Electron-Withdrawing Substituents Decrease the Electrophilicity of the Carbonyl Carbon. An Investigation with the Aid of ^{13}C NMR Chemical Shifts, ν(C=O) Frequency Values, Charge Densities, and Isodesmic Reactions To Interprete Substituent Effects on Reactivity

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^{13}C NMR chemical shifts and ν(C=O) frequencies have been measured for several series of phenyl- or acyl-substituted phenyl acetates and for acyl-substituted methyl acetates to investigate the substituent-induced changes in the electrophilic character of the carbonyl carbon. Charge density, bond order, and energy calculations have also been performed. The spectroscopic and charge density results indicate that opposite to the conventional thinking, electron-withdrawing substituents do not increase the electrophilicity of the carbonyl carbon but instead decrease it. On the other hand, reaction energies of the isodesmic reactions designed show that electron-withdrawing substituents destabilize the carbonyl derivatives investigated. So, a significant ground-state destabilization of carboxylic acid esters, and carbonyl compounds in general, due to the decreased resonance stabilization, is proposed as a novel concept to explain both the increase in their reactivity and the changes in the chemical shifts and carbonyl frequencies induced by electron-withdrawing substituents.

Introduction

The electrophilicity of the carbonyl carbon is the main character controlling the reactivity of several important classes of organic compounds, such as aldehydes, ketones, or carboxylic acid derivatives. Substituents in the reacting molecule still strongly adjust its reactivity. For instance, in nucleophilic acyl substitution reactions of carboxylic acid derivatives, electron-withdrawing substituents in the leaving group or in the nonleaving acyl group increase reaction rates, leading to positive slopes when correlating rate coefficients with Hammett or related substituent constants. In general, in addition of the possible transition state stabilization, this has been interpreted to reflect an increase in electrophilicity of the reaction center due to the electron withdrawal by substituents.[1,2] Although there is no doubt of the electrophilic nature of the carbonyl carbon, our recent studies concerning substituent effects on the reactivity and on the ^{13}C NMR spectroscopic characters of some carboxylic acid esters led us to suggest a different view.[3]

We demonstrated good correlations with negative slopes for the plots of log k versus δ_C(C=O) for several acyl transfer reactions including, for instance, neutral hydrolysis of phenyl dichloroacetates or alkaline hydrolysis of methyl benzoates.[3] An increase in the electron-withdrawing ability of the phenyl substituent of phenyl dichloroacetates or benzoyl substituent of methyl benzoates results in an upfield shift of the carbonyl carbon resonance. The upfield chemical shift indicates an increase in shielding of the carbon in question and therefore an increase in its electron density. One could assume this kind of change to decrease the electrophilicity of the carbonyl carbon and to cause an increase in $\Delta G^{\ddagger}$ values, because of less favorable electrostatic interactions between the nucleophile and the acyl derivative. However, despite the upfield shift of the δ_C(C=O) values, electron-withdrawing substituents increase the rate of nucleophilic acyl substitutions of the esters. The δ_C(C=O) characters together with the ν(C=O) values for some of the esters studied led us to suggest that the decreased resonance stabilization of the esters contributes to the increase in reactivity.[3]

To get our conclusions concerning this important topic on a firmer base, we have now systematically studied especially the effect of varying the aliphatic acyl substitution on the characters of the C=O group of carboxylic acid esters, a significant class of organic carbonyl group containing compounds. We have studied the infrared spectra both for the solid or liquid samples and for dilute


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solutions in CH_2Cl_2 for phenyl-substituted phenyl trifluoroacetates **1**, phenyl dichloroacetates **2**, and phenyl acetates **3** as well as for acyl-substituted phenyl acetates **4** and methyl acetates **5**. In addition, ^{13}C NMR shifts for series **1**, **3**, **4**, and **5** and for the 2,4-dinitrophenyl derivative of series **2** as well as for 2,4-dinitrophenyl chloroacetate (**6**) were measured.
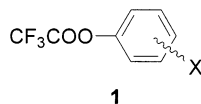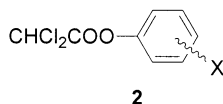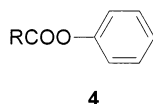
CF_3COO— (ring) —X

1

X = 4-OMe (**a**), 4-Me (**b**), H (**c**), 4-Br (**d**), 4-Cl (**e**), 4-CN (**f**), 4-NO_2 (**g**), 3-Cl (**h**), 3-NO_2 (**i**) or 2,4-diNO_2 (**j**)

CHCl_2COO— (ring) —X

2

X = 4-OMe (**a**), 4-Me (**b**), H (**c**), 4-Br (**d**), 4-Cl (**e**), 4-CN (**f**), 4-NO_2 (**g**), 3-Cl (**h**), 3-NO_2 (**i**) or 2,4-diNO_2 (**j**)

CH_3COO— (ring) —X

3
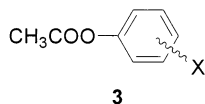
X = 4-OMe (**a**), 4-Me (**b**), H (**c**), 4-Br (**d**), 4-Cl (**e**), 4-CN (**f**), 4-NO_2 (**g**), 3-Cl (**h**), 3-NO_2 (**i**) or 2,4-diNO_2 (**j**)

RCOO— (ring)

4

R = CH_3CH_2 (**a**), CH_3 (= **3c**), PhCH_2 (**b**), CH_3OCH_2 (**c**), PhOCH_2 (**d**), CH_2Cl (**e**), CHCl_2 (= **2c**), CCl_3 (**f**) or CF_3 (= **1c**)

RCOOCH_3

5
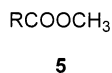
R = CH_3 (**a**), CH_3OCH_2 (**b**), CH_2Cl (**c**), CHCl_2 (**d**), CCl_3 (**e**) or CF_3 (**f**)

CH_2ClCOO— (ring) —NO_2, O_2N

6
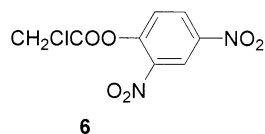
The relation between the spectroscopic data and the electron densities at particular atoms as well as some bond orders calculated by the PM3 method are discussed. Further, the calculated heat of formation values were used to evaluate the effect of substituents on the stabilities of the esters with the aid of relevant isodesmic reactions.

