Effects of α and γ Substituents on the Relative Reactivity of Pyrylium and Thiopyrylium Cations

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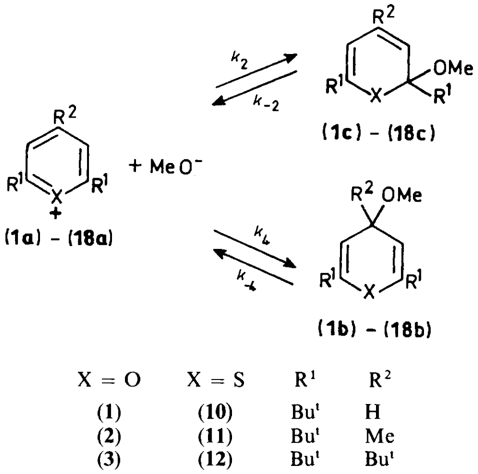
The rates of methoxide attachment to the γ position of nine pyrylium cations, symmetrically substituted at the α position with Ph and Bu^t, and at the γ position with H, Me, Bu^t, Ph, and OMe, have been compared with those of the corresponding thiopyrylium cations. The results suggest that the effect of the α substituent depends on the nature of the ring heteroatom. Steric inhibition to solvation of the ring heteroatom is taken into account to explain such features. By contrast the effect of the γ substituent, with the exception of the OMe group, is independent of the ring heteroatom. It is suggested that such invariance is only apparent due to the equality of the steric effect in the two series which tends to conceal small differences in sensitivity to electronic effects.

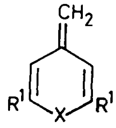
Pyrylium[1] and thiopyrylium[2] cations are highly electrophilic heterocycles of considerable practical and theoretical interest. There is only limited knowledge of their reactivity towards nucleophiles, especially from a quantitative and systematic standpoint.[3–6] This prompted us to investigate in considerable detail the reactions of these cations with a common nucleophilic system, *i.e.* methoxide ion in methanol. The results obtained so far have given valuable information not only about the ring heteroatom and substituent effects,[7,8] but also about some relevant mechanistic aspects of cation–anion combination reactions.[9]

In order to gain a deeper understanding of the effects of the α and γ substituents, we undertook a comparative study of the reactivity of the pyrylium series **(1a)**–**(9a)** and of the corresponding thiopyrylium series **(10a)**–**(18a)**. In general the reaction proceeds as illustrated in the Scheme, which shows the formation of both the 4*H* adducts **(1b)**–**(18b)** and the 2*H* adducts **(1c)**–**(18c)**. Many of the kinetic data were already available from our previous work [**(1a)**–**(4a)**,[8] **(5a)**,[10] **(8a)**,[11] **(9a)**,[11] **(13a)**,[9] **(14a)**,[11] **(16a)**–**(18a)**[11]]. Here we report a kinetic and thermodynamic study of the reaction of the cations **(6a)**, **(7a)**, **(10a)**–**(12a)**, and **(15a)**.



X = O	X = S	R¹	R²
(1)	**(10)**	Bu^t	H
(2)	**(11)**	Bu^t	Me
(3)	**(12)**	Bu^t	Bu^t
(4)	**(13)**	Bu^t	Ph
(5)	**(14)**	Ph	H
(6)	**(15)**	Ph	Me
(7)	**(16)**	Ph	Bu^t
(8)	**(17)**	Ph	Ph
(9)	**(18)**	Ph	OMe

Scheme.



(6d) X = O, R¹ = Ph
(11d) X = S, R¹ = Bu^t
(15d) X = S, R¹ = Ph

Results

The kinetic experiments were carried out in methanol at 25 °C, under pseudo-first-order conditions, by mixing the substrates with a large excess of sodium methoxide or Et_3N–Et_3NH^+ buffers depending on the reactivity of the substrate. In all the kinetic experiments carried out with Et_3N–Et_3NH^+ buffers there was no evidence of general acid–base buffer catalysis. Upon mixing, all the substrates completely disappeared. The relaxation time[12] of this process, τ_1, could be related to the reaction products by taking into account the results of a previously reported ^1H n.m.r. study of the reactions carried out at −40 °C under kinetically controlled conditions.[13] Under these conditions, the cation **(6a)** showed the simultaneous formation of the adducts **(6b)**, **(6c)** and of the anhydro base **(6d)**, therefore equation (1) holds, where the kinetic constant k_{anh} refers to the

