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Nucleophilic substitution in ionizable Fischer thiocarbene complexes: steric effect of the alkyl substituent on the heteroatom†

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A detailed kinetic study has been carried out for the aminolysis of ionizable Fischer thiocarbene complexes $(CO)_5M{=}C(SR)CH_3$ (M = Cr, W; R = iPr, *n*Bu, *c*Hex, *t*Bu) with five primary amines and one secondary amine in aqueous acetonitrile solutions (50% MeCN–50% water (v/v)). The observed rate constants for the reaction with primary amines showed a first-order dependence on the amine concentration, while with morpholine, the rate constant has second-order dependence. The general base catalysis process was confirmed by the variation of the rate constants with the concentration of an external catalyst and the pH. The results agree with a stepwise mechanism where the nucleophilic addition to the carbene carbon to produce a tetrahedral intermediate ($\mathbf{T}^{\pm}$) is the first step, followed by a rapid deprotonation of $\mathbf{T}^{\pm}$ to form the anion $\mathbf{T}^{-}$ which leads to the products by general-acid catalysed leaving group (–SR) expulsion. In general, it was found that the chromium complexes are less reactive than the tungsten analogues. The obtained Brønsted parameters for the nucleophilic addition (β_{nuc}) indicate that C–N bond formation has made little progress at the transition state. By using Charton's correlation, the role that the steric factor plays throughout the mechanism has been unraveled. The nucleophilic addition to the thiocarbenes is less sensitive to steric effects than the alkoxycarbenes regardless of the nature of the metal centre. Conversely, the steric effects on the general-base catalysis can be strong depending on the volume of the catalyst and the metal centre. On the basis of the structure–reactivity coefficients β and ψ and comparison with alkoxycarbene complexes, esters and thiolesters, insights into the main factors ruling the reactivity in terms of transition state imbalances are discussed.

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1. Introduction

Group 6 Fischer carbene complexes are invaluable organometallic building blocks for organic synthesis.[1] Due to their multifunctional structure, many recent investigations have aimed at developing efficient diastereoselective multicomponent sequential coupling reactions where these compounds are involved.[2] In most of these reactions, the key lies in the pronounced electron deficiency of the carbene carbon atom since nucleophilic attachments trigger further transformations.[3]

Interestingly, nucleophilic substitution reactions are also an easy way to exchange the π-donor heteroatom linked to the carbene carbon, providing an efficient method to tune both the reactivity and the stability of these complexes.[4] Among the examples regarding the reactivity patterns, the well-known Dötz reaction is one of the most attractive since when amino groups are used instead of alkoxy groups the cyclopentannulation reaction is favoured over the benzannulation reaction.[5] In addition, Aumann and co-workers have recently reported that alkoxy- and thiocarbene complexes afford different types of products on the reaction with imidoyl derivatives.[6] The experimental and theoretical characterizations carried out so far have shown a great variety of electrochemical and photophysical properties and how they are influenced by the substituents on the carbene moiety.[7] For instance, the synthesis and photophysical characterization of novel BODIPY-Fischer alkoxy-, thio- and aminocarbene complexes have been recently reported,[8] and it has been proved that the

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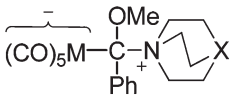
corresponding absorption and emission spectra sharply depend on the nature of the π-donor heteroatom. Furthermore, it has been suggested that transition metal-carbonyl complexes are attractive CO-release molecules with the same biological effects as gaseous CO in a number of applications.[9] Thus, different substitutions offer considerable potential for modulating CO-release rates, *i.e.*, rapid CO-release is observed in the case of sulphur- and oxygen-stabilized carbenes, whereas in the case of amino-substituted carbenes, release is far more sluggish.

The differences in the properties of Fischer carbenes have been ascribed to the π-donor substituent strength. A landmark study has been reported by Wang *et al.*, who suggested that the π-bond character of the metal–carbene bond can be represented as a four-electron three-centre bond.[10] Furthermore, theoretical studies have agreed that stronger π-donor heteroatoms attached to the carbene carbon lead to lower electrophilicity as well as weaker M–C_{carb} bonds and stronger M–CO_{trans} bonds.[11] For this reason, the aminolysis reactions have been regarded as one of the most extensively used transformations because of the relative simplicity of the reaction, the increased stability of the products formed and the ease of subsequent metal moiety removal.[12] This methodology has been widely used for synthesizing amino acids, amides and thioamides with structures that cannot be accessed by conventional strategies.[13] Some other applications include protein labelling of amino groups,[14] PEGylation of proteins,[15] immobilization of the proteins and amines on glass and silicon surfaces[16] and detection methods for proteins.[17]

Despite the extensive studies undertaken to develop synthetic strategies, no comparable effort has been made to clearly understand the effects of the substituent on the π-donor group in the reaction mechanism. About twenty years ago, Bernasconi reported a comprehensive kinetic study of the reaction of Fischer methoxy carbene complexes in aqueous acetonitrile solution with amines, and the detailed mechanism proposed is shown in Scheme 1.[18] This mechanism was then extended to the corresponding thiomethoxy analogues.[19]

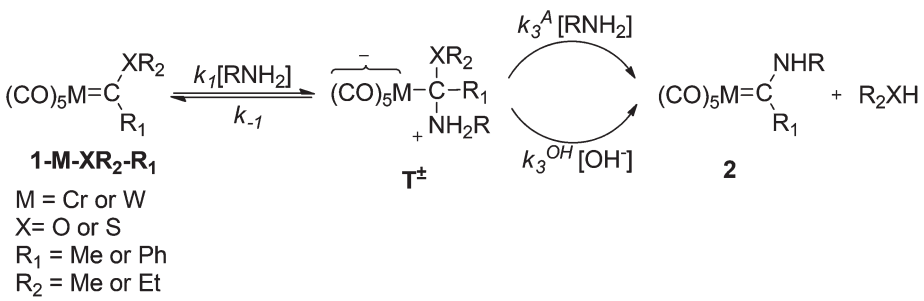
It has been demonstrated that the reaction proceeds in a stepwise fashion with the formation of a tetrahedral zwitterionic intermediate, $T^{\pm}$, in analogy to the aminolysis of carboxylic esters.[12,18,20] Although no intermediate is detectable in the aminolysis of Fischer carbene complexes, evidence has come from the direct detection of the intermediate in the reaction of **1-Cr-OMe-Ph** with thiolate ions in aqueous acetonitrile and the demonstration that the observed intermediate is indeed on the reaction coordinate.[21] Additional support to this mechanism has been given by the early isolation of adducts such as **3** from ether solutions of **1-Cr-OMe-Ph** and DABCO or quinuclidine[22] and its latest kinetic study.[23]



3 X = N or CH
M = Cr or W

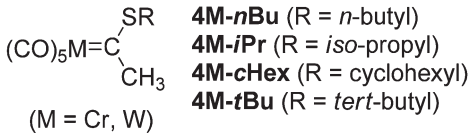
In a recent computational study performed by some of us, the ammonolysis of Fischer alkoxy- and thiocarbene complexes has been addressed.[24] Remarkably, all the calculations led to the conclusion that the most favourable reaction pathway involves a zwitterionic intermediate; this has been attributed to the high stabilization of the negative charge on the metal moiety in $T^{\pm}$. A thorough mechanistic study on the aminolysis by Bernasconi *et al.* provided further information. These reactions were shown to undergo a specific base-general acid catalysis. This means that the reaction involves an additional step that converts the initially formed zwitterionic intermediate into its anionic form before it breaks down to products. This three-step mechanism has generated particular interest because of possible changes in the rate-limiting steps with changing reaction conditions as well as structural features.[18,19,23,25] All the kinetic studies carried out so far have mainly focused on the electronic effects and how they are changed by the π-donor heteroatom nature. But, surprisingly, no systematic study has taken care of the steric effect on the aminolysis reactions.

Some years ago, we initiated a programme aimed at studying some reactions in which the carbene complexes are involved, with an emphasis on the exploration of the steric effect in proton transfer reactions and nucleophilic substitutions.[11d,24,26] We have been inspired by the increasing number of asymmetric synthesis studies with the application of the linear free energy relationships (LFERs) – concerning steric effects – to elucidate the interactions responsible for the asymmetric inductions and hence provide a platform for improving



Scheme 1 General mechanism for the aminolysis reaction of Fischer carbene complexes.

the enantio- and diastereo-selectivity performances.[27] We are aware that Fischer carbene complexes can induce such kinds of reactions by the modification of their structures, and the aminolysis reactions play a crucial role in most of them.[28] Herein, by means of classical kinetic tools, we have performed a detailed study to establish how the size of the alkyl group attached to the π-donor sulphur substituent may affect the reactivity and the aminolysis mechanism. To this end, we have explored the nucleophilic substitution for a series of Fischer thiocarbene complexes **4M-R** (R = *n*-butyl, iso-propyl, cyclohexyl, *tert*-butyl) with several amines in 50% MeCN–50% water (v/v) at 25 °C. We found that the steric effects not only affect the addition of the nucleophile to form zwitterionic intermediate $\mathbf{T}^{\pm}$, but also influence the base catalysed decomposition of it.



