

Correlation analysis of carbonyl carbon ^{13}C NMR chemical shifts, IR absorption frequencies and rate coefficients of nucleophilic acyl substitutions. A novel explanation for the substituent dependence of reactivity

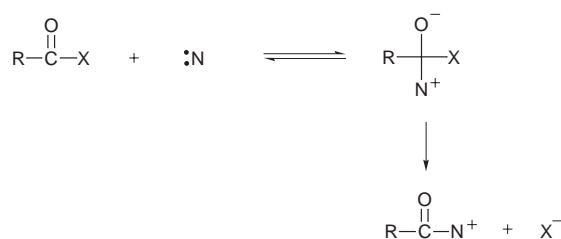
Helmi Neuvonen* and Kari Neuvonen

Department of Chemistry, University of Turku, FIN-20014 Turku, Finland

Received (in Cambridge) 6th January 1999, Accepted 26th April 1999

Rate coefficients of nucleophilic acyl substitutions, carboxylate carbon ^{13}C NMR chemical shift values and $\nu(\text{C}=\text{O})$ frequencies of several series of aryl and acyl substituted aryl acetates or alkyl benzoates have been investigated. An increasing electron-withdrawal by the acyl or aryl substituents results in higher reaction rates, upfield ^{13}C NMR chemical shifts and higher frequencies of the $\text{C}=\text{O}$ stretching. Good correlations are observed for the $\log k$ versus $\delta_{\text{C}}(\text{C}=\text{O})$ plots. The increase of the reaction rate with increased electron density at the $\text{C}=\text{O}$ carbon (as proved by ^{13}C NMR shifts) contradicts the previous concept of increased electrophilicity of the carbonyl carbon by electron-withdrawing substituents. The rate increase is now attributed to the decrease of the ester ground state resonance stabilization caused by electron-withdrawing substituents. The use of $\log k$ versus $\delta_{\text{C}}(\text{C}=\text{O})$ correlations is presented as a practical method to evaluate rate coefficients especially for compounds for which Hammett type correlations cannot be used.

The significance of acyl compounds is well-established in organic chemistry and in biochemistry, and the understanding of the factors affecting their reactivity is of primary importance. Most acyl transfer reactions are thought to occur *via* a tetrahedral intermediate as shown in Scheme 1. Reactivity of



Scheme 1

the carbonyl carbon of RCOX towards a nucleophilic attack is known to depend on the electron-withdrawing ability of R or X as reflected by the linear free energy correlations often observed.¹ The Hammett equation [eqn. (1)] is most often used

$$\log(k/k_0) = \rho\sigma \quad (1)$$

to correlate reaction rates and equilibria of side-chain reactions of *para*- and *meta*-substituted aromatic compounds. The standard reaction by which the substituent constants σ have been defined is the aqueous dissociation equilibrium of *para*- and *meta*-substituted benzoic acids. In eqn. (1), k is a rate coefficient for the *para*- or *meta*-substituted compound, k_0 that for the unsubstituted derivative, and ρ is the Hammett reaction constant.^{1b-d} For aliphatic compounds an analogous relationship [eqn. (2)] is known as the Taft equation, where the polar substituent constants σ^* for groups R have been determined with the aid of alkaline and acid hydrolysis of esters RCOOR' . The rate coefficient k_0 corresponds to the reaction for $\text{R} = \text{CH}_3$. In eqn. (2), ρ^* is the polar reaction constant.^{1b-d}

$$\log(k/k_0) = \rho^*\sigma^* \quad (2)$$

The value of the reaction constant ρ or ρ^* shows the sensitiv-

ity of the reaction to the influence of the substituents. Although reaction conditions, such as solvent or temperature, also affect ρ , the most important factor controlling its value is the susceptibility of the reaction to electronic effects. Because of the definition of σ and σ^* values, the reaction constants ρ and ρ^* are positive for reactions facilitated by electron-withdrawing substituents and negative for those reactions facilitated by electron donors. Substituent effects on the rate of a reaction reflect the effect of substituents on the activation energy and they can therefore reflect the substituent effect on the ground state and/or transition state.² It is usually considered that a positive ρ means the development of a negative charge (or reduction of a positive charge) at the reaction site in the transition state and correspondingly a negative ρ means that a positive charge is developed (or a negative charge is lost). For example, for alkaline hydrolysis of ethyl benzoates the ρ value 2.27 is consistent with a mechanism where a negative charge is developed at the reaction site in the transition state. Furthermore, it is usually considered that the electron-withdrawing substituents facilitate the nucleophilic attack by increasing the electrophilicity of the $\text{C}=\text{O}$ carbon through the reduction in its electron density.^{1b,c}

^{13}C NMR spectroscopy is a useful tool. Especially for aromatic compounds containing a $\text{C}=\text{O}$, $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, $\text{C}=\text{N}$ or $\text{C}\equiv\text{N}$ system in their side chain, the substituent chemical shifts of these unsaturated carbons have been shown to be systematic and electronic in origin reflecting mainly the changes in the π -electron density of the carbon in question.³⁻⁵ The upfield shift of the carbon resonance corresponds to the increasing electron shielding of the carbon. The π -electron density calculations performed for some series of aromatic side chain derivatives are consistent with the NMR data.^{3b,d,e,4}