$$1/\tau_1 = (k_2 + k_4 + k_{anh})[MeO^-] \qquad (1)$$

deprotonation of the γ methyl group to yield the anhydro base. The other cations showed only the formation of the corresponding adducts. All of the three possible patterns were observed, *i.e.*, exclusive formation of the 2*H* adduct in the case of the cation **(7a)**, exclusive formation of the 4*H* adduct in the case of the cations **(10a)** and **(11a)**, and simultaneous formation of both the adducts in the case of the cations **(12a)** and **(15a)**. These patterns are described by equations (2)–(4), respectively.

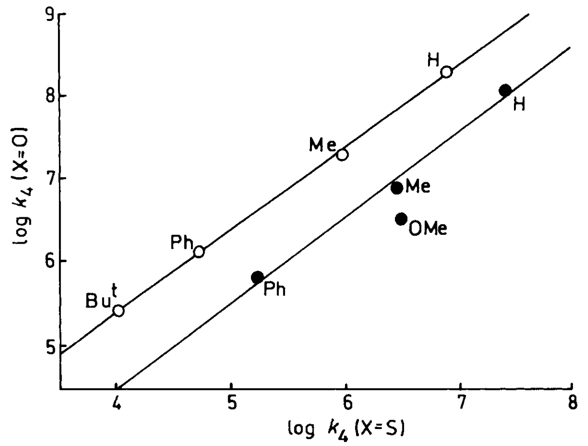


Figure 1. Plot of log k_4 of the pyrylium cations against log k_4 of the corresponding thiopyrylium cations. Open and filled circles refer to R^1 = Bu^t and R^1 = Ph, respectively. The R^2 substituents are indicated.

$$1/\tau_1 = k_2[\mathrm{MeO}^-] \quad (2)$$

$$1/\tau_1 = k_4[\mathrm{MeO}^-] \quad (3)$$

$$1/\tau_1 = (k_2 + k_4)[\mathrm{MeO}^-] \quad (4)$$

Note that equation (2) or (3) holds when $k_2 \gg k_4$ or $k_4 \gg k_2$, respectively.

All the reactions, except that of the cation (**7a**), showed slower equilibration processes widely separated from the first one. However, since we are mainly interested in the kinetic and thermodynamic parameters relative to the formation of the adducts, we investigated only the equilibration processes relative to the cations (**10a**) and (**12a**). This was because the ^{1}H n.m.r. study at 25 °C, under thermodynamically controlled conditions,[13] had shown that (**10a**) and (**12a**) yield, as final products, a mixture of both the corresponding adducts, whereas the cations (**6a**), (**11a**), and (**15a**) yield the anhydro bases (**6d**), (**11d**), and (**15d**), respectively.

The equilibration process between the 4*H* and 2*H* adducts, whose relaxation time[12] is shown by τ_2, occurs through the intermediacy of the substrate which is present in steady state concentration. Therefore the application of the steady-state approximation affords equation (5), where K_2 $(=k_2/k_{-2})$ and

$$1/\tau_2 = \frac{k_2 k_4}{k_2 + k_4}\left(\frac{1}{K_2} + \frac{1}{K_4}\right) \quad (5)$$

K_4 $(=k_4/k_{-4})$ are the equilibrium constants relative to the formation of the 2*H* and 4*H* adduct, respectively. In the case of the cation (**10a**), since $k_4 \gg k_2$ equation (5) reduces to equation (6).

$$1/\tau_2 = k_2\left(\frac{1}{K_2} + \frac{1}{K_4}\right) \quad (6)$$

The kinetic and equilibrium constants were evaluated as follows.

Cation (**6a**). A plot of $1/\tau_1$ *vs.* $[\mathrm{MeO}^-]$ afforded the term $k_2 + k_4 + k_{\mathrm{anh}}$ as slope. In order to estimate the individual constants we assumed that the molar ratios (**6b**)/(**6c**) $(=k_4/k_2)$ and (**6d**)/(**6c**) $(=k_{\mathrm{anh}}/k_2)$ obtained by n.m.r. at −40 °C[13] are independent of temperature in the range −40 to 25 °C. Although there is ample evidence that this assumption holds as far as k_4/k_2 is concerned,[8,11,13] the same cannot be said about k_{anh}/k_2. However, since this ratio is relatively small (0.24), a possible variation is not expected to affect the k_2 and k_4 constants significantly.