4M-R Fischer carbene complexes studied.

2. Results

2.1 General procedures

All the experiments of the reactions between the complexes **4M-R** and *n*-butylamine, methoxyethylamine, benzylamine, furfuryl amine, glycine ethyl ester and morpholine were performed in 50% MeCN–50% water at 25 °C. The kinetic runs were conducted under pseudo-first-order conditions with the carbene complexes as the minor component.

Fig. 1, which is representative, shows time-resolved spectra for the reaction of morpholine with **4Cr-*c*Hex**. It shows a blue shift in the UV-visible spectrum due to the conversion of the thiocarbene complex into the corresponding aminocarbene. These spectral changes are similar to those reported in the reactions of **1-M-XR$_2$-R$_1$** (Scheme 1) with primary and secondary amines to form the amino substituted derivatives.[18,19,23,25] The identity of the products was confirmed by comparison of the spectrum of the solution after completion of each reaction with that of the corresponding aminocarbene complex synthesized independently.

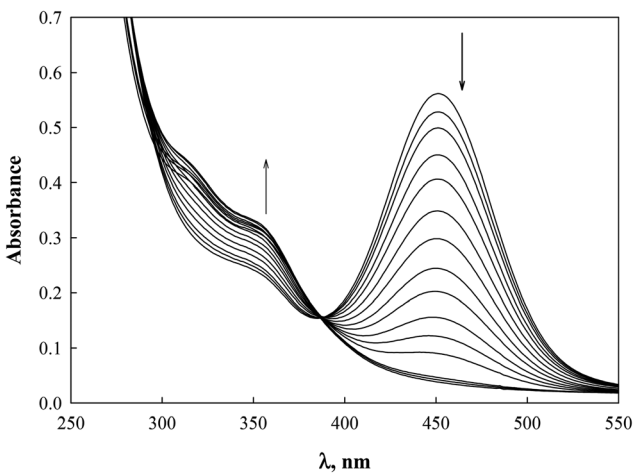


Fig. 1 Time resolved spectra for the reaction of **4Cr-*c*Hex** with morpholine in 50% MeCN–50% water at pH 8.70, 25° C, ionic strength = 0.1 M (KCl), $[\mathbf{4Cr\text{-}cHex}]_0 = 1.0 \times 10^{-4}$ M and $[\text{Morph}]_f = 0.02$ M. The first spectrum was taken immediately after mixing. The time lapse between the first and the last spectra is 10 min.

The reactions were monitored by following the reactants' vanishing ($\lambda_{max} \approx 450$ nm and 435 nm for the complexes of Cr and W, respectively) and the products' formation ($\lambda_{max} \approx 355$ and 335 nm for the complexes of Cr and W, respectively). Both rate constants led to the same values within the experimental error, indicating that no accumulation of any intermediates is taking place throughout the reactions. It is important to mention that when the kinetic trace is followed at the wavelength of maximum absorption for the reactant, two kinetic processes can be observed (Fig. S1†). The fastest one has already been assigned to the proton transfer reaction,[26c,d] and the slowest one corresponds to the nucleophilic reaction. The pseudo-first-order rate constants of the second process (k_{obs}) were calculated from the exponential equation $A_\infty - A_t = (A_\infty - A_o)\exp(-k_{obs}t)$. All the k_{obs} values obtained in this way are summarized in the ESI (Tables S2–S42†).

Two kinds of kinetic experiments were carried out; some experiments were carried out at constant pH values and different amine concentrations while in others the concentration of the amine was kept constant and the OH^- or the external buffer tertiary amine (triethyl amine, TEA) concentrations were varied.

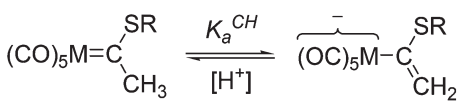
2.2 Reactions with primary amines

The nucleophilic reactions of the Fischer thiocarbenes **4W-R** were studied with five primary amines: *n*-butylamine, benzylamine, 2-methoxyethylamine, furfurylamine and glycine ethyl ester. The reactions of carbene **4Cr-R** were studied with three primary amines, namely, *n*-butylamine, benzylamine and furfurylamine.

All the reactions of tungsten derivatives showed strictly second-order kinetics, *i.e.*, first-order with respect to carbene concentration and first-order with respect to amine concentration. Competing hydrolysis of the carbenes was negligible and hence the observed pseudo-first-order rate constant (k_{obs}) is given by eqn (1) where k_A is the second-order rate constant.

$$k_{obs} = k_A[RNH_2] \quad (1)$$

The carbene complexes **4M-R**, under the conditions employed, are deprotonated (Scheme 2)[26c,d] and the anion



Scheme 2 Acid–base equilibrium for ionizable Fischer carbene complexes.

formed does not react with the amine nucleophiles,[12] and therefore the observed rate constant must be corrected as in eqn (2).

$$k_{\text{obs-corr}} = k_{\text{obs}}\left[\frac{[\text{H}^+] + K_a^{\text{CH}}}{[\text{H}^+]}\right] = k_{\text{A-corr}}[\text{RNH}_2] \qquad (2)$$

The K_a^{CH} values used here for **4M-R** are those reported previously.[26c,d] Fig. 2 shows the plots of $k_{\text{obs-corr}}$ *vs.* $[\text{RNH}_2]$ for the complex **4W-*t*Bu** with different amines at pH = pK_a^{AH} (pK_a of the conjugated acid of the amine). The slope values ($k_{\text{A-corr}}$) obtained are shown in Table 1.

The complexes **4Cr-R** showed a different behaviour depending on the basicity of the amine. For *n*-butylamine a similar behaviour to that previously observed with **4W-R** was displayed (Fig. 2), whereas for furfurylamine and benzylamine, a curvilinear dependence of the observed second-order rate constant ($k_{\text{A-corr}}$) on the amine concentration was observed (Fig. S2†).

2.3 Reactions with morpholine

For all the reactions of carbenes **4M-R** with morpholine, the plots of $k_{\text{obs-corr}}$ *vs.* [Morph] exhibited an upward curvature giving hints of an observable general base catalysis (Fig. S3†). All the plots have a negligible intercept within the experimental errors. This is reminiscent of what has been reported for the reactions of alkoxycarbene complexes with primary and secondary amines as well as for some thiocarbene analogues with morpholine.[18,25a,c,d] The observed second-order rate constants ($k_{\text{A-corr}}$) showed linear dependence with the amine concentration (Fig. 3 is representative).

In order to test the general base catalysis of these reactions, two different experiments were carried out. Firstly, the concentration of an external catalyst (TEA) was varied in the range of

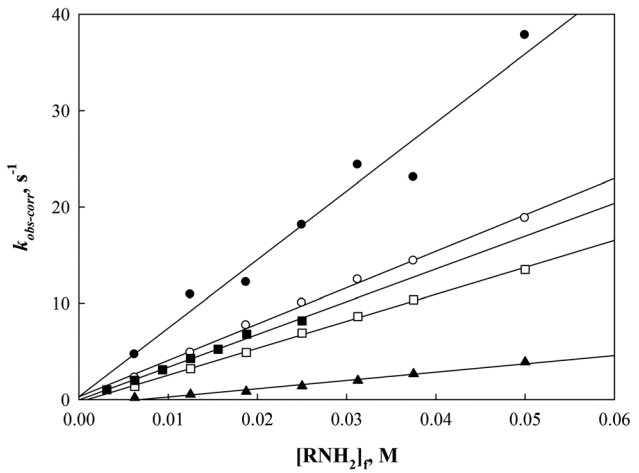


Fig. 2 Plot of $k_{\text{obs-corr}}$ *vs.* $[\text{RNH}_2]_f$ for the reaction of **4W-*t*Bu** in 50% MeCN–50% water with: (●) *n*-butylamine, pH = 10.4; (○) benzylamine, pH = 9.12; (■) methoxyethylamine, pH = 9.39; (□) furfurylamine, pH = 8.58; (▲) glycine ethyl ester, pH = 7.43, ionic strength = 0.1 M (KCl), 25 °C.