Inspection of the previous works of Bromilow *et al.*,^{3c} O'Connor *et al.*⁶ and Dell'Erba *et al.*,⁷ shows that electron-withdrawing substituents in the aromatic acyl or alcoholic moiety of esters cause upfield shifts of the carbonyl carbon resonance. This is inconsistent with the usual concept that the electrophilicity of the carbonyl carbon increases with electron-withdrawing substituents. That contradiction has not been discussed previously. The aim of our work was to study systematically the correlations between the reactivity of carboxylic

acid esters towards a nucleophilic attack and the ^{13}C NMR chemical shift of the carboxylate carbon of the ground state molecules to clarify the origin of the effect in question exerted by the substituents in the aromatic ring and also by the substituents in the aliphatic acyl group. In addition, we see the use of reactivity *versus* $\delta_{\text{C}}(\text{C}=\text{O})$ correlations as a potential method to estimate the reactivity of compounds with known $\text{C}=\text{O}$ carbon ^{13}C NMR chemical shifts.

^{13}C NMR shift, $\nu(\text{C}=\text{O})$ frequency and reactivity measurements have been performed with the series **1** and **2**. Furthermore, we have correlated existing reactivity and spectroscopic results for compounds of series **3** and **4**. In these cases, one set of data used is always obtained from one source.



1

X = 4-NO₂, 4-CN, 4-Cl, 4-Br, H, 4-Me, 4-OMe, 3-NO₂ or 3-Cl



2

R = CH₃, CH₂Cl, CHCl₂, CCl₃ or CF₃



3

X = 4-NO₂, 4-COMe, 4-CN, 4-CO₂Et, 4-F, 4-Br, 4-Cl, H, 4-Me, 4-OMe, 4-NH₂, 3-NO₂, 3-CN, 3-CO₂Et, 3-F, 3-Cl, 3-Br, 3-Me, 3-COMe or 3-OMe



4

X = 4-NO₂, 4-Br, H, 4-Me, 4-OMe, 3-NO₂, 3-Br, 3-Me, 3-OMe or 3-N(Me)₂

Experimental

Materials

The preparation and purification of the 4-nitrophenyl esters of acetic,^{8a} chloroacetic^{8b} and dichloroacetic^{8b} acids as well as those of 3-nitro-, 4-chloro- and 4-methoxyphenyl dichloroacetates^{8c} were as described in previous works. The other esters of dichloroacetic acid were prepared from dichloroacetyl chloride and the appropriate phenol by the dropwise addition of an equivalent amount of pyridine to a stirred mixture of dichloroacetyl chloride and the appropriate phenol in dry diethyl ether at room temperature.⁹ The esters were recrystallized from hexane. The melting points of the compounds were as follows: 4-methylphenyl dichloroacetate 53.5–54.5 °C, phenyl dichloroacetate 46–47 °C (lit.¹⁰ 45–47 °C) and 4-bromophenyl dichloroacetate 72–73 °C. 4-Cyanophenyl dichloroacetate was obtained as an oil. 3-Chlorophenyl dichloroacetate was distilled under reduced pressure 140–141 °C/13 mmHg. 4-Nitrophenyl trichloroacetate was prepared from 4-nitrophenol and trichloroacetyl chloride in dry benzene^{9,11} and it was recrystallized twice from a diethyl ether–petroleum ether (1 : 2 v/v) mixture, mp 63–64 °C (lit.¹¹ 64 °C). Acetonitrile (Aldrich, spectrograde) used in the preparation of the reaction solutions and the stock solutions of the esters as well as deuteriochloroform (Sigma, 99.8 atom%) employed in NMR measurements were used as received.

Spectroscopic measurements

The ^{13}C NMR spectra were recorded at 125.78 MHz with a 45° pulse and a digital resolution of 0.92 Hz on a JEOL JNM-A500 spectrometer in CDCl₃ at 27 °C at a concentration of 0.1 mol dm⁻³. The deuterium of the solvent was used as a lock signal.

Table 1 Carbonyl carbon ^{13}C NMR chemical shifts, IR $\text{C}=\text{O}$ stretching frequencies and rate coefficients of the neutral hydrolysis in 20% acetonitrile–water at 298.2 K for phenyl substituted phenyl dichloroacetates $\text{CHCl}_2\text{COOC}_6\text{H}_4\text{X}$

X	$\delta(\text{C}=\text{O})^a/\text{ppm}$	$\nu(\text{C}=\text{O})/\text{cm}^{-1}$	$k_o^b/10^{-3} \text{ s}^{-1}$
4-NO ₂	162.13	1788; 1767	14.4 ± 0.2
3-NO ₂	162.43	1775 ^c	8.43 ± 0.09
4-CN	162.20	1781	8.74 ± 0.09
4-Cl	162.78	1762 ^c	1.36 ± 0.04
3-Cl	162.65	1783	1.88 ± 0.03
4-Br	162.70	1767	1.27 ± 0.03
H	163.02	1777	0.476 ± 0.008
4-CH ₃	163.20	1765	0.273 ± 0.002
4-OCH ₃	163.37	1763	0.349 ± 0.006

^a In CDCl₃. ^b The k_o values are averages of four determinations and the error shown is a standard deviation. ^c Ref 8c.

