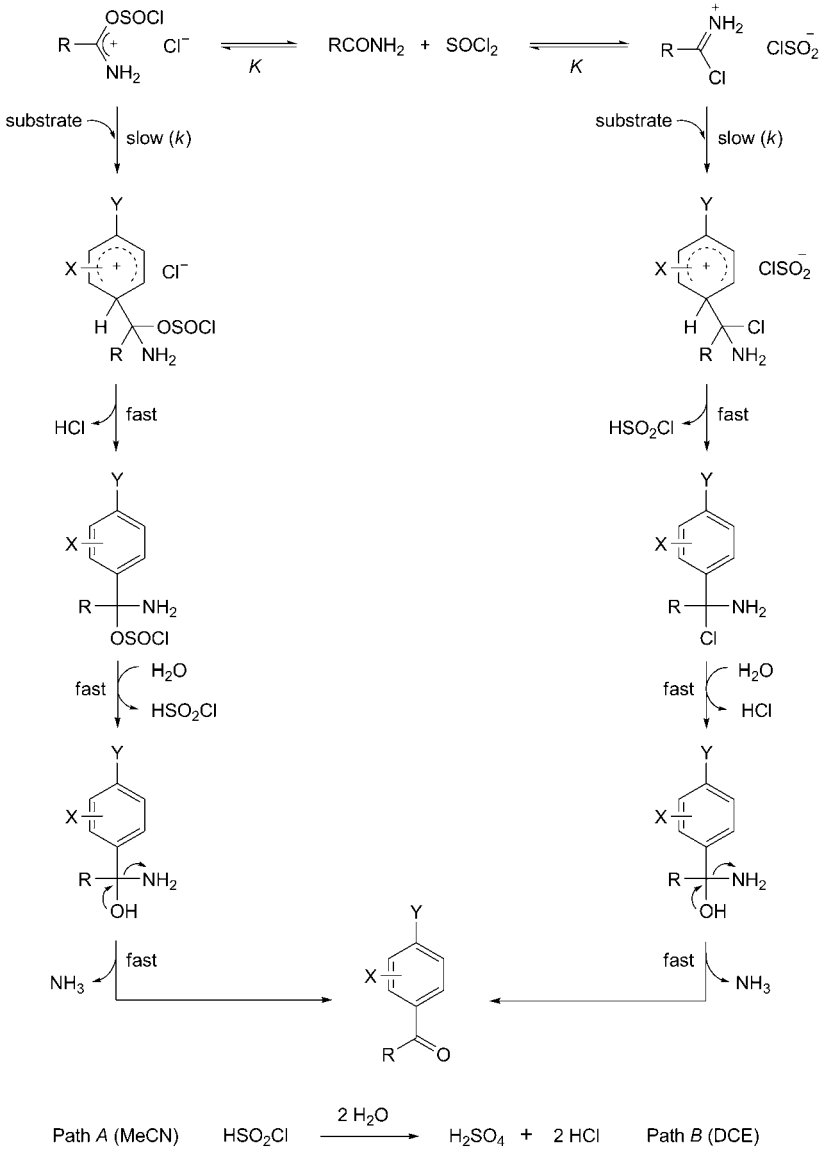
Scheme 2



$$\frac{-d\,[\text{substrate}]}{dt} = k\,[\text{substrate}]\,[VH\text{adduct}] \tag{6}$$

It is of interest to note that the free energies of activation ($\Delta G^{\#}$) for the studied *VH* reactions are negative for all the substrates showing the spontaneous nature of the reaction. This factor could also be seen from large entropies of activation ($\Delta S^{\#}$), which are presented in *Tables 11–14*. The plots $\Delta H^{\#}$ *vs.* $\Delta S^{\#}$ for both acetamide/$SOCl_2$ and

Scheme 3



R = Me if VHR = acetamide/$SOCl_2$ or acetamide/$POCl_3$
Y = CHO, Ac
X = electron-donating or electron-withdrawing groups

acetamide/$POCl_3$ systems (*Figs. 5* and *6*) were perfectly linear according to *Leffler*'s theory [23]. When a series of structurally related substrates undergo the same general reaction or when the reaction conditions for a single substrate are changed in a systematic way, the enthalpies and entropies of activation sometimes satisfy the relation of *Eqn 7*. This equation (or some equivalent form) is said to represent an 'isokinetic relationship', and β represents the 'isokinetic temperature', the temperature (T) at which all members of a series obeying the isokinetic relationship react at the same rate. However, the supposed isokinetic relationships as established by direct correlation of $\Delta H^{\#}$ with $\Delta S^{\#}$ are often spurious and the calculated value of β is meaningless because errors in $\Delta H^{\#}$ lead to compensating errors in $\Delta S^{\#}$ [24][25]. In spite of this criticism, according to *Shorter*'s classification of reaction series [26], the linearity of *Leffler*'s plot is still valid, which indicates that reactions are controlled by compensation of both enthalpy and entropy factors. An almost similar magnitude of free energies of activation ($\Delta G^{\#}$) probably indicate that a similar type of mechanism is operative in both *VH* systems studied, irrespective of the nature of the oxychloride used for *VH* reagent.