Results and Discussion

The increase in the electron-withdrawing ability of the phenyl substituent causes a systematic upfield shift of the C=O carbon resonance in all three series **1**−**3** (Table 1). The range of the C=O carbon resonance is on the higher field the more electronegatively substituted the acyl group is. The significant effect of the aliphatic acyl substitution is more clearly seen in Table 2, where the ^{13}C NMR chemical shifts for the carbonyl and α-carbons of acyl-substituted phenyl acetates (**4**) and methyl acetates (**5**) are given. The opposite behavior of the reso-

TABLE 1. Carbonyl Carbon ^{13}C NMR Chemical Shifts δ(C=O) (in ppm) in CDCl_3 for Substituted Phenyl Acetates (3), Phenyl Dichloroacetates (2), and Phenyl Trifluoroacetates (1) RCOOAr

Ar	σ^a	R		
		CH_3	CHCl_2	CF_3
4-OMeC_6H_4	−0.27	169.87	163.37^b	156.17
4-MeC_6H_4	−0.17	169.69	163.20^b	156.02
HC_6H_4	0	169.49	163.02^b	155.85
4-BrC_6H_4	0.23	169.07	162.70^b	155.52
4-ClC_6H_4	0.23	169.17	162.78^b	155.61
3-ClC_6H_4	0.37	168.97	162.65^b	155.47
4-CNC_6H_4	0.66	168.46	162.20^b	155.06
3-NO_2C_6H_4	0.71	168.70	162.43^b	155.32
4-NO_2C_6H_4	0.78	168.38	162.13^b	154.99
2,4-(NO_2)_2C_6H_3		167.60	161.36	154.42

^{a} Reference 6. ^{b} Reference 3.

nances of the carbonyl and α-carbons in both series **4** and **5** is also evident. For 2,4-dinitrophenyl chloroacetate (**6**), the ^{13}C NMR chemical shift value of 164.58 ppm (not shown in tables) was detected.

Carbonyl stretching frequencies of series **1**−**5** both for the solid or liquid film samples and for the 0.1 M solutions in CH_2Cl_2 are given in Tables S1−S4 (Supporting Information). Although ν(C=O) appears as a singlet in all of the solid or liquid IR spectra, with the only exception of 4-nitrophenyl dichloroacetate, and for all of the CH_2Cl_2 solutions of phenyl-substituted phenyl trifluoroacetates (**1**), a doublet is observed in some solution spectra. We previously introduced two possible explanations, a conformational equilibrium and Fermi resonance, for the appearance of the doublet in the liquid film IR spectra of 4-nitrophenyl dichloroacetate.[3]

Effect of the Leaving Group Substituents on the Electronic Properties of the C=O Group. ^{13}C NMR spectroscopy is a useful tool to study substituent effects on the electronic environment of a carbon.[5] A good correlation but with a reverse behavior is observed between the ^{13}C NMR chemical shift of the C=O carbon of monosubstituted phenyl trifluoroacetates (**1**) and the Hammett σ substituent constant[6] (Figure 1; Table 3, line 1). Hammett σ values describe the electronic effects of aromatic ring substituents on the reactive center.[1,2,7] The good correlation between δ_C(C=O) and σ indicates that electronic effects control the substituent-induced changes in the C=O carbon resonance. Electron-withdrawing substituents cause an upfield shift, indicating increased shielding at the C=O carbon.

Bromilow et al.[8] have previously reported a reverse behavior of the carbonyl carbon ^{13}C NMR shift for para- and meta-substituted phenyl acetates. The slope of 0.96 ± 0.01 (r^2 = 0.9990) between our SCS values for series **3** and those reported by Bromilow et al.[8] for the common substitutions shows a good agreement.

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TABLE 2. Carbonyl and α-carbon ^{13}C NMR Chemical Shifts (in ppm) for Substituted Phenyl Acetates RCOOPh (4) and Methyl Acetates RCOOMe (5)^a

R	$\sigma^{*\,b}$	RCOOPh				RCOOMe	
		δ(C=O)	δ(C-α)	δ(C=O)^c	δ(C-α)^c	δ(C=O)	δ(C-α)
CH$_3$CH$_2$	−0.1	173.05	27.78	172.51	26.86		
CH$_3$	0	169.49	21.14	169.14	20.81	171.57	20.70
PhCH$_2$	0.215	170.00	41.45	170.04	40.11		
MeOCH$_2$	0.520	168.78	69.79	168.95	68.87	170.69	69.79
PhOCH$_2$	0.850	167.53	65.49	167.73	64.57		
CH$_2$Cl	1.05	165.86	40.89	166.35	41.29	167.80	40.68
CHCl$_2$	1.94	163.02	64.21	163.41	64.95	165.08	64.03
CCl$_3$	2.65	160.55	89.61	160.35	88.92	162.66	89.60
CF$_3$	2.60	155.85	114.61	155.14	114.35	158.04	114.54

^{a} In CDCl$_3$, if not otherwise stated. ^{b} Reference 10. ^{c} In DMSO-d_6
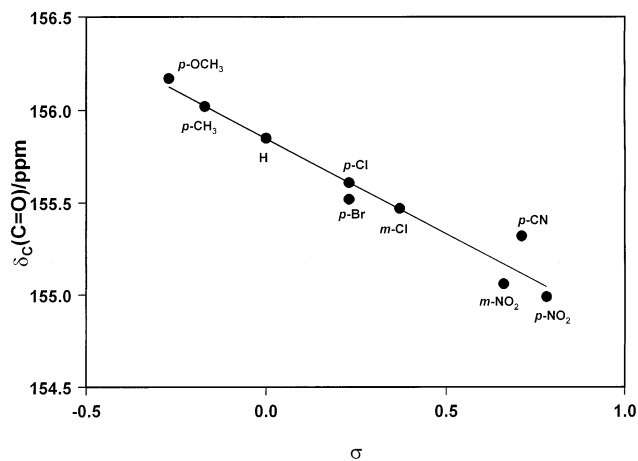
FIGURE 1. A plot of the ^{13}C NMR chemical shifts of the carbonyl carbon of phenyl-substituted phenyl trifluoroacetates (**1**) in CDCl$_3$ versus Hammett substituent constants σ.

The slopes 0.86 and 0.77 are obtained, respectively, for the correlations between the δ_C(C=O) of phenyl dichloroacetates (**2**) and phenyl acetates (**3**) and between those of phenyl trifluoroacetates (**1**) and phenyl acetates (**3**). These correlations include both the monosubstituted derivatives and the 2,4-dinitro-substituted compounds. The correlations are good in both cases (Table 3, lines 2 and 3), and the values of the slopes—both smaller than 1 and a smaller value in the latter case—show that *the more electron-withdrawing substituents the acyl group owns, the less sensitive is the carbonyl carbon resonance to the electronic influence of the phenyl substitution.* The results indicate the decreased polarization of the carbonyl bond when electron-withdrawal by the acyl substituents is increased.