The spectra were measured with a ^1H broad-band decoupling technique. The chemical shifts are expressed in ppm relative to TMS used as an internal reference. The infrared spectra were recorded for capillary films or KBr discs on a Mattson Galaxy 6020 FTIR spectrometer.

Kinetics

Reaction rates of the neutral hydrolysis of substituted phenyl dichloroacetates in 20% (v/v) acetonitrile–water were determined spectrophotometrically by observing the phenol release at a suitable wavelength (4-nitrophenol 310 nm, 3-nitrophenol 328 nm, 4-cyanophenol 250 nm, 4-chlorophenol 280 nm, 3-chlorophenol 280 nm, 4-bromophenol 280 nm, phenol 270 nm, 4-methylphenol 280 nm, 4-methoxyphenol 290 nm). The reaction of imidazole with 4-nitrophenyl trichloroacetate in acetonitrile was followed by detecting the increase in the absorption of 4-nitrophenol (310 nm) in first-order conditions (at least 80-fold excess of imidazole). A Gilford 2600 spectrophotometer equipped with a Gilford Thermostat Temperature Controller was used. The temperature was accurate to ±0.1 °C. In a typical experiment 250 mm³ of the reaction solution was prethermostatted in the optical cell (300 mm³). In hydrolysis reactions 3 mm³ of 0.03 M and in the reaction of imidazole with 4-nitrophenyl trichloroacetate 0.75–1.4 mm³ of 0.01 M acetonitrile solution of the ester was added into the cell, the solution was shaken thoroughly and the cell was placed into the thermostatted cell compartment. The reactions were followed for six half-lives and the final value was observed after ten half-lives if needed.

The first-order rate coefficients of the neutral hydrolysis were calculated by the method of Guggenheim.¹² The standard deviations of the individual rate coefficients were ≤0.3%. It was checked that good linear plots of $\ln(A_\infty - A_t)$ *versus* time were obtained ($r \geq 0.9999$ over 3 $t_{1/2}$). For the reaction of imidazole with 4-nitrophenyl trichloroacetate strict first-order kinetics were not observed. The rate coefficients were calculated by the plots of $\ln(A_\infty - A_t)$ *versus* time. The correlation coefficients of the plots were only satisfactory ($r = 0.996$ – 0.999) and the standard deviations of the calculated rate coefficients were 1.5–3%. However, from previous studies it is known that the reactions of imidazole with 4-nitrophenyl acetate, chloroacetate, dichloroacetate and trifluoroacetate in acetonitrile follow first-order kinetics.^{8a,b} The reason for this difference is under investigation. The rate coefficients given in Tables 1 and 2 are mean values of three or four determinations and the error given is a standard deviation.

Results and discussion

Tables 1 and 2 give the carboxylate carbon ^{13}C NMR chemical shifts, $\nu(\text{C}=\text{O})$ frequencies and the kinetic data, for series **1** and **2**, respectively. The appearance of the $\nu(\text{C}=\text{O})$ as a doublet

Table 2 Carbonyl carbon ^{13}C NMR chemical shifts, IR C=O stretching frequencies and rate coefficients for the nucleophilic reaction of imidazole for acyl substituted 4-nitrophenyl acetates $\text{RCOOC}_6\text{H}_4\text{-NO}_2$ in acetonitrile at 298.2 K

R	$\delta(\text{C=O})^a/\text{ppm}$	$\nu(\text{C=O})/\text{cm}^{-1}$	$k_1/10^{-1} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_2/\text{dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$
CH_3	168.38	1761	$0.0185^b \pm 0.0007$	$0.0143^b \pm 0.0004$
CH_2Cl	165.05	1772	$1.54^c \pm 0.11$	$7.66^c \pm 0.16$
CHCl_2	162.13	1767, 1788	$1.19^c \pm 0.46$	$544^c \pm 7$
CCl_3	159.73	1782	1.0 ± 2.0	250 ± 30
CF_3	155.1 ^d	1806 ^e	$6.3^b \pm 1.2$	$3360^b \pm 70$

^a In CDCl_3 . ^b Ref. 8a. ^c Ref. 8b. ^d Ref. 13a. ^e Ref. 13b.**Table 3** Correlations and cross-correlations of the ^{13}C NMR chemical shifts (δ_{CO}) or SCS values of the carbonyl carbons and for the logarithms of the rate coefficients of the neutral (k_o) or alkaline (k_{OH}) hydrolysis or of the rate coefficients of the nucleophilic reaction of imidazole (k_{im}) for compounds of series 1–4 and 15