Table. Rate and equilibrium constants for the reactions of the indicated cations with methoxide ion in methanol at 25 °C.

Cation	k_4/ dm^3 mol^{-1} s^{-1}	K_4/ dm^3 mol^{-1}	$k_2{}^a$/ dm^3 mol^{-1} s^{-1}	$K_2{}^a$/ dm^3 mol^{-1}
(**6a**)[b]	7.5×10^6		6.8×10^6	
(**7a**)			7.1×10^6	3.7×10^9
(**10a**)	7.7×10^6	1.7×10^7	1.8×10^4	1.1×10^8
(**11a**)	9.6×10^5			
(**12a**)	1.1×10^4	7.3×10^5	6.5×10^3	6.1×10^6
(**15a**)	2.9×10^6		$\sim 6 \times 10^4$	

[a] Uncorrected for the statistical factor. [b] Estimated values, see the text. Estimated value of $k_{\mathrm{anh}} = 1.6 \times 10^6$ s^{-1} dm^3 mol^{-1}.

Cation (**7a**). According to equation (2) a plot of $1/\tau_1$ *vs.* $[\mathrm{MeO}^-]$ afforded k_2. The equilibrium constant K_2 was obtained spectrophotometrically using appropriate buffer solutions (see the Experimental section).

Cation (**10a**). The constant k_4 was obtained as slope of the plot $1/\tau_1$ *vs.* $[\mathrm{MeO}^-]$. The equilibrium constant K_4 could be obtained by stopped-flow absorbance measurements with proper buffer solutions (see Experimental section). The equilibrium constant K_2 was calculated by the ratio (**10b**)/(**10c**) $(=K_4/K_2)$ obtained by n.m.r. at 25 °C.[13] The constant k_2 was evaluated by equation (6).

Cation (**11a**). The constant k_4 was evaluated as for the cation (**10a**).

Cation (**12a**). The constants k_2 and k_4 were evaluated from the terms $k_2 + k_4$ and k_4/k_2. The former term was obtained as slope of the plot $1/\tau_1$ *vs.* $[\mathrm{MeO}^-]$ and the latter was assumed to be coincident with the isomer ratio (**12b**)/(**12c**) obtained by n.m.r. at −40 °C.[13] The constants K_2 and K_4 were evaluated by the isomer ratio (**12b**/(**12c**) $(=K_4/K_2)$ obtained by n.m.r. at 25 °C[13] and by equation (5).

Cation (**15a**). The constants k_2 and k_4 were evaluated as for the cation (**12a**).

The kinetic and equilibrium constants are reported in the Table.

Discussion

The two series (**1a**)–(**9a**) and (**10a**)–(**18a**) form an interesting collection of the most common pyrylium and thiopyrylium cations.[1,2] Consequently rates and equilibria of the reactions of (**1a**)–(**18a**) with methoxide ion in MeOH constitute a useful reference set, to be taken into account as a guide to future studies on the reactivity of the two heterocyclic systems with other nucleophiles.

Some aspects of the methoxide attachment reaction, such as electronic effects of γ aryl substituents on pyrylium[7] and thiopyrylium[9] cations, thermodynamics of the isomerization of pyrans and thiopyrans,[7] ipso substituent effects,[8,11] polar and steric effects of γ substituents on pyrylium cations,[8] have already been discussed. Here we want to focus the discussion on the effects of α and γ substituents on the relative reactivity of the two heterocyclic systems.