$$\Delta H^{\#} = \beta \Delta S^{\#} + \Delta H_0{}^{\#} \tag{7}$$

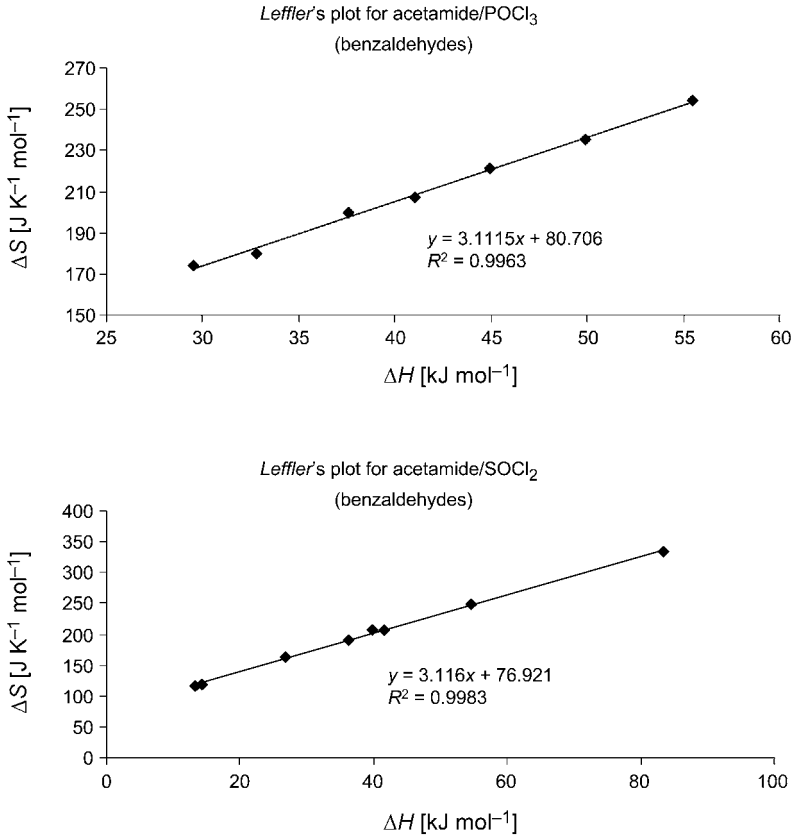


Fig. 5. Leffler*'s plots for* VH *acetylation reactions of benzaldehydes*

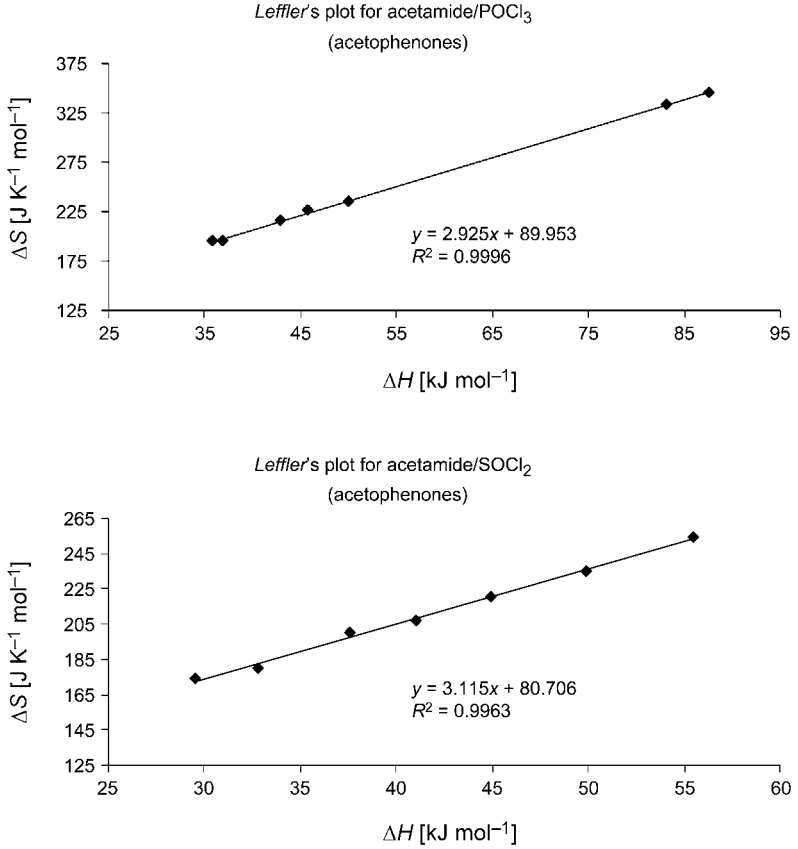


Fig. 6. Leffler*'s plots for* VH *acetylation reactions of acetophenones*

Conclusions. – In summary, we have successfully demonstrated the course of the *Vilsmeier–Haack* acetylation reactions with benzaldehydes and acetophenones in MeCN medium. The *VH* reactions followed second-order kinetics and afforded acetyl derivatives under kinetic conditions and irrespective of the nature of the oxychloride (*i.e.*, $SOCl_2$ or $POCl_3$), used for the preparation of *VH* reagent along with acetamide. The present finding contributes to the understanding of the nature of the reactive species of the *VH* reagent as well as of the acetylation mechanism.

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