Line	Type of correlation	Slope	s^a	r^b	n^c
1	$\log k_o(\text{series } 1)^d \text{ vs. } \sigma$	1.65	0.10	0.9864	9
2	$\log k_o(\text{series } 1)^d \text{ vs. SCS}(\text{series } 1)^e$	−1.46	0.14	0.9693	9
3	$\log k_{\text{im}}(\text{series } 3)^f \text{ vs. SCS}(\text{series } 3)^g$	−1.53	0.07	0.9897	13
4	$\log k_{\text{OH}}(\text{series } 3)^h \text{ vs. SCS}(\text{series } 3)^g$	−0.76	0.06	0.9701	14
5	$\log k_{\text{OH}}(\text{series } 3)^i \text{ vs. SCS}(\text{series } 3)^g$	−1.22	0.11	0.9688	10
6	$\log k_{\text{OH}}(\text{series } 4)^j \text{ vs. SCS}(\text{series } 4)^k$	−0.79	0.07	0.9755	9
7	$\text{SCS}(\text{series } 1)^e \text{ vs. SCS}(\text{series } 3)^g$	0.78	0.01	0.9994	8
8	$\delta_{\text{CO}}(\text{series } 2)^l \text{ vs. } \delta_{\text{CO}}(\text{series } 15)^m$	1.27	0.04	0.9990	4
9	$\delta_{\text{CO}}(\text{series } 2)^l \text{ vs. } \sigma^*$	−3.27	0.04	0.9998	4

^a Standard deviation. ^b Correlation coefficient. ^c Number of correlation points. ^d In 20% acetonitrile–water at 298.2 K (Table 1). ^e In CDCl_3 (Table 1). ^f In aqueous solution at 298.2 K; the values are from ref. 21. ^g In CDCl_3 ; the values are from ref. 3c. ^h In 3% ethanol–water at 298.2 K; the values are from ref. 19b. ⁱ In 56% acetonitrile–water at 274.2 K; the values are from ref. 19a. ^j In 85% methanol–water at 298.2 K; the values are from ref. 22. ^k In CDCl_3 ; the values are from ref. 23. ^l In CDCl_3 (Table 2). ^m In CD_2Cl_2 ; the values are from ref. 25.

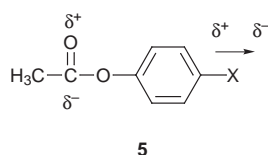
absorption for 4-nitrophenyl dichloroacetate is thought to be due to a conformational equilibrium,¹⁴ although the possibility of a Fermi resonance cannot be excluded. The IR spectrum for that compound was recorded as a capillary film.

On the C=O shifts

Electron-withdrawing substituents in both the acyl and aryl groups of the esters studied cause upfield shifts of the C=O carbon signal suggesting increased shielding (Tables 1 and 2). Analogous “reverse” substituent chemical shift (SCS) effects have been detected previously for several unsaturated carbons of aromatic side chains possessing a C=O, C=C, C≡C, C=N or C≡N system.^{3,4a,5–7} The excellent correlations obtained by eqn. (3) indicate the electronic origin of these relationships.^{3–5,15}

$$\text{SCS} = \rho_I \sigma_I + \rho_R \sigma_R \quad (3)$$

The DSP equation (3) dissects the substituent effects into inductive ($\rho_I \sigma_I$) and resonance ($\rho_R \sigma_R$) contributions. SCS means the ^{13}C chemical shift (in ppm) for a substituted compound relative to the unsubstituted one. The reverse trend of SCS effects ($\rho_I, \rho_R < 0$) has been explained by the π -polarization mechanism: the substituent dipole in the aromatic ring is thought to polarize each π -unit as a localized system as shown in 5 for substituted phenyl acetates.^{3c,d} The polarization of the



C=O group in the side chain by an electron-withdrawing substituent then results in an increase in the π -electron density and the upfield shift. The chemical shift dependence on electron density is normal but the substituent effect on the electron density is reversed. The π -polarization has been extensively

discussed elsewhere.^{3c,d,f,4} There are also the early theoretical calculations by Pople and Gordon¹⁶ which predicted that unsaturated bonds tend to polarize by the introduction of a polar substituent leading to alternation of charge.

An alternative explanation states that the non-linear Hammett correlations of the carbon shifts are due to the variation of the average excitation energy (ΔE) term in the Karplus–Pople equation.¹⁷ The latter describes in a simplified form the paramagnetic term of the shielding constant of a nucleus. However, the assumption that ΔE is not constant in a substituent series has not been proved. In any case, the proposed ΔE approach¹⁷ has not been able to explain the systematic reverse ^{13}C NMR shift correlations [negative ρ values in eqn. (3)] observed in numerous cases.^{3,4,5,7,18}

Reactivity and the C=O carbon shifts

As expected,¹ electron-withdrawing substituents in the acyl or aryl moiety of the ester increase the rate of a nucleophilic acyl substitution of substituted phenyl acetates as demonstrated by neutral hydrolysis or nucleophilic reaction of imidazole (Tables 1 and 2). A positive Hammett ρ value of 1.65 is observed for the neutral hydrolysis of series 1 (Table 3, line 1). The effect of varying the leaving group on the neutral hydrolysis of aryl esters has not been widely studied. However, with the aid of the rate coefficients of 4-nitro- and 4-methoxyphenyl dichloroacetates Fife and McMahon have previously calculated the ρ value of 1.3 in aqueous solution at 303 K.^{9b} For the neutral hydrolysis of substituted phenyl trifluoroacetates in 3.89 M water in acetonitrile we have previously observed the ρ value of 2.45.^{13a} For alkaline hydrolysis of substituted phenyl acetates ρ values from 1.0 to 1.8 in Hammett or Hammett type equations in water or in different acetone–water mixtures have been reported^{19a,20} and for the nucleophilic reaction of imidazole with substituted phenyl acetates in aqueous solution the ρ value of 1.76 has been observed.²¹