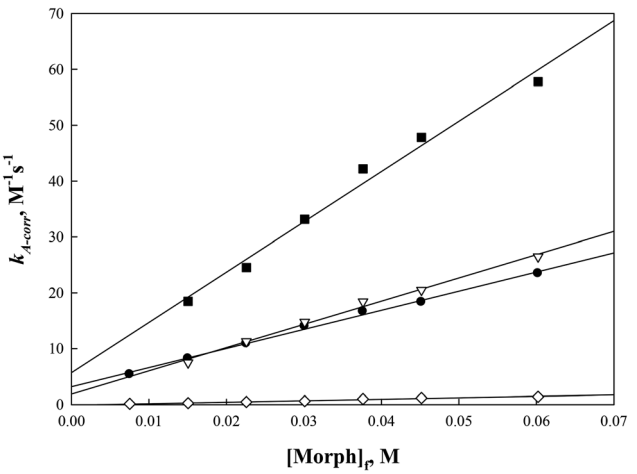


Fig. 3 Plots of $k_{\text{A-corr}}$ *vs.* $[\text{Morph}]_f$ for the reaction of morpholine with (■) **4W-*n*Bu**, (▽) **4W-*c*Hex**, (●) **4W-iPr** and (◊) **4Cr-*c*Hex** in 50% MeCN–50% water at pH = 8.88, ionic strength = 0.1 M (KCl), 25 °C.

Table 1 Second order rate constants (k_1, $M^{-1}\,s^{-1}$) for the reactions of **4M-R** with primary amines[a]

	4Cr-R				
Amine	pK_a^{AH}	*n*Bu	iPr	*c*Hex	*t*Bu
n-Butylamine	10.40	231 ± 5	209 ± 5	200 ± 6	124 ± 4
Benzylamine[b]	9.12	191 ± 5	140 ± 4	176 ± 6	103 ± 2
Furfurylamine[b]	8.58	122 ± 5	90 ± 5	98 ± 3	71 ± 6
	4W-R				
	pK_a^{AH}	*n*Bu	iPr	*c*Hex	*t*Bu
n-Butylamine	10.40			781 ± 70	711 ± 60
2-Methoxyethylamine	9.39	549 ± 35	429 ± 25	534 ± 13	340 ± 13
Benzylamine	9.12	715 ± 15	440 ± 12	524 ± 9	377 ± 9
Furfurylamine	8.58	364 ± 9	288 ± 8		279 ± 5
Glycine ethyl ester	7.43	220 ± 40	96 ± 3	148 ± 26	86 ± 5

[a] 50% MeCN–50% water as the solvent, ionic strength = 0.1 M (KCl), 25 °C. [b] The value of the rate constant reported corresponds to the value observed at the levelling off of the plot of $k_{\text{A-corr}}$ *vs.* amine concentration (see the main text).

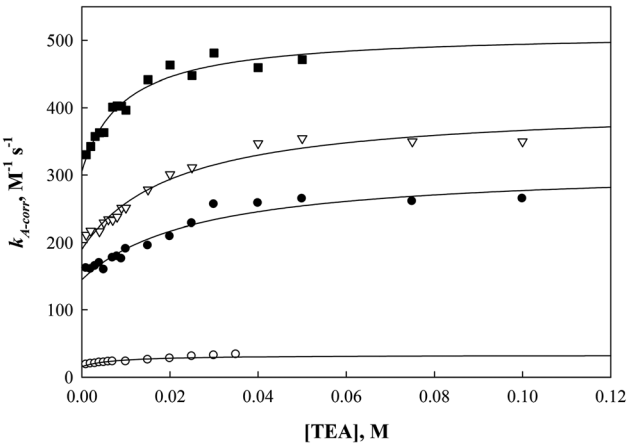


Fig. 4 Plot of $k_{A\text{-}corr}$ *vs.* $[TEA]_f$ for the reaction of morpholine with **4M-R** in 50% MeCN–50% water; (■) **4W-*n*Bu**, (▽) **4W-*c*Hex**, (●) **4W-iPr** and (○) **4Cr-*c*Hex**. Conditions: $[4M\text{-}R]_0 = 1.0 \times 10^{-4}$ M, $[Morph]_f$ = 0.01 M for **4W-R** and 0.02 M for **4Cr-*c*Hex**, pH = 10.78, ionic strength = 0.1 M (KCl), 25 °C.

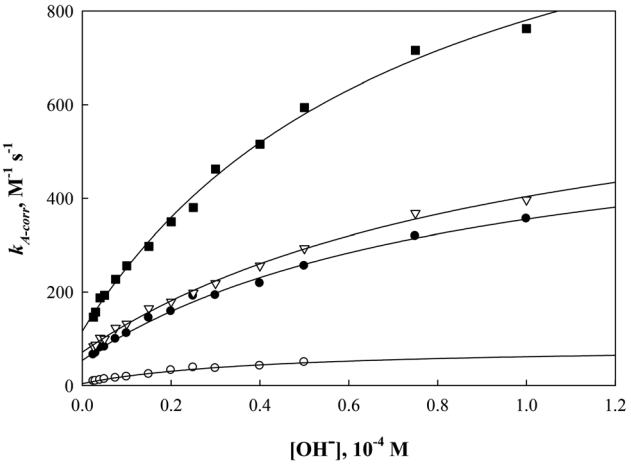


Fig. 5 Plot of $k_{A\text{-}corr}$ *vs.* $[OH^-]$ for the reaction of morpholine with **4M-R** in 50% MeCN–50% water; (■) **4W-*n*Bu**, (▽) **4W-*c*Hex**, (●) **4W-iPr** and (○) **4Cr-*c*Hex**. Conditions: $[4M\text{-}R]_0 = 1.0 \times 10^{-4}$ M, $[Morph]_f$ = 0.01 or 0.02 M, $[TEA]_f$ = 0.01 M, ionic strength = 0.1 M (KCl), 25 °C.

0.01–0.10 M at pH 10.78 and $[Morph]_f$ = 0.01 M and 0.02 M for the **4W-R** and **4Cr-R** series, respectively. Secondly, a variation of the pH from 8.18 to 11.18 at constant [TEA] = 0.01 M and $[Morph]_f$ = 0.01 M was performed. Fig. 4 shows some representative plots of $k_{A\text{-}corr}$ *vs.* $[TEA]_f$ at constant pH while Fig. 5 shows some representative plots of $k_{A\text{-}corr}$ *vs.* $[OH^-]$ at constant buffer concentration.

3. Discussion

This section is divided as follows: in section 3.1 the general mechanism and the nature of the base catalysis are discussed and in section 3.2 the structure–reactivity relationships are addressed.

3.1 Mechanism

3.1.1 Analysis of the data. As aforementioned, all the studies carried out so far on the mechanism of aminolysis of carbene complexes are consistent with the frame displayed in Scheme 1.[18,19,25] There is no reason to believe that any other mechanism is occurring herein. Our findings suggest the occurrence of a stepwise mechanism under the conditions employed. The experiments carried out with morpholine as the nucleophile and an external buffer resulted in a leveling off for the second-order rate constants (Fig. 4). This result points out the operation of at least two steps and the presence of at least one intermediate. Indeed, the existence of the general base catalysis was demonstrated.

The presence of an isosbestic point (Fig. 1) implies that the transformation into products is quite clean. The fact that the values of the rate constants measured at the reactant and product wavelengths are equal within experimental errors indicates that no accumulation of an intermediate to detectable levels is taking place. The expression for $k_{A\text{-}corr}$ is given by eqn (3) which can be easily derived considering steady state conditions (see Scheme 1).

$$k_{A\text{-}corr} = \frac{k_{obs-corr}}{[RNH_2]} = \frac{k_1\left(k_3^A[RNH_2] + k_3^{OH}[OH^-]\right)}{k_{-1} + k_3^A[RNH_2] + k_3^{OH}[OH^-]} = \frac{k_1\left(\left(k_3^A/k_{-1}\right)[RNH_2] + \left(k_3^{OH}/k_{-1}\right)[OH^-]\right)}{1 + \left(k_3^A/k_{-1}\right)[RNH_2] + \left(k_3^{OH}/k_{-1}\right)[OH^-]} \quad (3)$$

Two limiting situations can be extracted from this equation in order to explain the observed kinetic behaviours. On the one hand, when the nucleophilic attack of the amine, to form $T^{\pm}$, is the rate limiting step, the relationship in eqn (4) holds, giving $k_{A\text{-}corr} = k_1$. This situation applies to the reactions of complexes **4W-R** with primary amines (Fig. 2) and the reaction of **4Cr-R** with *n*-butylamine. On the other hand, when the base catalysed process is the slowest step of the mechanism, eqn (5) and (6) hold.

$$\left(k_3^A/k_{-1}\right)[RNH_2] + \left(k_3^{OH}/k_{-1}\right)[OH^-] > 1 \quad (4)$$

$$\left(k_3^A/k_{-1}\right)[RNH_2] + \left(k_3^{OH}/k_{-1}\right)[OH^-] \ll 1 \quad (5)$$

$$k_{A\text{-}corr} = k_1\left(\left(k_3^A/k_{-1}\right)[RNH_2] + \left(k_3^{OH}/k_{-1}\right)[OH^-]\right) \quad (6)$$