A fair correlation with a negative slope is verified between δ_C(C=O) of series **1** and the ν(C=O) of the same compounds (Table 3, lines 5 and 7, respectively). When the δ_C(C=O) values for series **2** and **3** are correlated with the ν(C=O) frequencies of the same series using the values for the higher frequency peaks in those cases where the carbonyl stretching occurs as a doublet, the correlations are only satisfactory (Table 3, lines 8 and 9, respectively). However, the slopes of the correlations are similar than for series **1** (−0.07 to −0.08).

For all three series **1**–**3**, an increase in ν(C=O) occurs at the same time as the carbonyl carbon resonance displaces upfield. Systematic substituent dependent changes in carbonyl frequency indicate primarily changes

TABLE 3. Statistical Data for Different Correlations and Cross Correlations of the Carbonyl Carbon or α-Carbon ^{13}C NMR Chemical Shifts, Substituent Constants σ or σ^*, ν(C=O) Stretching Frequencies, and PM3-Calculated Charges q_C(C=O) or q_O(C=O) or C=O Bond Orders for Phenyl-Substituted Phenyl Acetates (3), Phenyl Dichloroacetates (2), or Phenyl Trifluoroacetates (1) and for Acyl-Substituted Phenyl Acetates (4) or Methyl Acetates (5)^a

line	type of correlation	slope	s	r^2	n
1	δ_C(C=O)(**1**) vs σ	−1.03	0.08	0.9495	9
2	δ_C(C=O)(**2**) vs δ_C(C=O)(**3**)	0.86	0.02	0.9957	10
3	δ_C(C=O)(**1**) vs δ_C(C=O)(**3**)	0.77	0.01	0.9978	10
4	δ_C(C=O)(**1**) vs ν(C=O)(**1**)^b	−0.08	0.02	0.7235	10
5	δ_C(C=O)(**1**) vs ν(C=O)(**1**)^{b,c}	−0.08	0.01	0.9095	9
6	δ_C(C=O)(**1**) vs ν(C=O)(**1**)^d	−0.07	0.01	0.8294	10
7	δ_C(C=O)(**1**) vs ν(C=O)(**1**)^{c,d}	−0.07	0.01	0.9199	9
8	δ_C(C=O)(**2**) vs ν(C=O)(**2**)^d	−0.08	0.01	0.8644	10
9	δ_C(C=O)(**3**) vs ν(C=O)(**3**)^d	−0.07	0.01	0.8142	10
10	δ_C(C=O)(**4**)^e vs σ^*	−4.0	0.4	0.9488	8
11	δ_C(C=O)(**4**) vs δ_C(C=O)(**4**)^f	0.98	0.03	0.9943	9
12	δ_C(C=O)(**4**) vs ν(C=O)(**4**)^b	−0.32	0.08	0.7029	9
13	δ_C(C=O)(**4**) vs ν(C=O)(**4**)^{b,g}	−0.35	0.08	0.8090	6
14	δ_C(C=O)(**4**) vs ν(C=O)(**4**)^d	−0.33	0.06	0.8291	9
15	δ_C(C=O)(**4**) vs ν(C=O)(**4**)^{d,g}	−0.40	0.02	0.9858	6
16	δ_C(C=O)(**5**)^e vs σ^*	−3.5	0.2	0.9883	5
17	δ_C(C=O)(**5**) vs ν(C=O)(**5**)^b	−0.33	0.03	0.9646	6
18	δ_C(C=O)(**5**) vs ν(C=O)(**5**)^d	−0.30	0.04	0.9381	6
19	δ_C(C=O)(**5**) vs δ_C(C=O)(**4**)	0.98	0.01	0.9998	6
20	δ_C(C=O)(**7**)^h vs δ_C(C=O)(**4**)	0.99	0.01	0.9996	5
21	δ_C(C=O)(**8**) vs δ_C(C=O)(**4**)	0.98	0.03	0.9983	4
22	δ_C(C=O)(**9**) vs δ_C(C=O)(**4**)	0.77	0.03	0.9966	4
23	δ(C-α)(**4**)^i vs δ_C(C=O)(**4**)	−7.2	0.5	0.9874	5
24	δ(C-α)(**4**)^j vs δ_C(C=O)(**4**)	−7.7	2.4	0.8364	4
25	δ(C-α)(**5**)^i vs δ_C(C=O)(**5**)	−7.3	0.5	0.9857	5
26	δ_C(C=O)(**4**) vs q_C(C=O)(**4**)^k	343	34	0.9443	8
27	q_C(C=O)(**4**) vs $\sigma^{*\,l}$	−0.012	0.002	0.8784	9
28	q_C(C=O)(**4**) vs $\sigma^{*\,m}$	−0.010	0.001	0.9446	9
29	q_C(C=O)(**4**) vs q_O(C=O)(**4**)	−0.40	0.08	0.7923	9
30	ν(C=O)(**4**)^d vs (C=O) bond order (**4**)^n	757	170	0.7993	7
31	δ_C(C=O)(**3**) vs q_C(C=O)(**3**)^o	−162	28	0.8309	9
32	ν(C=O)(**1**)^d vs (C=O) bond order (**1**)	671	46	0.9640	10

^{a} ^{13}C NMR chemical shifts in CDCl$_3$, if not otherwise stated. ^{b} For IR of solid or liquid film samples. ^{c} p-CN substitution excluded. ^{d} For IR of 0.1 M solution in CH$_2$Cl$_2$. ^{e} The deviating CF$_3$ derivative excluded. ^{f} In DMSO-d_6. ^{g} The deviating points R = PhCH$_2$, MeOCH$_2$, PhOCH$_2$ excluded. ^{h} δ_C(C=O) values for 4-nitrophenyl chloroacetate and trichloroacetate from ref 3. ^{i} With R = CH$_3$, CH$_2$Cl, CHCl$_2$, CCl$_3$, CF$_3$. ^{j} With R = CH$_3$CH$_2$, PhCH$_2$, MeOCH$_2$, PhOCH$_2$. ^{k} CH$_3$CH$_2$ excluded. ^{l} The literature^{10} value of 2.60 for σ^*(CF$_3$) is used. ^{m} The value of 3.8 determined in this work for σ^*(CF$_3$) is used. ^{n} MeOCH$_2$ and CH$_2$Cl excluded. ^{o} For monosubstituted derivatives.
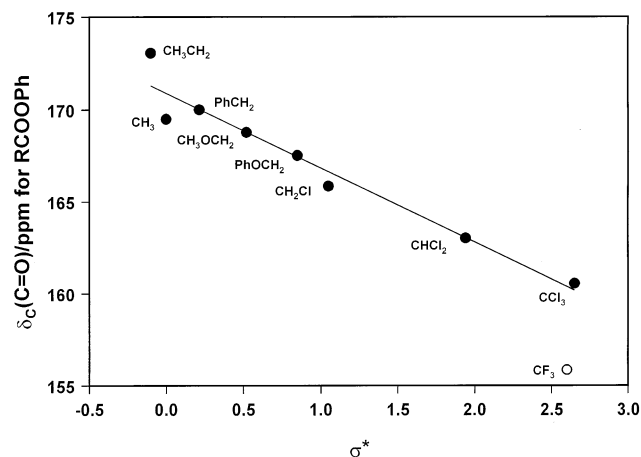
FIGURE 2. A plot of the ^{13}C NMR chemical shifts of the carbonyl carbon of acyl-substituted phenyl acetates (**4**) in $CDCl_3$ versus Taft's polar substituent constants σ^*.