The log k_4 of the pyrylium series against the corresponding data of the thiopyrylium series are plotted in Figure 1. The point relative to the couple (**7a**), (**16a**) is not reported as the k_4 constant for the cation (**7a**) was not experimentally accessible. It is interesting to note that the points are distinctly distributed along two straight lines of nearly unit slope. Each line refers to one of the two α substitutents considered (R^1 = Bu^t:slope = 0.99, intercept = 1.43, r = 0.999; R^1 = Ph:slope = 1.03, inter-

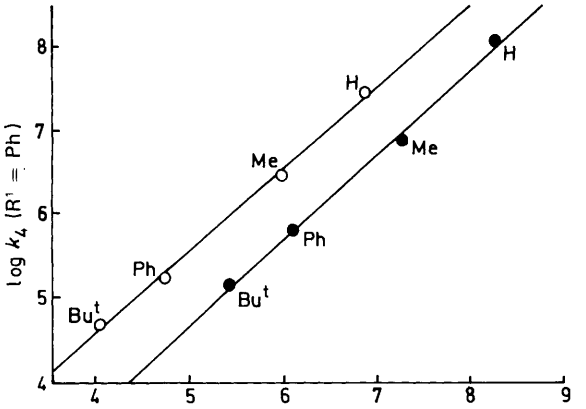


Figure 2. Plot of log k_4 of the 2,6-diphenyl-4-R^2 cations against the log k_4 of the corresponding 2,6-di-t-butyl-4-R^2 cations. Open and filled circles refer to X = S and X = O, respectively. The R^2 substituents are indicated.

cept = 0.34, r = 0.996). The point relative to the γ methoxy group [(**9a**),(**18a**)] shows a significant deviation from the 'α-phenyl' line and was not included in the correlation for reasons that will be made clear in the course of the discussion.

Since the k_4 constant for the cation (**16a**) is known, one can obtain by interpolation on the 'α-phenyl' line, the k_4 constant for the cation (**7a**). The value so obtained ($k_4 = 1.4 \times 10^5$ dm^3 mol^{-1} s^{-1}) is 50 times lower than the corresponding k_2 constant, and this would explain why the adduct (**7b**) escaped detection.

The two lines of unit slope in Figure 1 indicate that the effect of the γ substituent on k_4 is independent of the nature of the ring heteroatom, and that the relative reactivity of pyrylium and thiopyrylium, as measured by the intercepts, depends on the nature of the α substituents. In particular it can be seen that, although the k_4 constants referring to the pyrylium cations are always higher than those referring to the corresponding thiopyrylium ones, change of the α t-butyl groups with the α phenyl ones, causes a flattening of the relative reactivity of the two heterocyclic systems.

Furthermore, it can be noted that the points relative to a given couple of γ substituents are equidistant along the two lines. This implies that the effect of the γ substituent on k_4 is not only independent of the nature of the ring heteroatom, but also on the nature of the α substituents. This can be more clearly shown by plotting the log k_4 of the series formed by the 2,6-diphenyl-4-R^2 cations against the log k_4 of the corresponding 2,6-di-t-butyl-4-R^2 cations (Figure 2). In this plot the log k_4 of the cation (**7a**), estimated above, has also been included. Once again the points are distributed along two straight lines of nearly unit slope; one referring to the pyrylium cations (slope = 1.01, intercept = −0.37, r = 0.998) and the other to the thiopyrylium ones (slope = 0.97; intercept = 0.71; r = 0.999). Since the intercepts have different signs, the effect of t-butyl and phenyl as α substituents on k_4 is opposite in the two series, indeed Bu^t is more activating than Ph in the pyrylium series, but less activating in the thiopyrylium one. This calls for at least two mechanisms of charge stabilization by the α-substituents, of which at least one must depend on the nature of the ring heteroatom. We offer a tentative explanation which identifies the two mechanisms in the normal tendency of substituents to stabilize the positive charge in aromatic systems, and in the greater steric inhibition to solvation of the ring heteroatom offered by the α-t-butyl groups with respect to the α-phenyl ones. The latter factor should not be significant for the thiopyrylium cations, as sulphur, owing to its relatively large dimensions, can easily accommodate an electric charge without requiring extensive solvation and its size also makes it rather accessible to the solvent. Therefore, in the case of the thiopyrylium cations, the first factor, which is measured by the parameter σ_p^+, should prevail. Since the σ_p^+ of Bu^t is more negative than that of Ph (Bu^t −0.256; Ph −0.179),[14] the observed order of reactivity (2,6-diphenyl-4-R^2-thiopyrylium > 2,6-di-t-butyl-4-R^2-thiopyrylium) would be justified. Conversely, in the case of the pyrylium cations the effect of steric inhibition to solvation should prevail, which would make the α-t-butyl ions more reactive than the α-phenyl ones. The balance of these effects would explain not only the different intercepts in Figure 2, but also those in Figure 1. As to the effect of the γ substituents, the straight lines in Figure 1 suggest an equal sensitivity to their effects for the pyrylium and thiopyrylium series. The overall effect of the γ substituent has a steric component and an electronic one. As a consequence, the sensitivity to each component should be, respectively, the same for the two series. Although there is no reason to suspect a different sensitivity to the steric component, Hammett-type plots relative to the rates of methoxide attachment to the γ position of 2,6-di-t-butyl-4-aryl pyrylium (ρ 1.2)[7] and thiopyrylium (ρ 1.0)[9] cations, indicate that the sensitivity to the electronic component is not exactly the same. However, since the γ substituents considered, with the notable exception of the methoxy group, differ little in the electronic component but much in the steric one, the slightly different sensitivity to electronic effects in the two series passes unnoticed in the plots of Figure 1. In other words, the invariance of the effect of the γ substituents on changing the ring heteroatom is only apparent, being due to the equality of steric effects in the two series which tends to conceal small differences of sensitivity to electronic effects. By contrast, since the methoxy group is significantly more electron releasing than the other substituents, the higher sensitivity to electronic effects in the pyrylium series becomes apparent making the point relative to the methoxy group lie below the 'α-phenyl' line (see Figure 1).