The latter situation is truly applicable to the reaction rates of **4M-R** with morpholine at low catalyst concentration (Fig. 3) and also to the reactions of **4Cr-R** with furfurylamine and benzylamine. Depending on the relative values of the different rate constants of each individual step, in some cases, it is possible to have both situations within the range of concentrations used. This allows the determination of the k_1 values as well as the rate constant ratios k_3^A/k_{-1} and k_3^{OH}/k_{-1}. This turns out to be the case for the reactions of morpholine (see Fig. 4 and 5) and by fitting the kinetic data to eqn (3) the rate constants summarized in Table 2 were calculated. In all cases, the values of k_3^{TEA}/k_{-1} informed were calculated from the data of $k_{A\text{-}corr}$ *vs.* [TEA] at constant pH (Fig. 4) and the values of k_3^{OH}/k_{-1} from the dependence of $k_{A\text{-}corr}$ *vs.* $[OH^-]$ concentration at constant

Table 2 Calculated rate constants for the reactions of **4M-R** with morpholine in 50% MeCN–50% water at 25 °C[a]

4M-R	k_1[b] (M^{-1} s^{-1})	k_3^{morph}/k_{-1} (M^{-1})	k_3^{TEA}/k_{-1} (M^{-1})	k_3^{OH}/k_{-1} ($\times 10^3$ M^{-1})	k_3^{OH}/k_3^{morph}	k_3^{OH}/k_3^{TEA}
4W-Me[c]	883 ± 5	1.22 ± 0.01	386 ± 42	34 ± 3	2.78 × 104	87.7
4W-*n*Bu	548 ± 16	1.64 ± 0.09	261 ± 30	14 ± 2	0.85 × 104	53.6
4W-*c*Hex	413 ± 15	1.01 ± 0.08	89 ± 5	11 ± 1	1.09 × 104	123.6
4W-iPr	365 ± 21	0.94 ± 0.09	71 ± 5	12 ± 2	1.28 × 104	169.0
4Cr-Me[c]	62.7 ± 0.9	1.25 ± 0.01	228 ± 31	39 ± 3	3.08 × 104	169.0
4Cr-*c*Hex	33 ± 2	0.8 ± 0.1	23.5 ± 0.2	25 ± 7	2.13 × 104	1063

[a] Ionic strength = 0.1 M (KCl). [b] Data calculated from the variation of the rate constant with TEA. [c] Data taken from ref. 25*d*.

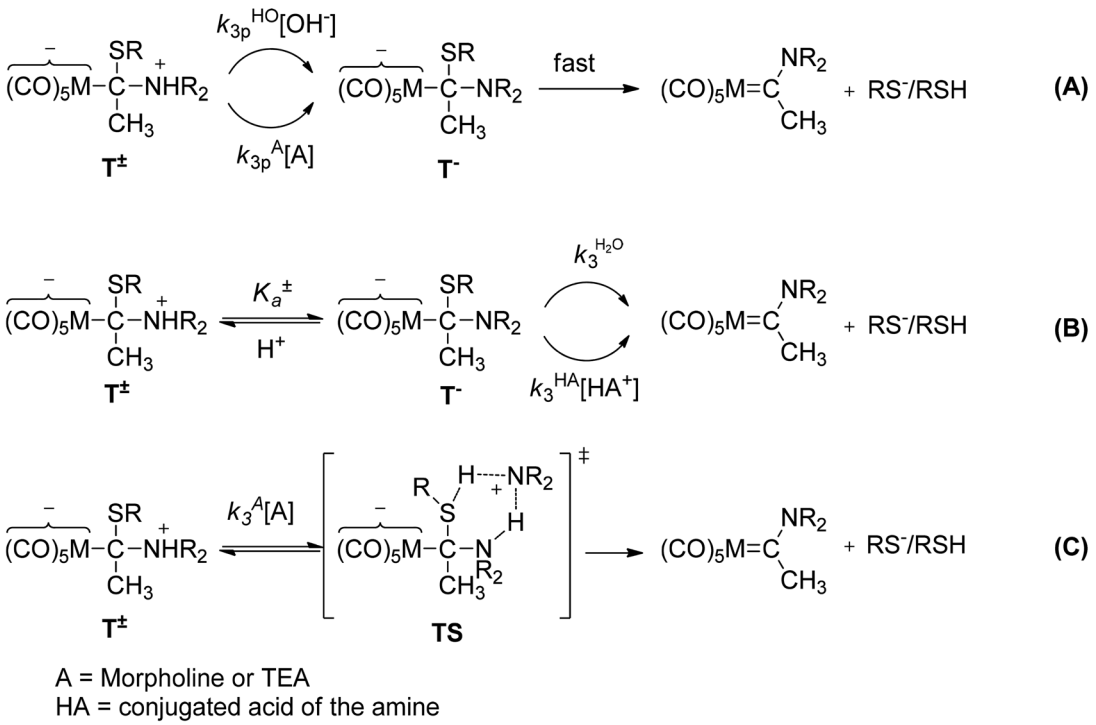
amine concentration (Fig. 5). On the other hand, the data for the catalysis by TEA were used to calculate k_1 since under these conditions the leveling off of the curve is fully reached.

Although the reactions of benzylamine and furfurylamine with **4Cr-*n*Bu** showed a curvilinear behaviour (see Fig. 2), the leveling off occurs at a relatively low amine concentration and therefore the calculation of the rate constants for the catalysed step was not possible because only a few points can be measured before the rate becomes independent of the base concentration.

3.1.2 General base catalysis. The nature of the general base catalysis has been discussed in detail elsewhere.[12,18,25a] However, it is noteworthy to briefly mention the main findings and how they fit to our system. There are three possible mechanisms for the general base catalysis pathways which are depicted in Scheme 3.

The mechanism **A** represents the situation where the deprotonation of the zwitterionic intermediate $\mathbf{T}^{\pm}$ is the rate-limiting step. Such a condition is typically observed in the aminolysis of carboxylic esters and thiolesters[29] and in some S_NAr reactions.[30] On the other hand, the mechanism **B** consists of a fast acid–base equilibrium, between $\mathbf{T}^{\pm}$ and $\mathbf{T}^{-}$, followed by the general-acid catalysed leaving group departure. This late sequence is known as specific-base general-acid catalysis[31] and is normally observed for strongly activated vinylic compounds such as β-methoxy-α-nitrosostilbene compounds.[32] Finally, the mechanism **C** takes into account the bifunctional character of some catalysts to accept and to donate a proton. This concerted mechanism have been proposed for reactions in organic solvents.[33] Besides, in recent computational results, **C** was suggested as the most favourable mechanism for the departure of the leaving group.[24]

The concerted mechanism described in **C** can be easily ruled out considering the experiments where TEA was used as an external buffer. Cleary, this tertiary amine cannot participate in a mechanism like **C** due to its inability to donate and accept a proton at the same time. The observation of an enhancement in the rates when the concentration of the TEA



Scheme 3 Three different mechanisms of the general base catalysed step within the aminolysis reaction.

is at least 10 times smaller than that of morpholine suggests that another mechanism is operating. Critical inspection of the values in Table 2 reveals that k_3^{TEA}/k_{-1} ratios are about two orders of magnitude higher than k_3^{morph}/k_{-1}. This leads to higher k_3^{OH}/k_3^{morph} (pK_a^{AH} = 8.70 in 50% MeCN–50% water) values than k_3^{OH}/k_3^{TEA} (pK_a^{AH} = 10.78 in 50% MeCN–50% water) for all the complexes. Indeed, these values are much higher than those reported in the literature for the reaction proceeding by pathway **A**. Normal values are within the range of 1–25 and they should be independent of the amine used.[34] Therefore, the high k_3^{OH}/k_3^{A} ratio is considered to be a common feature for the aminolysis reaction that proceeds through the **B** pathway.[12] This strong increase in the k_3^{OH}/k_3^{A} ratio with decreasing the basicity of the amine has already been explained by Bernasconi and co-workers.[18]

3.2 Structure–reactivity relationships

3.2.1 Nucleophilic attack (k_1) by primary amines

3.2.1.1 Brønsted plots. From the comparison of both series of metal carbene complexes (**4Cr-R** and **4W-R**, refer to the data in Table 1), it can be seen that the nucleophilic addition to the tungsten complexes is slightly more favoured than that to chromium complexes. The largest ratio k_1(**4W-R**)/k_1(**4Cr-R**) is 5.7 for **4M-*t*Bu** with *n*-butylamine while the lowest ratio is 2.9 for **4M-*n*Bu** with furfurylamine. Similar values for k_1 ratios have been reported for **4M-Me** with less basic amines.[25e] These results fall in the range of the previously reported differences for chromium and tungsten complexes reacting with other nucleophiles.[21,23,25d,f,35] The higher rate constant for W complexes in the nucleophilic attachment has been ascribed to the difference in the electronegativity. Since W is more electronegative than Cr,[36] the stabilization of the incipient negative charge on the transition state is higher, leading to an enhanced reactivity. The metal nature not only affects the rate of the nucleophilic attack but also, to a different extent, the equilibrium constant K_1. Although no equilibrium constant can be measured from our experiments, an indirect comparison can be made from the experiment with thiolate anions. For instance, the equilibrium constant (K_1) for the addition of $HOCH_2CH_2S^-$ to **1-Cr-SMe-Ph** (Scheme 1) is 3.07×10^5 while that for **1-W-SMe-Ph** is 3.76×10^6, from which a ratio of K_1(W)/K_1(Cr) = 12.2 is obtained.[21b] Thus, the nature of the metal centre may lead to some differences in this step that would cause a different degree of C–N bond formation at the transition state.