FIGURE 3. Plots of the ^{13}C NMR chemical shifts of the carbonyl carbon of acyl-substituted methyl acetates (**5**; ○), 4-nitrophenyl acetates (**7**; □), 2,4-dinitrophenyl acetates (**8**; ▲), and acetyl chlorides (**9**; ■) in $CDCl_3$ versus the ^{13}C NMR chemical shifts of acyl-substituted phenyl acetates (**4**) in $CDCl_3$.

in the force constant and hence in the bond length of the carbon oxygen bond.[9] Accordingly, the increase in $\nu(C=O)$ can be attributed to a shorter carbonyl bond and therefore to a higher double bond character of the C=O bond. Both the ^{13}C NMR and IR spectroscopic data suggest substituent-induced increase in electron density at the carbonyl carbon along with the increasing electron-withdrawal by the phenyl substituent.

Effect of Acyl Substitution on the Electronic Properties of the C=O Group. To study the effect of the structure of the aliphatic acyl group on the electronic character of the carbonyl unit, we have used different groups R−CO− (series **4** and **5**), where Taft's polar substituent constant σ^* for R varies from −0.1 to 2.65.[10]

Very large shift ranges are observed for the carbonyl carbon resonance in series **4** and **5**, 17.2 and 13.5 ppm, respectively. The correlation of $\delta_C(C=O)$ with σ^* [10] shows a good correlation with a negative slope both for series **4** and **5** (Table 3, lines 10 and 16, respectively). The carbonyl carbon resonates on the higher field, indicating increased shielding at the C=O carbon the more electron-withdrawing the group R is (Figure 2). We are not aware of similar systematic correlation for a wide set of aliphatic substitution, although reverse correlation of carbonyl carbon resonance on aromatic substitution of benzoic acid esters has been reported.[8,11] Correlation between the δ_C-(C=O) values in $CDCl_3$ with those measured in DMSO-d_6 for series **4** is excellent with a slope of close to 1 (Table 3, line 11). CF_3 was not included in the original set of the polar substituent constants[10a] and the σ^* value of 2.60 given in the literature for CF_3 is less accurate than the other ones.[10b] Therefore, we conclude that the deviation of the point for trifluoromethyl derivative (Figure 2; Table 3, lines 10 and 16) merely reflects an unsuitable value of $\sigma^*(CF_3)$. If extrapolation is used for the correlations of
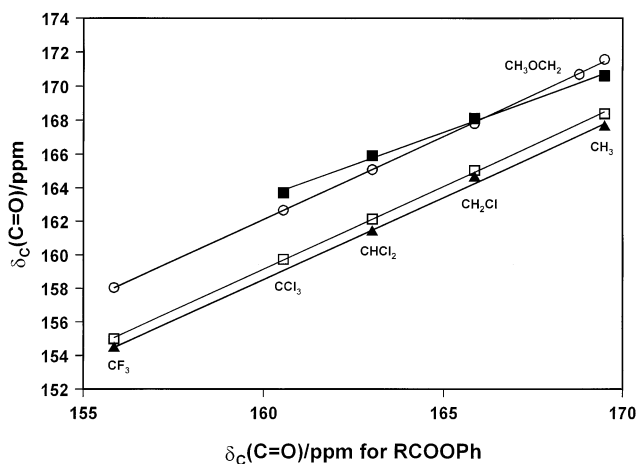
$\delta_C(C=O)$ with σ^* for series **4** and **5**, the value of 3.8 is obtained as a mean value for $\sigma^*(CF_3)$. This value can be tested in the future as a novel polar substituent constant of the trifluoromethyl group.

The slopes for the $\delta_C(C=O)$ vs $\nu(C=O)$ correlations for series **4** and **5** are ca. −0.3 (Table 3, lines 12−15, 17, and 18). Both upfield chemical shift (increased shielding of the carbonyl carbon) and higher $\nu(C=O)$ (a shorter C=O bond) follow the increasing polar character of the group R. Accordingly, electron-withdrawing acyl substituents obviously decrease the polarization of the carbonyl group.

To study *the effect of the ester leaving group on the sensitivity* of the C=O carbon resonance to the acyl substitution, we used some cross-correlations (Figure 3). The carbonyl carbon ^{13}C NMR shifts of methyl acetates (**5**), 4-nitrophenyl acetates (**7**) (the values for 4-nitrophenyl chloroacetate and trichloroacetate are from our previous study),[3] and 2,4-dinitrophenyl acetates (**8**) were plotted against those of phenyl acetates (**4**). In addition of these esters, the chemical shift values of substituted acyl chlorides (**9**) found in the literature[12] were also included. Correlations are excellent in all cases, and the points for the trifluoromethyl group nicely fit the lines. The slopes are close to 1 for all three ester series. Although acyl substitution effectively controls the sensitivity of C=O carbon resonance to phenyl substitution, the leaving group does not seem to possess a respective influence. This is in line with the different efficiencies of acyl and phenyl substitutions on the carbon resonance as such. However, acyl chlorides (**9**) behave differently. The correlation is excellent also in this case, but the sensitivity of the carbonyl carbon ^{13}C NMR chemical shift to the electron-withdrawing ability of acyl substituents is diminished as compared to that of esters. The slope is only 0.77 (Table 3, line 22). Chlorine instead of the alkoxy or aryl oxy group as the leaving group seems to decrease the polarization of the C=O group. Considerably higher $\nu(C=O)$ frequencies are observed for acyl chlorides (ca.

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RCOO—⟨phenyl⟩—NO₂
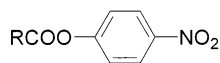
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R = CH₃ (= **3g**), CH₂Cl (**a**), CHCl₂ (= **2g**), CCl₃ (**b**)
or CF₃ (= **1g**)

RCOO—⟨phenyl⟩—NO₂
              |
             O₂N
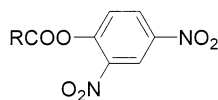
8

R = CH₃ (= **3j**), CH₂Cl (**6**), CHCl₂ (= **2j**), or CF₃ (= **1j**)

RCOCl

9

R = CH₃, CH₂Cl, CHCl₂, CCl₃

$1820\ cm^{-1}$) as compared with carboxylic acid esters (ca. $1750\ cm^{-1}$). The difference is thought to reflect the lower polarization of the carbonyl bond of acyl chlorides.[13] Accordingly, the decreased sensitivity of the carbonyl carbon resonance of acyl chlorides to acyl substitution obviously reflects the same fact.