Fig. 1 shows the good correlation between the rate coefficients of the neutral hydrolysis of substituted phenyl

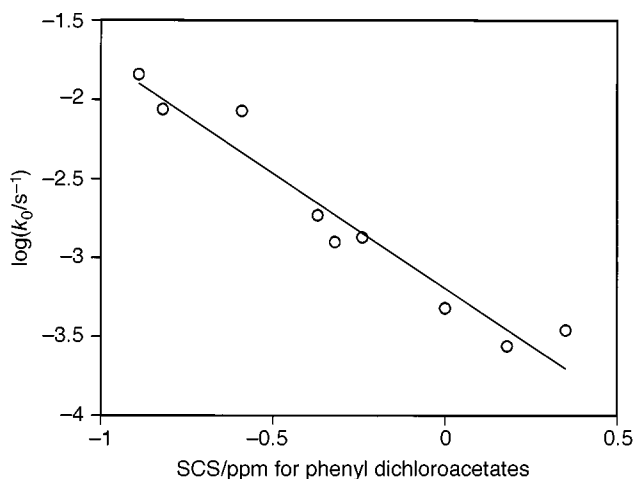


Fig. 1 A plot of the logarithms of the rate coefficients for the neutral hydrolysis of phenyl substituted phenyl dichloroacetates in 20% (v/v) acetonitrile–water versus the substituent chemical shift values (SCS means the ^{13}C NMR chemical shift for a substituted compound relative to the unsubstituted compound) for the carboxylate carbon of the esters in CDCl_3 . The values are from this work.

dichloroacetates and the substituent chemical shift (SCS) values for the $\text{C}=\text{O}$ carbon of the esters. A negative slope of -1.5 is observed (Table 3, line 2). The upfield shift of the carbon resonance and an increase in the reaction rate are accompanied by an increase in the electron-withdrawing power of the phenyl substituent. The upfield shift indicates an increased π -electron shielding of the carboxylate carbon. This contradicts the usual concept of the increased electrophilicity, *i.e.*, decreased electron density, of the carboxylate carbon as a reason for the increase of the rate of nucleophilic acyl substitutions by electron-withdrawing substituents.¹ An analogous behaviour is seen for the rate coefficients of the nucleophilic reaction of imidazole with a series of substituted phenyl acetates in aqueous solution and the SCS values of the carboxylate carbons of the substrate esters in CDCl_3 (Table 3, line 3). Negative slopes are also observed for the respective correlations for phenyl substituted phenyl acetates (Table 3, lines 4 and 5) and for benzoyl substituted methyl benzoates (Table 3, line 6), the correlation being in both cases between the rate coefficient of the alkaline hydrolysis and the SCS values of the ester $\text{C}=\text{O}$ carbon.

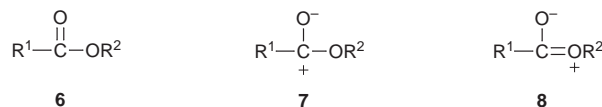
The reactions for which rate coefficients and SCS values are correlated (Table 3, lines 2–6) represent different types of reaction mechanisms and therefore different transition states: rate-limiting formation of a tetrahedral addition intermediate (alkaline hydrolysis),^{1a,b} rate-limiting breakdown of the addition intermediate (reaction of imidazole with phenyl acetates in an aprotic solvent)^{8a} or rate-limiting formation of the addition intermediate with the $\text{C}-\text{O}$ bond breaking possibly contributing to the rate of the reaction (neutral hydrolysis).¹³ The rate coefficients and the ^{13}C chemical shifts in Table 2 show that also with acyl substituted 4-nitrophenyl acetates (series 2) the increasing electron-withdrawal is accompanied both with an increase in the rate of the nucleophilic reaction of imidazole (k_1 refers to the uncatalysed nucleophilic reaction of imidazole and k_2 to the general base catalysed nucleophilic reaction of imidazole^{8a,b}) and with an upfield shift of the carboxylate carbon ^{13}C NMR chemical shift. Linear correlations between the rate coefficient and the $\text{C}=\text{O}$ shift are, however, not observed in that case, obviously because of steric effects.

There is little discussion about the correlation of the reaction rates with the $\text{C}=\text{O}$ carbon shifts in the literature, and the relevance of the reverse behaviour has not been discussed at all.⁶ π -Polarization can explain the reverse behaviour of the $\text{C}=\text{O}$ shifts, but what explains the increase in the reaction rates? Without neglecting the contribution of the stability of the transition state, an explanation for the substituent dependence of

reactivity, the ^{13}C chemical shifts and $\nu(\text{C}=\text{O})$ frequencies is discussed below.