Inspection of Table 1 suggests that the values of k_1 increase with the pK_a of the amine within each series. A representative Brønsted plot for the k_1 is shown in Fig. 6. In general, for all the remaining complexes there is a good correlation between the log(k_1) and pK_a^{AH} and the β_{nuc} values are summarized in Table 3.

All the values shown in Table 3 are within the range 0.24–0.42, in good agreement with previous reports.[19b,25e] The values of β_{nuc} can be considered as a measure of the bond formation degree at the transition state if no other process, such as desolvation of the nucleophile, is involved.[37]

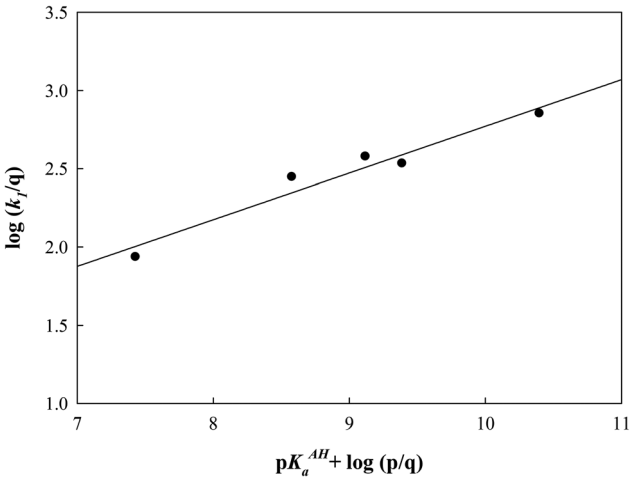


Fig. 6 Brønsted plot for the reaction of **4W-*t*Bu** with primary amines in 50% MeCN–50% water at 25 °C, ionic strength = 0.1 M (KCl).

Table 3 β_{nuc} values for the reactions of complexes **4M-R** with primary amines in 50% MeCN–50% water at 25 °C[a]

	M = Cr	M = W
4M-R	β_{nuc}	β_{nuc}
R = Me[b]	0.37 ± 0.01	0.33 ± 0.02
R = *n*Bu	0.36 ± 0.07	0.24 ± 0.06
R = *c*Hex	0.42 ± 0.09	0.25 ± 0.04
R = iPr	0.36 ± 0.05	0.35 ± 0.03
R = *t*Bu	0.30 ± 0.05	0.30 ± 0.04

[a] Ionic strength = 0.1 M (KCl). [b] Ref. 25*e*.

A small difference for the β_{nuc} can be distinguished out of the experimental error for complexes with *n*Bu and *c*Hex side groups. It is interesting to note that β_{nuc} is on average slightly higher for the chromium complexes. This observation can be interpreted in accordance with the Hammond–Leffler effect.[38] Taking into account that the formation of the zwitterionic intermediate $\mathbf{T}^{\pm}$ is thermodynamically more favoured when M = W due to its higher electronegativity, a less advanced transition state for **4W-R** is expected. It is noteworthy to compare the β_{nuc} values in reactions of different heterocarbene complexes. Thus β_{nuc} for thiocarbene complexes are significantly lower than those reported for the aminolysis of the alkoxycarbene complexes (0.60),[18] suggesting a smaller degree of bond formation at the transition state for the former. This finding has been explained due to different factors such as the inductive effect, the π-donor effect and heteroatom sizes. The experimental results published so far have indicated that the π-donor effect is dominant and offsets the other factors. In this context, the stronger π-donor character of oxygen results in a more effective stabilization of the reactants disfavouring the thermodynamics to form the zwitterionic intermediate $\mathbf{T}^{\pm}$.[21b] Thereby, by the Hammond–Leffler effect, the stronger the π-donor character of the

heteroatom, the more advanced the transition state. In contrast, their organic analogues, ester and thiolester, do not present such a dramatic heteroatom effect on the position of the transition state. For the aminolysis reactions, β_{nuc} values around 0.2 are considered normal for ester compounds,[20a,39] while for thiolester, values in the range 0.1–0.3 have been reported.[29,40] The comparison of the β_{nuc} values in reactions of esters and carbene complexes suggests that the position of the transition state sharply depends on the π-donor heteroatom for the organometallic compounds contrary to the situation for their organic analogues. The different behaviours of the two families of compounds are not clear so far; theoretical calculations are currently being performed in order to understand this issue.[41]

Remarkably, due to the strong π-donor effect of the heteroatom substituent, a minor role has been attributed to the steric hindrance in the kinetic studies reported. For example, Bernasconi and co-workers have evaluated the rate constant for **1-Cr-OMe-Ph** and **1-Cr-OEt-Ph** in the aminolysis and basic hydrolysis reactions.[25b] They have attributed the changes observed to the stronger π-donor character of EtO with respect to the MeO substituent.[42] On the other hand, a few studies have pointed out the importance of the volume of the substituent in the reactivity. Recently, it has been shown that alkoxycarbene complexes experience strong steric effects for the basis hydrolysis, even stronger than for esters.[26a] This observation was connected with the presence of the bulky $Cr(CO)_5$ moiety. On the basis of our discussion, an additional insight can be given, since it is not only a consequence of the presence of the metal pentacarbonyl fragment, but can also be attributed to the differences in the position of the transition states (see below). Strikingly, the steric effects exerted by $M(CO)_5$ and XR moieties can be high enough to inhibit the nucleophilic attack at the carbene carbon and direct it to an aromatic ring carbon[43] or to the carbonyl ligands.[44]

Given that the transition states for the studied thiocarbene complexes are less advanced than those for the alkoxycarbene derivatives, it is reasonable to expect that the reactivity is less dependent on the volume of the –SR group.

3.2.1.2 Polar vs. steric effects of –SR group. In order to shed light on the factors which determine the reactivity, we have used different linear free energy relationships (LFER) to evaluate the effects exerted by the –SR group.

The effect of changing the π-donor character was analyzed on the basis of the correlation between rate constants and substituent parameter R^+.[42] Our results show a poor correlation between $\log(k_1)$ and R^+ ($r^2 = 0.14$).

In a previous study we found that the hydrophobicity of the R group influences the rate of the proton transfer reaction between thiocarbene complexes **4M-R** and hydroxide anions in 50% MeCN–50% water.[26d] In this vein, we plotted $\log(k_1)$ against $\log P$,[45] but no correlation was found ($r^2 = 0.1$). As we have pointed out in our previous article, the hydrophobicity only plays an important role when one of the reactants is charged; hence a different scenario for reactions with uncharged nucleophiles is expected. From these results it becomes obvious that the polar effects do not adequately describe the origins of the factors under evaluation.

Steric, rather than electronic, effects appear to be primarily responsible for the decreasing reactivity in going from methyl to *tert*-butyl derivatives. A close inspection of Table 1 gives clues to the main factors taking place in these reactions. As can be seen, a trend following the bulkiness of the group is found, namely, the rate constants decrease in the order Me > *n*Bu > *c*Hex > iPr > *t*Bu. Thus, the correlations are better when steric parameters are used, for example, Taft's E_s[46] and Charton's ν_{CH_2R}[47] and ν_{SR}[48] parameters. The correlations with E_s and ν_{SR} are not very good (r^2 values were 0.6 and 0.4, respectively), but the correlation with ν_{CH_2R} is quite good ($r^2 = 0.987$). Fig. 7 (see also Fig. S4 and S5†) displays a representative plot for the reactions where glycine ethyl ester was used.

The linear correlation between $\log(k_1)$ and ν_{CH_2R} is clear evidence for the role of steric effects in controlling reactivity. Taft's E_s parameter contains a mixture of polar and steric contributions that are difficult to separate unambiguously. On the other hand, Charton's steric parameters are based on van der Waals radii of the constituted atoms and, therefore, should be free from complications caused by mixing of electronic and steric effects that might contribute to other parameters obtained from structure–reactivity correlations. As has been pointed out by Charton, better correlations with ν_{CH_2R} are obtained when the substituents are not directly bonded to the reaction site.[49] Indeed, this indicates that the size of the alkyl R group is influencing the rate constants. As can be observed, the iPr group displays a negative deviation in the correlations. Harper *et al.*[27g] have recognized that the application of the Charton parameter assumes a net conformer for the specific transition state, although the differences in energy of these rotational conformers are potentially high. This spherical assumption reasonably describes the steric influence of symmetric groups, but it is a limiting premise when the substituent is not symmetrical.