Effect of Acyl Substitution on the ¹³C NMR Chemical Shift of the α-Carbon. Although the carbonyl carbon ¹³C NMR shift shows a reverse trend, the α-carbon shift behaves normally (Table 2). A good linear correlation with a negative slope of −7.2 for phenyl acetates (**4**) and of −7.3 for methyl acetates (**5**) is observed between the chemical shift values of the α-carbon and the C=O carbon with R = CH₃, CH₂Cl, CHCl₂, CCl₃, or CF₃ (Table 3, lines 23 and 25, respectively). With the more crowded groups (R = CH₃CH₂, PhCH₂, PhOCH₂, or CH₃OCH₂), for phenyl acetates a separate but nearly parallel line with a slope of −7.7 is observed (Table 3, line 24). We conclude that these cross-correlations verify that field/inductive electronic effects are significant in determining the ¹³C NMR chemical shift of both carbons.

PM3 Charges and Bond Orders. Although the NMR shielding is not determined only by electron density, linear correlations with positive slopes between the charge densities and the ¹³C NMR chemical shifts for probe nucleus in closely similar surroundings have been observed in several systems when varying the substitution.[14−19] The carbon resonates on the higher field the higher the electron density at the carbon is. The Karplus−Pople approximation states that the paramagnetic term of the shielding constant, σ^p, which dominates the structure sensitivity of the chemical shift, is determined by eq 1

$$\sigma^p = -\text{constant} \times \Delta E^{-1} r^{-3} \mathbf{\Sigma q} \qquad (1)$$

where ΔE is the average excitation energy, r the mean radius of the 2p-orbital at the atom measured, and $\mathbf{\Sigma q}$ the charge density−bond order matrix that contains the electron density. The mean radius r is also closely related to changes in electron density.[20,21]

The correlation parameters given in Table 3 (lines 26−30) show that the results of PM3 calculations nicely accord with the experimental results for acyl-substituted phenyl acetates (**4**). The chemical shift dependence on electron density is normal (Table 3, line 26), while the substituent effect on the electron density is reversed (Table 3, lines 27 and 28). That is to say, carbonyl carbon resonates on the lower field the more positive the charge of the carbon is, as expected, but *electron-withdrawing substituents increase the electron density* of the carbon. Further, an opposite trend is observed between the charges of the carbonyl carbon and carbonyl oxygen (Table 3, line 29, negative slope). This reflects systematic substituent-dependent variation in the polarization of the C=O unit. The charge of oxygen is about twice as sensitive to substitution than that of carbon. This agrees with the reported good linear correlation with positive slope between ¹⁷O NMR chemical shift for the carbonyl oxygen of *p*-substituted methyl benzoates and the σ^+ parameter.[22] For methyl benzoates a reverse substituent dependence of ¹³C NMR chemical shift of the C=O carbon has also been reported.[8,11] An informative correlation with a positive slope is observed between the ν(C=O) frequency of acyl-substituted phenyl acetates **4** and the calculated C=O bond order (Table 3, line 30). So, as concluded in the discussion in the previous sections, the increase in ν(C=O) can be attributed to the increased double bond character of the carbonyl bond.

For series **1−3**, the substituent-induced changes in spectroscopic parameters are smaller than for acyl-substituted esters. The changes of q_C(C=O) are also smaller than for series **4**. For instance, for monosubstituted phenyl trifluoroacetates (**1**), the range of q_C(C=O) is only about $1/10$ of that for acyl-substituted phenyl acetates (**4**). A clear systematic variation in q_C(C=O) of series **1** could not be observed. For phenyl-substituted phenyl acetates (**3**), the range of q_C(C=O) is 3 times as large as for **1** and the variation of q_C(C=O) along substitution is more systematic. However, surprisingly in that case, the correlation between δ_C(C=O) and q_C-(C=O) gives a negative slope (Table 3, line 31). The PM3 results show increase in the charge of the carbonyl carbon by electron-withdrawing substituents. Consequently, the C=O carbon resonates on the higher field the more positive the calculated charge of the carbon is. This is contrast to the usually observed correlations.[14−19] At this moment, we have no distinct explanation for this fact, but we think that in the structural systems such as substituted phenyl esters, where the polarizable C=O unit studied is not joined directly to the substituted ring, the PM3 method can fail. Perhaps the calculation "sees" as the dipole in the molecule framework most clearly the ether oxygen−carbonyl carbon bond that is directly joined to the aromatic ring. For series **3**, the charges of q_C(C=

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O) and $q_O(C=O)$ change to the same direction and the range of $q_O(C=O)$ is slightly less than the range of q_C-$(C=O)$, while the range of $q_O(-O-)$ is higher than that for $q_C(C=O)$. Further, $q_O(-O-)$ shows a reverse trend; i.e., electron-withdrawing substituents increase the electron density at the ether oxygen. Due to the linear correlation of the ^{13}C NMR chemical shift for series **1**−**3** with Hammett σ and the observed correlations between the ^{13}C NMR chemical shifts and $\nu(C=O)$, we, however, think that the substituent-induced changes in chemical shift reflect electronic changes at the carbonyl carbon and that upfield shifts of the carbonyl carbon reflect an increase in electron density.

Interestingly, for series **1** a fair correlation with a positive slope prevails between $\nu(C=O)$ and the C=O bond order, indicating that an increase in $\nu(C=O)$ caused by electron-withdrawing substituents reflects an increase in the double bond character of the carbon−oxygen bond (Table 3, line 32). Also for series **2** and **3**, both $\nu(C=O)$ and C=O bond order increase with increasing the electron withdrawal of phenyl substituents.

Mode of Interaction between the Carbonyl Group and Substituents. Substituent Effects and Reactivity. The spectroscopic results suggest that electron-withdrawing substituents both in the acyl group and in the leaving group of an ester shorten the C=O bond and increase shielding at the carbonyl carbon. The shortening of the carbon oxygen bond can be attributed to an increase in its double bond character. As regards the aliphatic acyl substitution, PM3 calculations support the experimental results, verifying both the increase in electron density at the carbonyl carbon and the increase in the bond order of the carbon oxygen bond by electron-withdrawing substituents.