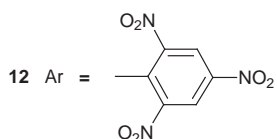
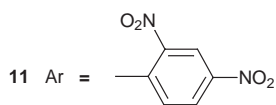
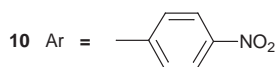
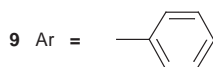
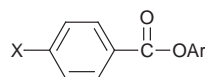
An explanation for the reactivity versus $\text{C}=\text{O}$ shift and $\nu(\text{C}=\text{O})$ frequency behaviour: ester ground state destabilization

The cross-correlation between the $\text{C}=\text{O}$ carbon shifts of phenyl substituted phenyl dichloroacetates and phenyl acetates is good (Table 3, line 7). The slope 0.78 reflects the lower susceptibility of the $\text{C}=\text{O}$ bond polarization to *para*-substituents in the case of phenyl dichloroacetates and indicates the higher $\text{C}=\text{O}$ double bond character of phenyl dichloroacetates as compared to phenyl acetates. This concept is confirmed by the increasing carbonyl stretching frequencies with increasing electron-withdrawal by acyl substituents in a series of substituted 4-nitrophenyl acetates (Table 2). In a series of acyl-halogenated ethyl acetates, $\nu(\text{C}=\text{O})$ also gradually shifts towards higher frequencies with increasing electron withdrawal. This has been explained by the electron-withdrawing effect of the halogen substituents which suppress the polarization of the $\text{C}=\text{O}$ bond.^{14a} In a series of phenyl substituted phenyl dichloroacetates (Table 1) or phenyl trifluoroacetates,^{13a} the $\text{C}=\text{O}$ stretching frequency also shifts towards higher wavenumbers with increasing electron-withdrawal, indicating an increase in the strength of the $\text{C}=\text{O}$ bond. Satisfactory linear correlations between the carbonyl stretching frequency and substitution (ν_{CO} versus σ or σ^*) have been reported in some cases^{20,24} although the significance of the correlation has hardly been discussed. These results can be understood by considering the ester resonance structures (6–8).



The electron-withdrawing substituents in the acyl (R^1) and aryl (R^2) groups of the ester destabilize the resonance form 7 and those in the aryl group also destabilize the resonance form 8 and thereby increase the relative contribution of the structure 6. The increasing importance of structure 6 is evidenced by the increasing shielding, *i.e.*, by the upfield ^{13}C NMR shifts, of the carbonyl carbon and by the higher $\nu(\text{C}=\text{O})$ frequencies. Accordingly, in agreement with the ^{13}C NMR and IR results the increase in the reaction rate of nucleophilic acyl substitutions by electron-withdrawing substituents, which means positive reaction constants ρ or ρ^* in Hammett or Taft equations, respectively, can be explained by the ground state destabilization of the substrate. This ground state destabilization is due to the diminished overall resonance stabilization. So, reaction rates increase despite the decrease in the electrophilicity of the acyl carbon. The above interpretation is in accordance with the ^{13}C NMR spectroscopic study of Dell'Erba *et al.*^{7b} The comparison of the sensitivity of the carbonyl carbon resonance to the benzoyl substituent in four series of the nitro-substituted phenyl benzoates with methyl benzoates (13) and acetophenones (14) showed along the 9–12 series a gradual shift from a 13-like to a 14-like behaviour. Therefore, increasing electron-withdrawal by the aryl group was proposed to decrease the significance of the normal ester resonance.

Analogy with acyl chlorides. There are only a few relevant studies concerning aliphatic substituent effects on the $\text{C}=\text{O}$ carbon ^{13}C NMR chemical shifts. However, the chemical shift behaviour of chloro substituted acetyl chlorides (series 15) is known:²⁵ the ^{13}C chemical shifts of the acyl carbons of acetyl, chloroacetyl, dichloroacetyl and trichloroacetyl chlorides in CD_2Cl_2 are 170.6, 168.1, 165.9 and 163.7 ppm, respectively. Further, the complexation behaviour of these compounds with AlCl_3 , and the efficiency of these complexes in an aromatic



acylation, have been studied.²⁵ During the interaction of acyl chlorides with AlCl₃, the C=O bond is weakened and the carbonyl carbon chemical shifts are displaced downfield while the carbonyl oxygen ¹⁷O chemical shifts are displaced upfield. Interestingly, acetyl chloride is much more reactive than trichloroacetyl chloride in the AlCl₃ promoted acylation.²⁵ The complexation of trichloroacetyl chloride with AlCl₃ is much weaker than that of acetyl chloride and therefore a much smaller change as a consequence of the complexation was observed in the ¹³C and ¹⁷O chemical shifts of trichloroacetyl chloride as compared to acetyl chloride. This, together with the C=O ¹³C chemical shift behaviour in the series of chloro-substituted acetyl chlorides, indicates the more fixed C=O double bond character in the case of trichloroacetyl chloride as compared to acetyl chloride. According to our postulation the increased double bond character can be attributed to the decreased resonance contribution of form **16** relative to **15** due to the electron-withdrawal by acyl substituents. In the Friedel–Crafts acylation this effect results in competition. While the chloro substituents make the acyl chloride more prone to a nucleophilic attack, they make it less susceptible to complexation with AlCl₃ because of diminished C=O bond polarization and diminished basicity of the carbonyl oxygen toward a Lewis acid. Consequently, the chloro substituents decrease the total reactivity.