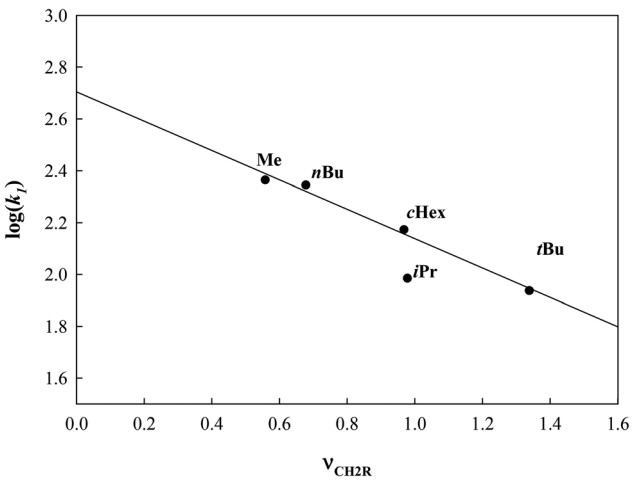


Fig. 7 Plot of $\log(k_1)$ *vs.* ν_{CH_2R} for the reaction of **4W-R** with glycine ethyl ester in 50% MeCN–50% water at 25 °C and ionic strength = 0.1 M (KCl).

Table 4 Summary of the ψ values of the nucleophilic attachment in the aminolysis reactions of esters and Fischer carbene complexes

	Reactant	Nucleophiles	ψ (ψ^{OH}, $\Delta^{OH}_{\psi-\psi}$)
1	O═C(OPh)R	*n*-Butylamine	−1.83 ± 0.23[a] (−3.12[b], 1.29[c])
2	O═C(SPh)R	Benzylamine	−1.13[d]
3	$(CO)_5Cr$═C(OR)Ph	*n*-Butylamine	−2.29[e] (−3.84[f], 1.55[c])
4	$(CO)_5Cr$═C(SR)CH_3 (**4Cr-R**)	*n*-Butylamine	−0.42 ± 0.08
5	$(CO)_5Cr$═C(SR)CH_3 (**4Cr-R**)	Benzylamine	−0.41 ± 0.08[g]
6	$(CO)_5W$═C(SR)CH_3 (**4W-R**)	Benzylamine	−0.42 ± 0.08[h]
7	$(CO)_5W$═C(SR)CH_3(**4W-R**)	Glycine ethyl ester	−0.57 ± 0.05[g,h]

[a] Data taken from ref. 50 in MeCN at 25.4 °C. [b] Data taken from ref. 49. [c] Difference between the ψ values for the aminolysis and hydrolysis reactions. [d] Data taken from ref. 51 in MeCN at 45 °C. [e] Calculated with two points taken from ref. 18 and 25*b*. [f] Data taken from ref. 26*a*. [g] This work. [h] Slope of Fig. 7 excluding the point corresponding to R = iPr.

The correlation between $\log(k_1)$ and ν_{CH_2R} can be described by Charton's equation (eqn (7)), where ψ measures the sensitivity of the reaction to the steric parameter.

$$\log(k_1) = \psi\nu_{CH_2R} + h \quad (7)$$

In Table 4, the ψ parameters for nucleophilic attachment step of the aminolysis of Fischer carbene complexes and some related reactions are shown.

From the comparison of **4Cr-R** and **4W-R** with the same amine (entries 5 and 6 in Table 4), it can be seen that the change in the metallic centre has no detectable effect on the sensitivity of the reaction to the steric effect ψ. Likewise, changing the nucleophile does not lead to any appreciable modification in the sensitivity (entries 4 and 5, Table 4).

It might be possible that a decrease of the nucleophilicity yields a more advanced transition state and hence it might lead to a higher steric effect; however the results do not support this statement (see Table S1†).

Inspection of the ψ values in Table 4 shows that the value obtained for the aminolysis of the alkoxycarbene complexes is five to six times greater than any of the values for the thiocarbene analogues. Since this observation is based on a ψ value obtained with only two points, ψ^{OH} values corresponding to the basic hydrolysis reaction for both families O═C(OR)Ph and $(CO)_5Cr$═C(OR)Ph have been included in Table 4, which were obtained with a larger number of points. The respective differences with ψ values for the aminolysis reactions ($\Delta^{OH}_{\psi-\psi}$) were added too. As can be seen, the differences are similar, which supports the estimated ψ value for the aminolysis reaction of $(CO)_5Cr$═C(OR)Ph.

According to the discussion of the previous section this result can be attributed to differences in the position of the transition states, *i.e.*, an earlier transition state for the thiocarbenes. Additionally, there must be an extra contribution due to the different sizes of the side groups, *i.e.*, phenyl and methyl groups for the alkoxy- and thiocarbenes, respectively. To the best of our knowledge, there are no data in the literature regarding the aminolysis of ionizable Fischer alkoxycarbene complexes $(CO)_5Cr$═C(OR)Me, but we can gain a clue about the minimum value that the change from Ph to Me can have on ψ. Taking into account that the ψ values reported for the hydrolysis of esters O═C(OR)Ph and O═C(OR)Me are −3.12 and −3.04, respectively,[49] it is expected that the impact of changing the side group from Ph to Me should be at least 0.08 unit. In fact, the contribution should be somewhat higher in the case of the carbene complexes due to the more advanced C–N bond formation at the transition state. Nonetheless, it is not likely that this difference will be large enough to overshadow the *ca.* 1.9 units between alkoxy- and thiocarbene complexes.

The different reactivities of alkoxy and thiocarbene complexes have been attributed to several factors and in some cases it appears that the steric effect due to the larger size of the –SMe group compared with –OMe is the most important one.[23,25d,e] Our data include an extensive change in size of the group; therefore more information about the relative importance of the steric effect can be obtained. From the discussion that follows, we conclude that the main factors that explain the different reactivities between alkoxy and thiocarbene complexes can be ascribed to the π-donor effect.

Interestingly, for alkoxycarbenes the ψ values are higher than for the esters while for thiocarbenes the ψ values are lower than for the thiolesters. This translates into a wider range of steric effects experimented by the organometallic complexes (a range of *ca.* 1.9 ψ units) with respect to their organic counterparts (0.7 ψ units).

At this point a comparison between organometallic and organic agents with the same heteroatom π-donor is instructive. Regarding the oxygen derivatives, alkoxycarbenes and esters, the data collected in Table 4 indicate a difference of 0.46 ψ units, in close agreement with the difference of 0.32 ψ units[52] found for the hydrolysis reactions. As we mentioned before, this might be a consequence of the higher resemblance of the transition states to the zwitterionic intermediate $\mathbf{T}^{\pm}$ in the case of the alkoxycarbenes; this can be seen by comparing the values reported in Table 3 with those reported in ref. 18. On the other hand, thiocarbene complexes exhibit steric effects that are 0.56 to 0.72 ψ units lower than their organic analogues. As there is no report on the aminolysis reaction of thiolesters O═C(SR)Me, a direct comparison is not possible. Based on the data available for the alkaline hydrolysis of O═C(SR)Me[48] and $(CO)_5Cr$═(SR)Ph,[53] additional support can be obtained. The difference in steric effects observed for these reactions, ψ = −1.07 for the hydrolysis of thioesters and ψ = −0.60 for the thiocarbenes, is similar to what is observed for the reactions with amines.

It is interesting to note that **4M-R** complexes possess a lower sensitivity to the steric effects than the thiolesters in spite of similar β_{nuc} values.[51] These results indicate that there must be significant differences in the progress of the steric effects with respect to the bond formation at the transition state depending on the interplay between the π-donor and π-acceptor groups attached to the reaction centre.