Reverse substituent chemical shift effects have been previously detected for some unsaturated carbons in the side chains of aromatic rings. The behavior has most often been explained by the so-called π-polarization.[8,20,23−25] The substituent dipole is thought to polarize each π-unit as a localized system (**10**). So, the chemical shift depen-

10
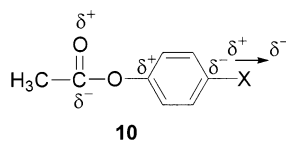
dence on electron density is thought to be normal, while the substituent effect on the electron density is reversed. π-Polarization mechanism was recently criticized, but any alternative explanation was not given.[26] To our knowledge, systematic reverse behavior of carbonyl carbon ^{13}C NMR chemical shift by polar aliphatic substitutions for a wide range of substitutions has not been described previously. A π-polarization mechanism can explain the reverse trend in the C=O carbon shifts, but

it does not give any explanation for the substituent effects on the reactivity of carboxylic acid esters. A clear increase in reaction rate of nucleophilic acyl substitutions occurs, involving as nucleophiles for instance water, the hydroxide ion, ammonia, or amines, when the electron-withdrawing ability of substituents in the acyl or leaving group moiety of the ester increases.[1−4,27−31] So, for instance, for the neutral hydrolysis of phenyl-substituted phenyl trifluoroacetates in 3.89 M water in acetonitrile, eq 2

$$\log(k/k_o) = \rho\sigma \qquad (2)$$

gives a Hammett reaction constant (ρ) of 2.45.[27] For the alkaline hydrolysis of phenyl-substituted phenyl acetates in aqueous solution, a ρ value of 1.1 has been reported.[30] For acyl-substituted esters of aliphatic acids, the polar effects dominate, although steric effects also contribute.[31] A ρ^* value of 2.7 and S value of 1.6 were obtained by us when the rate coefficients of alkaline hydrolysis of acyl-substituted ethyl acetates in aqueous solution[31] were correlated by eq 3,

$$\log(k/k_o) = \rho^*\sigma^* + SE_s \qquad (3)$$

where E_s refers to steric parameters.

So, both the ^{13}C NMR chemical shift of the ester carbonyl carbon and the reactivity of esters toward nucleophiles correlate with Hammett or related substituent constants. As discussed in the Introduction, good correlations between $\log k$ and $\delta_C(C=O)$ with negative slopes have been demonstrated for several acyl substitutions.

Nucleophilic acyl substitution (Scheme 1) is stepwise via a reactive intermediate, or it occurs as a concerted process if the intermediate is very unstable but still exists or is too unstable to exist at all.[32,33] The increase in

SCHEME 1
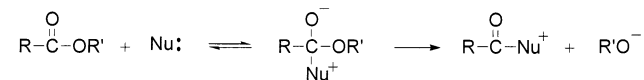
reactivity by electron-withdrawing substituents is conventionally explained by the *increase in electrophilicity* (decreased electron density) of the carbonyl carbon by electron withdrawal, as well as by stabilization of the transition state in those cases where negative charge is developed on going from ground state to the transition state.[1,2] If the rate-determining step of the reaction is the leaving-group expulsion, an increase in the rate of this step contributes because electron-withdrawing substit-

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uents in the leaving group increase its nucleofugality. Electron-withdrawing substituents in the acyl group, on the other hand, decrease the relative nucleofugality of alkoxy or aryl oxide ions relative to amine nucleophiles.[32c,34] Alkaline ester hydrolysis is a reaction with rate-determining attack of the nucleophile. This reaction is strongly accelerated by electron-withdrawing acyl substituents and moderately accelerated by electron-withdrawing substituents in the leaving group.[1,2,31] Further, for instance, the rate of the two-step pyridinolysis of 2,4-dinitrophenyl benzoates with rate-determining leaving-group expulsion is increased by electron-withdrawing benzoyl substituents, despite the unfavorable effect of the acyl substituents on the departure of the aryloxy group.[34] In that reaction the intermediate is not negatively charged but zwitterionic (cf. Scheme 1). Now the present results show that the increase in reaction rates of carboxylic acid esters is *not caused by the increase in their electrophilicity*, because an increase in electron density of the carbonyl carbon is observed by electron-withdrawing substituents.

The data discussed above gives strong verification for our previous proposal.[3] The substituent effects can be considered with the aid of the resonance structures of an ester as follows (Scheme 2). The electron-withdrawing

SCHEME 2
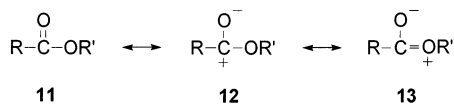
substituents in the acyl (R) and aryl/alkyl (R′) groups of the ester destabilize the resonance form **12**, carrying a positive charge at the carbon, and those in R′ also destabilize the resonance form **13**. Consequently, an increase in the contribution of the resonance form **11** and thereby an increase in the electron density at the carbonyl carbon and in the bond order of the C=O bond occur. In the case of acyl substituents, not only inductive effects but also electrostatic effects or repulsive dipole−dipole interaction are possible as the destabilization mechanism of structure **12**. When electron-withdrawing substituents decrease the contribution of resonance forms **12** and/or **13**, *the resonance stabilization of the ester decreases and its reactivity increases*. An increase in reaction rate means a decrease in free energy of activation: $\Delta G^{\ddagger} = G$(transition state) $- G$(ground state). Although—opposite to the conventional thinking—it is now shown that electron-withdrawing substituents decrease the electrophilicity of the carbonyl carbon, they can increase reactivity of carboxylic acid derivatives because of ground-state destabilization, i.e., by an increase in G(ground state). This explanation does not exclude the contribution of the changes in G(transition state).

Isodesmic Reactions. With the aid of the spectroscopic data and atomic charge variations, we suggest above that electron-withdrawing substituents in the acyl

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TABLE 4. Calculated Energies (ΔE_{iso} in kcal mol^{-1}) of the Two Isodesmic Reactions Shown in Scheme 3 for RCOOPh (4)[a]

R	$\sigma^{*\,b}$	ΔE_{iso}	
		a	b
CH_3CH_2	0.1	−2.22	−1.35
CH_3	0	0	0
$PhCH_2$	0.215	−0.26	−0.46
CH_3OCH_2	0.520	−4.04	−2.94
$PhOCH_2$	0.850	−4.88	−3.74
CH_2Cl	1.05	−4.77	−3.65
$CHCl_2$	1.94	−7.54	−6.40
CCl_3	2.65	−10.43	−8.12
CF_3	2.60/3.8[c]	−11.55	−7.50

[a] A negative ΔE_{iso} value indicates the substituted derivative to be less stable than the parent compound CH_3COOPh. [b] Reference 10, if not otherwise stated. [c] Determined in this work.

or leaving group destabilize the ester structure because of the decreased resonance stabilization. To verify this conclusion, we also performed isodesmic calculations. The effect of the group R (relative to R = CH_3) on the stability of RCOOPh (**4**) was evaluated by the pair of isodesmic reactions shown in Scheme 3. The results presented in

SCHEME 3
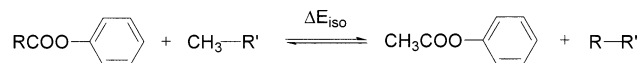
a: R′ = CH_3

b: R′ = $CH=CH_2$

R = CH_3CH_2, CH_3, $PhCH_2$, CH_3OCH_2, $PhOCH_2$, CH_2Cl, $CHCl_2$, CCl_3 or CF_3

terms of ΔE_{iso} in Table 4 (derived from the heat of formation values of the species in the isodesmic reactions) clearly show that *electron-withdrawing acyl substituents destabilize the ester*. The effect is the stronger the higher the polar substituent constant σ^* for the group R is. The only clearly deviating result is the negative ΔE_{iso} for R = CH_3CH_2, for which a value close to 0 is to be expected. Corresponding results are obtained by the both isodesmic reactions.