Interestingly, an excellent correlation is seen ($r = 0.999$) between the C=O carbon shifts of acyl substituted 4-nitrophenyl acetates and acetyl chlorides (Table 3, line 8). Further, the C=O carbon ¹³C chemical shifts of 4-nitrophenyl acetates versus the Taft's polar σ^* parameters show an excellent correlation when the clearly deviating point of the trifluoroacetyl group is excluded ($\rho^* = -3.27$, Table 3, line 9). This correlation also shows that in this aliphatic substitution series electronic effects dominate the substituent chemical shift effects. Furthermore, the negative slope suggests that the electron-withdrawing acyl substituents suppress the ester resonance and increase the carbonyl carbon shielding. We are not aware of similar previous correlations. At the present time it is not known why the CF₃ group does not fit the correlation line.

Other evidence. The concept of a noticeable contribution of the ground state resonance stabilization to the dependence of reaction rates on the substrate structure in nucleophilic acyl substitution is supported by the high values of the localization energies (14–18 kcal mol⁻¹ for esters) estimated for addition of nucleophiles to acyl derivatives.²⁶ Furthermore, the recent

quantum mechanical gas phase calculations performed by Kallies and Mitzner²⁷ show that the lower reactivity of *N,N'*-dimethylurea (DMU) as compared to *N*-methyl acetamide (MAM) reflects the higher overall resonance stabilization of the former compound despite the fact that the lone pair of one nitrogen is less delocalized with DMU than MAM.

Estimation of rate coefficients with the aid of C=O shifts

The utilization of the reactivity versus carbonyl carbon ¹³C chemical shift correlation to predict rate coefficients was tested for the neutral hydrolysis of substituted phenyl dichloroacetates. With the equation $\log k_o = (-1.5 \pm 0.1) \times \text{SCS} - (3.2 \pm 0.1)$, obtained from the phenyl dichloroacetates other than the 4-bromo substituted example (Table 1), the calculated value $(1.9 \pm 0.7) \times 10^{-3} \text{ s}^{-1}$ was obtained for k_o of 4-bromophenyl dichloroacetate in 20% acetonitrile–water at 298.2 K. This value is a satisfactory estimate of the experimental value $1.3 \times 10^{-3} \text{ s}^{-1}$ (Table 1). The use of $\log k$ versus $\delta_C(\text{C=O})$ plots is a convenient way to obtain at least a first approximation for a rate coefficient. This can be especially important for substituted derivatives for which the substituent constants are not known and therefore any Hammett type correlations cannot be used for the evaluation of the rate coefficient.

Conclusions

Electron-withdrawing substituents increase the rates of nucleophilic acyl substitutions of esters. The electron-withdrawal by the substituents also results in an upfield shift of the ¹³C NMR resonance of the C=O carbon and a higher wavenumber of the $\nu(\text{C=O})$ frequency. The upfield chemical shifts and the higher wavenumbers of the C=O stretching reflect the increased double bond character of the C=O bond. As for the rate increase in the nucleophilic acyl substitutions, the results suggest a significant decrease in the ester ground state stability due to the decreased resonance stabilization, in contrast to the conventional concept according to which electron-withdrawing substituents increase the reaction rate by the increased electrophilicity of the C=O carbon and by the stabilization of the negative charge developed at the transition state. As a first approximation, the use of $\log k$ versus $\delta_C(\text{C=O})$ correlations is an alternative way to evaluate rate coefficients especially for substituted derivatives for which the substituent constants are not known and therefore Hammett type correlations cannot be used.

References

- (a) A. J. Kirby, in *Comprehensive Chemical Kinetics*, eds. C. H. Bamford and C. F. H. Tipper, Elsevier Publishing Company, Amsterdam, 1980, vol. 10, chapter 2, p. 161; (b) K. A. Connors, *Structure Reactivity Relationships: the Study of Reaction Rates in Solution*, VCH Publishers, New York, 1990, chapter 7, p. 311; (c) G. W. Klumpp, *Reactivity in Organic Chemistry*, Wiley, New York, 1982, chapter 3, p. 103; (d) O. Exner, in *Advances in Linear Free Energy Relationships*, Plenum Press, London, 1972, chapter 1, p. 1.
- K. A. Connors, *Structure Reactivity Relationships: the Study of Reaction Rates in Solution*, VCH Publishers, New York, 1990, chapter 5, p. 187.
- (a) J. Bromilow, R. T. C. Brownlee and D. J. Craik, *Aust. J. Chem.*, 1977, **30**, 351; (b) R. T. C. Brownlee and D. J. Craik, *Org. Magn. Reson.*, 1981, **15**, 248; (c) J. Bromilow, R. T. C. Brownlee, D. J. Craik, P. R. Fiske, J. E. Rowe and M. Sadek, *J. Chem. Soc., Perkin Trans. 2*, 1981, 753; (d) D. J. Craik and R. T. C. Brownlee, *Prog. Phys. Org. Chem.*, 1983, **14**, 1 and references therein; (e) R. T. C. Brownlee, M. Sadek and D. J. Craik, *Org. Magn. Reson.*, 1983, **21**, 616; (f) W. F. Reynolds, *Prog. Phys. Org. Chem.*, 1983, **14**, 165.
- (a) G. K. Hamer, I. R. Peat and W. F. Reynolds, *Can. J. Chem.*, 1973, **51**, 897, 915; (b) W. J. Hehre, R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, 1976, **12**, 159.
- (a) K. Neuvonen, F. Fülöp, H. Neuvonen and K. Pihlaja, *J. Org. Chem.*, 1994, **59**, 5895; (b) K. Neuvonen, F. Fülöp, H. Neuvonen, M. Simeonov and K. Pihlaja, *J. Phys. Org. Chem.*, 1997, **10**, 55.