For better comprehension of this, it is useful to discuss in terms of the intrinsic rate constant ($\log k_0$),[54] which is a pure kinetic quantity corrected for differences in the equilibrium constants. Changes in the intrinsic rate constant are indicative of transition state imbalances[55] where one or several factors (like inductive, steric, solvation and π-donation) lag behind or ahead of the bond formation. Due to these imbalances, the relative importance of these factors and how they affect the rate constants are different from how they affect the equilibrium constant, and this is reflected as differences in the intrinsic rate constants. The principle of nonperfect synchronization (PNS) provides guidance as to what factors play a central role.[56]

Unfortunately, the equilibrium constant K_1 values for these systems could not be calculated. However, based on the reaction of thiolate ions with Fischer carbene complexes and ester derivatives, an indirect comparison can be drawn for the trend in the reactivity. For the reaction of the propanethiolate ion (PrS^-) with Fischer carbene complexes **1-Cr-OMe-Ph** and **1-Cr-SMe-Ph**, k_1 values are 1.34×10^4 and 5.33×10^2, respectively; while the corresponding K_1 values are 1.06×10^4 and 1.1×10^6.[21] This leads to $\log k_0$[57] of 2.11 and −0.29 for **1-Cr-OMe-Ph** and **1-Cr-SMe-Ph**, respectively. From the side of the organic derivatives the data available are remarkably limited. However, it is possible to draw an approximate idea of the intrinsic rate constant by taking into account the rate constants published by Hupe and Jencks[58] and some approximations made by Guthrie.[59] Based on Guthrie's estimated values for the addition of ethanethiolate (EtS^-) to acetic acid in water at 25 °C, namely, $K_1 \approx 7.9 \times 10^{-14}$ and $k_1 \approx 7.9 \times 10^{-4}$, a value of $\log k_0 \approx 3.45$ can be calculated.[59] The thiolester reactions with thiolates are expected to have a similar intrinsic rate constant, and $\log k_0$ is roughly estimated as 2.7.[60] Overall, the intrinsic rate constant trend for the thiolate addition is $\log k_0$(esters) ≈ $\log k_0$(thiolesters) > $\log k_0$ (alkoxycarbene complexes) ≫ $\log k_0$(thiocarbene complexes) and it is expected that the nucleophilic attack step by amines follows the same order.[12]

It has been claimed that there are at least three factors responsible for those differences, namely, the steric effect, the π-donor effect and the inductive effect.[21,23,25] In some cases the steric effect has been pointed out as the most important,[19,21,25a,b] while in other cases the influence of the π-donor strength on the preorganization of the $(CO)_5M$ moiety into its adduct configuration has been suggested as the ruling factor.[23,25d,e]

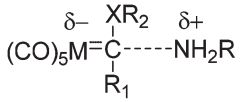
Our results allow us to gain further insight into the nature of the main factors ruling the reactivity of the nucleophilic addition of amines to the organometallic carbene complexes.

According to the PNS, the steric hindrance is a product destabilizing factor and when its development is ahead of the bond formation, $\log k_0$ is lowered; conversely, when it lags behind bond formation, $\log k_0$ is enhanced. Predictions with respect to whether the development of steric effects at the transition state is generally ahead of bond formation or lags behind it have always been difficult to make.[55b] Evidence from previous nucleophilic vinylic substitution studies has suggested that early development of steric hindrance appears to be the rule.[61]

As can be seen, our results suggest that steric effects lag well behind bond formation for thiocarbene complexes, while for alkoxycarbenes, esters and thiolesters it is more advanced, although the scene is not completely clear.

If steric effects were the main factor ruling the reactivity, it should then be expected that, according to the PNS, the intrinsic rate constants for the thiocarbene derivatives would be higher than for the alkoxycarbene complexes. Since our results suggest otherwise, *i.e.* that the intrinsic reactivity of the thiocarbenes is actually lower than that for the alkoxy derivatives, this means that other factors play a major role.

The inductive effect has been pointed out as an important factor at the transition state of addition reactions where the nucleophile is bearing a negative charge (7). Although this effect is thought to develop synchronously with bond formation, its contribution to the intrinsic rate constant arises from the impact on the resonance/delocalization effect.[55a–c] Basically, inasmuch as the negative charge is closer to X at the transition state than in the adduct, the transition state derives a disproportionately strong stabilization from the inductive effect of X compared to the adduct. This should enhance the intrinsic rate constant for the oxygen derivatives more than for the sulphur compounds. However, this effect for neutral nucleophiles should not be strong since the charges are offsetting each other (**6**).



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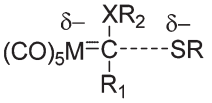

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The π-donor effect influences the intrinsic rate constant in different ways.[12] One is the loss of resonance stabilization of the reactant that is expected to run ahead of bond formation and, according to PNS, lower $\log k_0$. Since the π-donor ability of oxygen is stronger than that of sulphur, there will be a stronger reduction in $\log k_0$ for the compound with oxygen substituents. The other interaction mechanism is the preorganization of the structure of the $M(CO)_5$ moiety in Fischer complexes toward its electronic configuration in the adducts that results from the π-donor effect. As a consequence, the lag in the charge delocalization into the CO ligands at the transition state is reduced, and the intrinsic rate constant is not as strongly depressed by the PNS effect associated with this lag. We believe that the second mechanism of the π-donor effect is ruling the intrinsic rate constant in the aminolysis of Fischer carbene complexes. This is not because of how it affects $\log k_0$ *per se*, but because of how it influences the solvation sphere around the transition state. Computational studies have suggested that the solvation of the zwitterionic intermediate is highly important, *i.e.*, *ca.* 5 kcal mol^{-1}.[24] PNS predicts that solvation should lag behind bond formation.[55a–c] Thus, the more preorganized is the compound, the less imbalanced the transition state, explaining the differences found for alkoxy- and thiocarbene derivatives.

On the basis of our results a decisive answer cannot be given as it respects to which interaction is the dominant one, but at least we can have clues to the role of the steric effects on this step. Although steric effects command the differences in the reactivity within the heteroatom-substituted compound series, it is not the main factor responsible for the depression in the intrinsic rate constant when oxygen is replaced by sulphur. The fact that $\log k_0$ of alkoxycarbene complexes exceeds $\log k_0$ of the thiolated derivatives by more than 2 units suggests that the preorganization of the compound as well as the solvation sphere may have a strong contribution. Note, though, that this is not a firm conclusion, and that other factors may be contributing as well. The importance of the preorganization of the reactants as a key factor determining the differences in reactivity between alkoxy- and thiocarbenes has been previously pointed out by Bernasconi.[21b]

3.3 Nucleophilic attack (k_1) and leaving group expulsion (k_3^A/k_{-1}) for secondary amine

The data in Table 2 show that the rate constants for the nucleophilic addition of morpholine (k_1) have a trend to decrease as R becomes bulkier, *i.e.*, R = Me > *n*-Bu > *c*Hex > iPr. This undoubtedly indicates that the same factors, as those already described for the primary amines, are operating. In Fig. 6 a plot of $\log k_1$ *vs.* Charton's parameter ν_{CH_2R} is shown.

The ψ value for morpholine (−0.88) is slightly higher than for those values obtained for primary amines (−0.41 to −0.57, Table 4). This higher sensitivity for the secondary amine can be easily explained in terms of the Hammond–Leffler postulate.[38] Since the formation of the zwitterionic intermediate is thermodynamically less favourable due to increased steric crowding, the transition state should be more advanced. This is in good agreement with the 0.42–0.60 β_{nuc} values reported for the reaction of secondary alicyclic amines with **1-Cr-SMe-Ph** complexes.[19b] Strikingly, comparing the values of primary (see Table 3) and secondary amines a 2-fold increase in β_{nuc} produces a concomitant 2-fold increase in the steric sensitivity of the reaction. The nature of the metallic centre does not affect considerably the change in k_1 with the volume of the R. This outcome arises from the ratios k_1(**4W-Me**)/k_1(**4W-*c*Hex**) = 2.1 and k_1(**4Cr-Me**)/k_1(**4Cr-*c*Hex**) = 1.9.

The analysis of the k_3^A/k_{-1} ratios in Table 2 suggests that the volume of the R group modifies the velocity of the general base catalysed step. Due to the particular features of the system, we were only able to measure the general base catalysis for three of the bases used, namely, OH^-, morpholine and triethylamine (TEA). The size of these bases increases in the sense OH^- < Morpholine < TEA while the pK_a^{HA} values follow the order Morpholine ≪ TEA ≪ OH^-. Comparing each of the bases their values of k_3^A/k_{-1} fall in the order dictated by the pK_a^{HA}. Interestingly, the smaller bases (morpholine and OH^-) do not show a clear trend with the size of the R group, but TEA presents a similar trend to that displayed by the nucleophilic attachment step. The correlation of k_3^{TEA}/k_{-1} ratios with Charton's steric parameter is shown in Fig. 8.

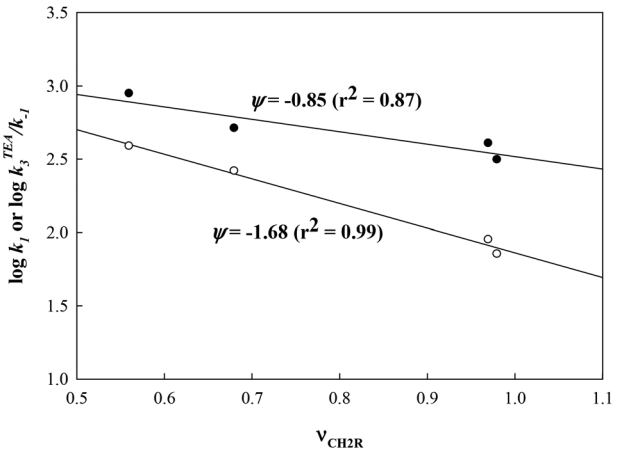

Fig. 8 Plots of $\log k_1$ (●) and $\log k_3^{TEA}/k_{-1}$ (○) *vs.* ν_{CH_2R} for the reaction of **4W-R** with morpholine in 50% MeCN–50% at 25 °C and ionic strength = 0.1 M (KCl).