Similarly, to study the influence of the phenyl substituent X (relative to X = H) on the stabilities of ester series **1**−**3**, the pair of isodesmic reactions shown in Scheme 4 was used. For all three ester series unambigu-

SCHEME 4
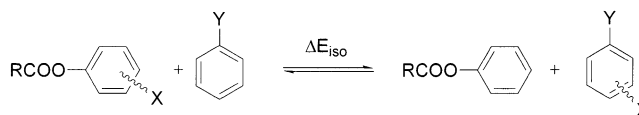
a: Y = CH_3

b: Y = OH

X = 4-OMe, 4-Me, H, 4-Br, 4-Cl, 4-CN, 4-NO_2, 3-Cl, 3-NO_2 or 2,4-diNO_2

ous results are obtained (Table 5). Electron-donating substituents stabilize the ester structure relative to the unsubstituted one, while *electron-withdrawing phenyl substituents clearly destabilize it*. Deviating values are only obtained for series **3** by the reaction with the 2,4-dinitrophenyl derivative and with X = 3-NO_2, shown in Scheme 4.

TABLE 5. Calculated Energies (ΔE_{Iso} in kcal mol^{-1}) of the Two Isodesmic Reactions Shown in Scheme 4 for RCOOAr (Series 1, R = CF$_3$; Series 2, R = CHCl$_2$; Series 3, R = CH$_3$)[a]

| | | ΔE_{iso} | | | | | |
| | | series **1** | | series **2** | | series **3** | |
Ar	σ^b	a	b	a	b	a	b
4-OMeC$_6$H$_4$	−0.27	0.15	0.80	0.04	0.69	−0.04	0.61
4-MeC$_6$H$_4$	−0.17	0.12	0.21	0.06	0.15	0.02	0.11
HC$_6$H$_4$	0	0	0	0	0	0	0
4-BrC$_6$H$_4$	0.23	−0.75	−0.73	−0.50	−0.48	−0.30	−0.28
4-ClC$_6$H$_4$	0.23	−0.60	−0.48	−0.41	−0.29	−0.27	−0.15
3-ClC$_6$H$_4$	0.37	−0.73	−0.59	−0.51	−0.37	−0.35	−0.21
4-CNC$_6$H$_4$	0.66	−1.44	−1.53	−0.92	−1.01	−0.51	−0.60
3-NO$_2$C$_6$H$_4$	0.71	−2.42	−1.28	−1.71	−0.57	−0.93	0.21
4-NO$_2$C$_6$H$_4$	0.78	−2.52	−3.13	−1.60	−2.21	−0.80	−1.41
2,4-(NO$_2$)$_2$C$_6$H$_3$		−3.73	−10.15	−1.03	−7.45	0.10	−6.32

[a] A negative value indicates the substituted derivative to be less stable than the parent compound (Ar = C$_6$H$_5$). [b] Reference 6.

In the case of both the acyl and leaving group substitutions of carboxylic acid esters, the isodesmic reaction energies support the concept derived on the basis of the spectroscopic and reactivity considerations. Electron-withdrawing substituents destabilize the ester molecule.

Related Compounds. Although our experimental study concerns only esters, the results and conclusions help to explain the behavior of other carbonyl compounds too. Bigi et al.[12] studied the complexation of acyl chlorides with AlCl$_3$ in CD$_2$Cl$_2$ and also the effect of substitution on reactivity in AlCl$_3$-catalyzed aromatic acylation. During the interaction of acyl chlorides with AlCl$_3$ (the carbonyl oxygen being involved in the metal coordination), the C=O bond is weakened, and the carbonyl carbon ^{13}C NMR chemical shifts are displaced downfield, while the carbonyl oxygen ^{17}O NMR chemical shifts are displaced upfield. Moreover, there is a linear correlation between $\Delta\delta$ ($\Delta\delta$ = the chemical shift difference between the complexed and the free acyl chloride) for the ^{13}C and ^{17}O chemical shifts when the group R in RCOCl varies in the order of CH$_3$, CH$_2$Cl, CHCl$_2$, and CCl$_3$. Upon increasing the electron-withdrawing substituents in R, a reduction in $\Delta\delta$ values was observed. This reflects a decreased degree of complexation when the electron-withdrawal by acyl substituents increases. In the same order, the reactivity of acyl chloride toward acylation *decreases*. This can be explained as follows.[3] While the halogen substituents can enhance the reactivity because of the decreased resonance stabilization (analogously with esters), they decrease the reactivity by the diminished complexation due to the decreased C=O bond polarization and consequently diminished basicity of the carbonyl oxygen toward the Lewis acid. The latter effect is dominating and chloro substituents decrease the reactivity. The present work supports this interpretation.

In a quite recent paper, Asao et al.[35] report that a 1:1 mixture of *p*-methylbenzaldehyde (**14**) and *p*-trifluoro-methylbenzaldehyde (**15**) with 1 equiv of allyltributyl-stannane give as the major product the alcohol derived from the trifluoromethyl derivative **15**, as expected, and only trace amounts of the alcohol derived from **14** are observed. However, in the Lewis acid BF$_3$·OEt$_2$-