- 6 C. J. O'Connor and T. D. Lomax, *Aust. J. Chem.*, 1983, **36**, 917; C. J. O'Connor, D. J. McLennan, D. J. Calvert, T. D. Lomax, A. J. Porter and D. A. Rogers, *Aust. J. Chem.*, 1984, **37**, 497.
- 7 (a) C. Dell'Erba, F. Sancassan, M. Novi, G. Petrillo, A. Mugnoli, D. Spinelli, G. Consiglio and P. Gatti, *J. Org. Chem.*, 1988, **53**, 3564; (b) C. Dell'Erba, F. Sancassan, G. Leandri, M. Novi, G. Petrillo and A. Mele, *Gazz. Chim. Ital.*, 1989, **119**, 643; (c) C. Dell'Erba, A. Mele, M. Novi, G. Petrillo, F. Sancassan and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1990, 2055.
- 8 (a) H. Neuvonen, *J. Chem. Soc., Perkin Trans. 2*, 1987, 159; (b) H. Neuvonen, *J. Chem. Soc., Perkin Trans. 2*, 1995, 951; (c) H. Neuvonen, *Ber. Bunsenges. Phys. Chem.*, 1996, **100**, 1231.
- 9 (a) T. H. Fife, *J. Am. Chem. Soc.*, 1965, **87**, 4597; (b) T. H. Fife and D. M. McMahon, *J. Am. Chem. Soc.*, 1969, **91**, 7481.
- 10 K. Koehler, R. Skora and E. H. Cordes, *J. Am. Chem. Soc.*, 1966, **88**, 3577.
- 11 R. Buyle, *Helv. Chim. Acta*, 1964, **47**, 2449.
- 12 A. A. Frost and R. G. Pearson, *Kinetics and Mechanisms*, Wiley, New York, 1961, p. 27–55.
- 13 (a) H. Neuvonen, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1141; (b) H. Neuvonen, Dissertation, University of Turku, Turku, 1985.
- 14 (a) M. Avram and GH. D. Mateescu, *Infrared Spectroscopy: Applications in Organic Chemistry*, Wiley, New York, 1972, chapter 8, p. 416; (b) Y. Mido and M. Hashimoto, *J. Mol. Struct.*, 1985, **131**, 71.
- 15 D. F. Ewing, in *Correlation Analysis in Chemistry: Recent Advances*, eds. N. B. Chapman and J. Shorter, Plenum Press, New York, 1978, p. 357.
- 16 J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, 1967, **89**, 4253.
- 17 H. Dahn and P.-A. Carrupt, *Magn. Reson. Chem.*, 1997, **35**, 577.
- 18 R. Noto, L. Lamartina, C. Arnone and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1987, 689; 1988, 887.
- 19 (a) J. J. Ryan and A. A. Humffray, *J. Chem. Soc. B*, 1966, 842; (b) T. Nishioka, T. Fujita, K. Kitamura and M. Nakajima, *J. Org. Chem.*, 1975, **40**, 2520.
- 20 L. A. Cohen and S. Takahashi, *J. Am. Chem. Soc.*, 1973, **95**, 443.
- 21 A. Williams and R. A. Naylor, *J. Chem. Soc. B*, 1971, 1967.
- 22 A. D. Campbell, S. Y. Chool, L. W. Deady and R. A. Shanks, *Aust. J. Chem.*, 1970, **23**, 203.
- 23 M. Buděšinsky and O. Exner, *Magn. Reson. Chem.*, 1989, **27**, 585.
- 24 R. D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 193; S. Takahashi, L. A. Cohen, H. K. Miller and E. G. Peake, *J. Org. Chem.*, 1971, **36**, 1205; A. S. Shawali and N. F. Eweiss, *Can. J. Chem.*, 1977, **55**, 3967.
- 25 F. Bigi, G. Casnati, G. Sartori and G. Predieri, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1319.
- 26 J. Fastrez, *J. Am. Chem. Soc.*, 1977, **99**, 7004.
- 27 B. Kallies and R. Mitzner, *J. Chem. Soc., Perkin Trans. 2*, 1996, 397.

Paper 9/00189A