The obtained value of ψ = −1.68 is sensibly higher than that for k_1. These results indicate that steric effects play a significant role also in the base catalysed pathway. These changes of the k_3^A/k_{-1} ratios with the volume of R could be a consequence of an increase of k_{-1}, a decrease of k_3^A or both. The values of k_{-1} should increase with the size of R because a bulky R group destabilizes the tetrahedral intermediate $\mathbf{T}^{\pm}$, and therefore, its breakdown back to reactants should be faster. On the other hand, k_3^A according to the mechanism **B** in Scheme 3 can be expressed as $k_3^A = k_3^{HA} K_a^{\pm}/K_a^{HA}$. Based on the $K_a^{\pm}/K_a^{HA}$ values reported for similar systems,[62] this ratio should be approximately constant for the series studied and therefore a variation on k_3^{HA} should be mirrored on k_3^A. The steric hindrance would have two modes for affecting k_3^{HA}. On the one hand, a more crowded $\mathbf{T}^-$ should enhance the k_3^{HA} values to yield the aminolysis products. In this way, the effects on k_{-1} and k_3^A would offset each other and no clear trend should be observed. This is indeed the case when the catalysts are small, like with OH^- or morpholine. On the other hand, if the catalyst is bulky (like with TEA), the k_3^{HA} values should decrease with increasing size of the R group due to the difficulty for the catalyst to approach the leaving group (–SR). A noticeable decrease in the reactivity of the TEA base catalysis is indeed observed for the thiocarbene complexes **4M-R**. It is noteworthy that the pK_a^{HSR} of the leaving groups does not change significantly throughout the series studied.

Interestingly, the steric effects on the k_3^A/k_{-1} are significantly affected by the nature of the metal centre. As can be seen from Table 2, (k_3^{TEA}/k_{-1})(**4W-Me**)/(k_3^{TEA}/k_{-1})(**4W-*c*Hex**) = 4.3 while (k_3^{TEA}/k_{-1})(**4Cr-Me**)/(k_3^{TEA}/k_{-1})(**4Cr-*c*Hex**) = 9.7. This means that by replacing the tungsten by chromium the steric effects are enhanced 2-fold. This can be ascribed to the less electronegative character of Cr in comparison with W, which leads to less stable $\mathbf{T}^{\pm}$ and $\mathbf{T}^-$ intermediate and hence to less advanced transition states to either reactants or products. This is finally reflected in the more pronounced dependence of the velocity on the volume of the R group.

4. Conclusions

From the kinetic studies reported in this paper, the following conclusions can be drawn:

(i) The reaction of **4M-R** with amines leads to a substitution of the thioalkyl group by a stepwise mechanism involving a nucleophilic addition to the carbene carbon followed by specific base-general acid catalysed leaving group expulsion. For the reactions with primary amines (*n*-butylamine, methoxyethylamine, benzylamine, furfuryl amine, glycine ethyl ester), the first step is rate-limiting. On the other hand, for the reaction with morpholine at low amine and OH^- concentrations, the leaving group departure step is rate-limiting, while at high amine or OH^- concentrations, the nucleophilic attack is the rate limiting step.

(ii) Tungsten complexes are more reactive than the chromium derivatives in the nucleophilic addition; the k_1(**4W-R**)/k_1(**4Cr-R**) ratios are between 2.9 and 5.7, indicating a small enhancement of the electrophilicity when M = W.

(iii) The β_{nuc} values for the nucleophilic addition are small, indicating that C–N bond formation has made little progress at the transition state. The size of the R group has no influence on the degree of bond formation and the metal nature exerts a small effect on the position of the transition state. On average, chromium complexes have slightly higher β_{nuc} than tungsten complexes. This is attributed to the difference in electronegativity, which leads to a better stabilization of the intermediate $\mathbf{T}^{\pm}$.

(iv) Charton's plots revealed that the size of the R group is mainly responsible for the decreasing reactivity within the **4M-R** series. The obtained ψ coefficients for the nucleophilic attack step suggest that the sensitivity to the steric effects exerted by R is significantly weaker for thiocarbenes than for alkoxycarbenes. Furthermore, neither the metal centre nor the nucleophile has a detectable influence on the ψ values.

(v) The comparison of the Charton data between thiocarbene and alkoxycarbene complexes and between thiolester and ester shows that organometallic derivatives experience a wider range of steric effects on nucleophilic attack. While thiocarbenes exhibit lower ψ values than thiolesters, alkoxycarbenes exhibit higher ψ values than the thiocarbene complexes.

(vi) The fact that steric effects are more important in the alkoxycarbene reactions than in the thiocarbene reactions indicates that they cannot be responsible for the differences in the reactivity. Based on the PNS, our data suggest that the factor ruling the reactivity trend is the interplay between π-donor and π-acceptor groups attached to the reaction centre and how they affect the solvation sphere.

(vii) The nucleophilic attachment of a secondary amine to **4M-R** is more sensitive to the steric effects due to a more advanced transition state. This is in good agreement with the higher β_{nuc} values.

(viii) The steric effects exerted by the R group are strong in the general base catalysed step. This is due to the fact that a bulkier R group destabilizes $\mathbf{T}^{\pm}$ and $\mathbf{T}^-$ intermediates and slows down the catalyst approach. Remarkably, the nature of the metal centre can modify the steric sensitivity of this process.

5. Experimental section

5.1 Materials

The Fischer carbene complexes were synthesized according to the procedure of Yamashita *et al.*[63] The products were characterized by NMR spectroscopy (400 MHz, $CDCl_3$), FT-IR (KBr), HRMS (FAB) and UV-Vis spectrophotometry. The full characterization of the Fischer carbene complexes **4M-R** has been published.[26c,d]

Acetonitrile was of reagent grade and was used without further purification. Water was taken from a Milli-Q water purification system. The liquid amines were freshly distilled before use. The solid amines were recrystallized from ethanol.

5.2 Kinetic experiments

The stock solutions of the carbene complexes were prepared in pure acetonitrile, and appropriate solutions in 50% MeCN–50% water were prepared just prior to use. All kinetic experiments were performed using a stopped-flow spectrophotometer. In a syringe was placed the solution of the carbene complex and in the other one the buffer solution with the nucleophiles. The reactions were performed under pseudo first-order conditions with the carbene complex as the minor component. The final concentrations of **4M-R** were *ca.* 1×10^{-4} M. The ionic strength was kept at 0.1 M with KCl. The reactions were followed at the maximum wavelength of the amino carbene complex reaction product, 355 nm for chromium complexes and 335 nm for tungsten complexes.

For reactions with morpholine buffer, seven solutions were prepared at pH 8.88 in the range of total buffer concentration of 0.0125–0.1 M.

The reactions where triethylamine (TEA) buffer was the catalyst and morpholine was the nucleophile were performed in two different ways: (a) at constant pH = 10.78 and a constant concentration of morpholine (0.01 M), varying the concentration of TEA in the range 0.001–0.1 M. (b) At constant concentrations of morpholine (0.01 M) and TEA (0.01 M), changing the pH in the range 9.60–11.19.

In all cases, the k_{obs} values were obtained as the averages of at least four experiments.

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52 In the original article (ref. 26*a*) a difference of 0.57 unit was reported for the ψ values obtained in the correlation between $\log(k_1)$ *vs.* ν_{OR}. In the present report the values were recalculated with the correlation $\log(k_1)$ *vs.* ν_{CH_2R}.

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54 The intrinsic rate constant of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $k_0 = k_1 = k_{-1}$ when the equilibrium constant $K_1 = 1$ ($\Delta G^0 = 0$).

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56 The PNS states that if the development of a product stabilizing factor lags behind bond changes or charge transfer at the transition state, k_0 is reduced. The same is true if the loss of a reactant stabilizing factor runs ahead of bond changes or charge transfer. For product stabilizing factors that develop early or for reactant stabilizing factors that are lost late, k_0 is enhanced. For product or reactant destabilizing factors, the opposite relationships hold.

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60 The estimation is rooted in the data published for the hydrolysis of thiolesters, where for $CH_3C(O)SEt$ the value for $\log K_1^{OH} = -6.3$ and $\log k_1^{OH} = -0.93$.[59] With these values the intrinsic rate constant is *ca.* 2.23. This value is slightly lower than that obtained for the hydrolysis and methanolysis of benzylacetate, *i.e.*, $\log k_0 = 2.4$ and 3.10, respectively.[35a] Based on the fact that the carbon basicity of sulphur in a thiolate anion is 10 times larger than similar amines and oxygen anions and that the equilibrium constants for the addition to carbonyl groups are approximately 10^3 larger for thiolates than for alcohols,[39a,58,64] it is expected that the intrinsic rate constant is around 0.5 unit higher than the value for hydrolysis.

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