Experimental

Materials.—Reagents and corresponding purification procedures have already been described.[8]

4-Methyl-2,6-diphenylpyrylium perchlorate (**6a**), 2,6-diphenyl-4-t-butylpyrylium perchlorate (**7a**), 2,6-di-t-butylthiopyrylium perchlorate (**10a**), 4-methyl-2,6-di-t-butylthiopyrylium tetrafluoroborate (**11a**), 2,4,6-tri-t-butylthiopyrylium perchlorate (**12a**), and 4-methyl-2,6-diphenylthiopyrylium perchlorate (**15a**) were available from previous work.[13]

Rate Measurements.—Kinetic experiments were carried out on a Durrum 110 stopped-flow spectrophotometer or on a Cary 219 spectrophotometer, at 25 °C, under pseudo-first-order conditions, with MeONa or Et_3N–Et_3NH^+ buffers in methanol. The methoxide ion concentration of each buffer was calculated from the pK_a value of Et_3N (10.88)[15] and from the methanol autoprotolysis constant (pK_{MeOH} 16.92).[16] Substrate concentrations were in the range 1–4 × 10^{-5} mol dm^{-3}. Ionic strength was below 5 × 10^{-3} mol dm^{-3} in all the experiments. The reaction solutions were freshly prepared and handled under argon. The reactions were monitored at the following wavelengths: (**6a**), 390 nm (τ_1); (**7a**), 390 nm (τ_1); (**10a**), 310 nm (τ_1), 300 nm (τ_2); (**11a**), 310 nm (τ_1); (**12a**), 310 nm (τ_1), 294 nm (τ_2); (**15a**), 410 nm (τ_1).

Equilibrium Measurements.—The equilibrium constant K_4 for the cation (**10a**) was determined at 25 °C on a Durrum 110 stopped-flow apparatus. The reaction was carried out at MeO$^-$ concentrations low enough to leave a detectable amount of the substrate in equilibrium with the 4*H* adduct at the end of the first process. The buffer used was Et_3N–Et_3NH^+. Measurements of the absorbance of the substrate at zero time (A_0) and at the end of the first process ($A_{\infty 1}$) afforded the equilibrium constant K_4 [equation (8)]. The equilibrium constant K_2 for

$$K_4 = \frac{(A_0 - A_{\infty 1})}{A_{\infty 1}[\mathrm{MeO}^-]} \qquad (8)$$

the cation (**7a**) was determined at 25 °C on a Cary 219 spectrophotometer by measuring the residual absorbance of the substrate (A_∞) after equilibration with $ClCH_2CO_2H$–$ClCH_2CO_2^-$ buffers (pK_a 7.7).[17] The addition of an excess of methanolic $HClO_4$ to these mixtures shifts the equilibrium completely towards the substrate, thus permitting the measurement of A_0, after correction of the observed A value for dilution. The K_2 value was obtained by equation (9).

$$K_2 = \frac{(A_0 - A_\infty)}{A_\infty[\mathrm{MeO}^-]} \qquad (9)$$

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