mediated reaction, only 25% of the product was the derivative of **15** and 75% that of **14**, which was an unexpected result. Ab initio calculations showed that the basicity of the oxygen atom of acetaldehyde is higher than that of trifluoroacetaldehyde possessing the electron-withdrawing substituents, making the complexation with BF$_3$ easier in the former case. On the experimental level, the complexations of acetophenone (**16**) and trifluoro-acetophenone (**17**) were studied.[35] The carbonyl carbon
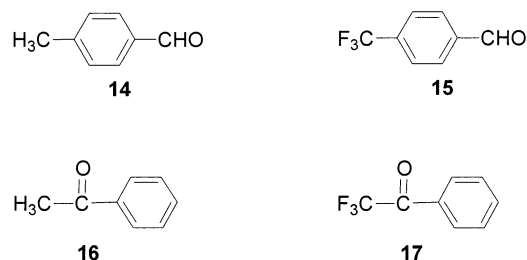
^{13}C NMR signals 197.94 and 179.59 ppm, respectively, were observed for the noncomplexed **16** and **17**. Analogously with our present results, the signal displaces upfield by the trifluoro substitution. The authors did not discuss this fact, but we attribute it to the decreased electrophilicity of **17**. Treatment of a 1:1 mixture of **16** and **17** with 1 equiv of BF$_3$·OEt$_2$ showed that no complexation of **17** with the Lewis acid occurred, while one with **16** was observed. The carbonyl carbon of the latter complex is deshielded, the ^{13}C NMR signal appearing at 214.65 ppm. It is seen that a carbonyl compound bearing an electron-withdrawing group does not form a Lewis acid complex easily. We conclude that the latter result is due to the decreased polarization of the carbonyl unit.

Conclusions

Electron-withdrawing substituents in the leaving group and especially those in the aliphatic acyl group of an ester increase the electron density at the carbonyl carbon, and at the same time the C=O bond order increases. Consequently, the electrophilicity of the carbonyl carbon decreases. Although *electron-withdrawing substituents decrease the electrophilicity of the carbonyl carbon*, ground-state destabilization of the reacting ester—due to the decreased resonance stabilization—can effectively contribute to the rate increase of nucleophilic acyl substitutions, because of the decrease in $\Delta G^{\ddagger}$ of the nucleophilic attack. Charge density, bond order, and isodesmic reaction energy calculations support the conclusions based on the spectroscopic data. The present experimental data concern carboxylic acid esters. However, the same idea offers an explanation, for instance, for the observations concerning the important Lewis acid-mediated electrophilic reactions of acyl chlorides and aldehydes.

Experimental Section

Materials. 1e,[27] **1g**,[27] **1h**,[27] **1i**,[27] **1j**,[27] **2a**,[4] **2b**,[3] **2c**,[3] **2d**,[3] **2e**,[4] **2f**,[3] **2g**,[28] **2h**,[3] **2i**,[4] **3e**,[4] **3g**,[29] **3i**,[4] and **3j**[29] were prepared as reported.

1a, bp 84−85 °C/10 mmHg (lit.[36] bp 150−160 °C); **1b**, bp 64−65 °C/10 mmHg (lit.[37] bp 88.5 °C/40 mmHg); **1c**, bp 37−

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38 °C/8 mmHg (lit.[36] bp 123 °C); **1d**, bp 80 °C/15 mmHg (lit.[36] bp 135−142 °C); and **1f**, bp 114−116 °C/15 mmHg, were prepared from trifluoroacetic anhydride and the appropriate phenol by slightly modifying the method of Sakakibara and Inukai.[36] Toluene was used as the solvent instead of benzene and the reaction mixture was heated on an oil bath at 80 °C for 5−8 h.

2j, mp 97−98 °C (from diethyl ether-petroleum ether, bp 40−60 °C); **3a**, mp 31−32 °C (lit.[38] mp 32−33 °C); **3b**, bp 98−99 °C/15 mmHg (lit.[38] bp 210−213 °C); **3d**, bp 120 °C/13 mmHg; **3f**, mp 54.5−55.5 °C (lit.[38] mp 56.7 °C); **3h**, bp 110 °C/16 mmHg (lit.[38] bp 101−103 °C/15 mmHg); and **6**, mp 92−93 °C (from hexane), were prepared from acetyl chloride and the appropriate phenol by a standard method in diethyl ether in the presence of pyridine. **3c**, bp 78−79 °C/14 mmHg (lit.[39] bp 72−74 °C/11 mmHg), was prepared from acetic anhydride and phenol by the method described by Chattaway.[40]

4a, bp 130−142 °C/60−67 mmHg (lit.[39] bp 82−83 °C/2 mmHg), was prepared from propionic acid and phenol in the presence of dicyclohexyl carbodiimide (DCC) in chloroform by following the general method described by Bruice et al.[41] **4b**, mp 38.9−39.3 °C (from hexane) (lit.[41] mp 39.5−40 °C), and **4d**, mp 55.0−55.7 °C (from diisopropyl ether) (lit.[41] mp 56.5−57.5 °C), were prepared from the appropriate carboxylic acid and phenol in diethyl ether in the presence of DCC and the catalyst 4-*N,N*-(dimethylamino)pyridine according to the general method described by Hassner and Alexanian[42] for the esterification of carboxylic acids. **4c**, bp 114−116 °C/8 mmHg (lit.[39] bp 127−128 °C/13 mmHg, lit.[41] bp 69−70 °C/1.1 mmHg) was prepared according to the method described by Bruice et al.[41] **4e**, mp 40.0−40.5 °C (from petroleum ether, bp 40−60 °C) (lit.[39] mp 40−41 °C), and **4f**, bp 122−127 °C/14 mmHg (lit.[43] bp 122 °C/14 mmHg), were prepared by a standard method

from the appropriate acyl chlorides and phenol in diethyl ether in the presence of pyridine.

Commercial methyl acetates **5a−f** were used as received.

Spectroscopic Measurements. The ¹³C NMR spectra (500 MHz) were recorded in CDCl₃ or DMSO-d_6 at 27 °C at a concentration of 0.1 mol dm⁻³. A low sample concentration was used to avoid any disturbances from intermolecular associations. The deuterium of the solvent was used as a lock signal. The spectra were measured with the ¹H broad-band decoupling technique. The chemical shifts are expressed in ppm relative to TMS used as an internal reference. The infrared spectra of the liquid samples were recorded for capillary films and those of solid samples for KBr disks or by a reflection method. The infrared spectra for the CH₂Cl₂ solutions were recorded using sealed cells with KBr windows. The concentration of the solutions was 0.1 mol dm⁻³ and the path length was 0.1 mm.

PM3 Calculations. The 3D structures of the compounds were composed by employing the program SYBYL[44] and the structures thus obtained optimized with the TRIPOS force field. The resulting conformations were used as starting structures for the semiempirical calculations of conformations, heats of formation, and atomic charges. These calculations were performed using the semiempirical quantum mechanical method PM3[45] of the program MOPAC 7.0.[46] All structures were optimized without any restriction. The quantum chemical calculations were processed on the SGI "Octane" (2 × R 12000) computer of the University of Potsdam.

Supporting Information Available: IR stretching frequencies for series **1−5** (Tables S1−S4), heat of formation values and C=O bond orders for series **1−4** (Tables S5 and S6), and information about the σ* constant. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020121C

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