Effects of the alkyl substituent in the π-donor heteroatom on the kinetic and thermodynamic acidities of Fischer thiocarbene complexes†

Martin Eduardo Zoloff Michoff, Diego Marcelo Andrada,
Alejandro Manuel Granados* and Rita Hoyos de Rossi*

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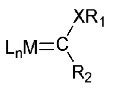
Rate constants for the proton transfer reaction from Fischer thiocarbene complexes $(CO)_5M{=}C(SR_1)CH_3$ (M = Cr or W; R_1 = *n*-butyl, isopropyl, *tert*-butyl, cyclohexyl) to OH^- and various primary and secondary amines were determined in 50% acetonitrile–50% water at 25 °C. These measurements allowed the determination of the thermodynamic and kinetic acidities for these substrates. The results obtained show that there is a slight effect of the substituent on the thermodynamic acidity, which is governed by its hydrophobicity; whereas the effect on the kinetic acidity is more noticeable and is due to the steric effect of the substituent.

Introduction

The chemistry of Fischer carbene complexes, **1**, has been largely developed since the first synthesis of one such complex by Fischer and Maasböl in 1964.[1] Most of the investigations performed so far have aimed at applications in the area of organic synthesis.[2] Their special electronic characteristics and multifunctional structure make these compounds very versatile synthons.

Fischer carbene complexes have been shown to undergo a variety of reactions such as nucleophilic addition/substitution on the carbene carbon,[3] interchange of ligands,[4] insertion on C–H[5] and C–C bonds[6] and cycloadditions.[7] Recently it has been reported that the carbene carbon can undergo an insertion on a S–S bond in a pseudo-aromatic heterocycle,[8] and that these compounds are capable of reacting with electron transfer reagents or an electrospray source to form radical species with distinct reactivity.[9]



M = Cr, W, Mo
L = CO, NO, PR_3
X = N, O, S
R_1 = Alkyl
R_2 = Alkyl, alkenyl, alkynyl, aryl

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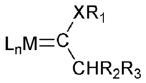

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One of the major characteristics of these compounds is the high acidity of the hydrogens in the α-position with regard to the carbene carbon.[10] This has opened the possibility of enlarging the range of carbene complexes that can be obtained,[11] and has also inspired numerous synthetic studies in which the α-anions of acidic Fischer carbenes such as **2** have been successfully used as nucleophiles in, for example, stereoselective aldol additions to aldehydes and ketones,[12] and asymmetric Michael additions to α,β-unsaturated ketones.[13]

Although most of the synthetic applications of these α-anions have been focused on alkoxycarbene and aminocarbene complexes, it has recently been reported that the corresponding carbanions obtained from thiocarbene complexes can undergo distinct reaction pathways leading to products that cannot be obtained from the isostructural alkoxycarbene complexes.[14]

Notwithstanding their usefulness as synthons in organic synthesis, it was not until recently that some of the mechanistic aspects of the reactions of these α-anions were reported. These studies were performed mainly by Bernasconi *et al.*[3a,15] and deal with some of the factors that affect the thermodynamic and kinetic acidity of these compounds.

The findings of those studies can be summarized as follows: (i) the high acidity of these complexes is mainly due to the electron-withdrawing nature of the metal moiety. A wide range of acidities was found, spanning a pK_a interval of 25 units. Some of the more important factors that affect the acidity of these compounds are the nature of the ligands L, and the heteroatom X. The nature of the substituents R_2 and R_3 also has some influence on the acidity constants of these compounds, but it is not as dramatic; (ii) the intrinsic rate constants, *i.e.* the rate constants extrapolated to a situation in which the thermodynamic driving force of the reaction is zero, for these reactions are typically low, usually lower than for other carbon acids. This is a consequence of the charge being delocalized into the metal moiety, combined with the fact that charge delocalization lags behind proton transfer. This causes the transition state for these reactions to be imbalanced which, according to the principle of non-perfect synchronization (PNS),[16] leads to low intrinsic rate constants. Some of the factors that affect the intrinsic reactivity of acidic Fischer carbene complexes have also been evaluated.

In the aforementioned studies, the effect of the nature of the R_1 substituent has not been explored in depth. Only its electronic effect has been assessed from studies involving the

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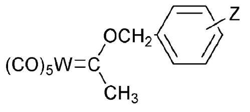
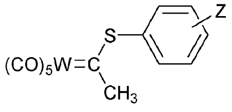
Instituto de Investigaciones en Fisicoquímica de Córdoba, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, Córdoba, Argentina. E-mail: ale@mail.fcq.unc.edu.ar. E-mail: ritah@mail.fcq.unc.edu.ar; Fax: +54 3514333030; Tel: +54 3514334170

† Electronic supplementary information (ESI) available: Fig. S1, plots of k_{obsd} *vs.* [KOH] for **5-Cr-R$_1$**; Table S1 containing the k_{obsd} values for the reactions of **5-W-*i*Pr** in morpholine buffers. Characterization and IR, ^1H and ^{13}C NMR spectra of carbene complexes **5-M-R$_1$**. See DOI: 10.1039/b709504j

benzoxy carbene complexes **3-W-Z** and the thiophenoxy carbene complexes **4-W-Z**.[17]



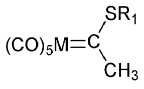
3-W-Z



4-W-Z

The only alkyl substituents studied so far are either methyl (with X = O[18] and S[19]) or ethyl (with X = O[20]). However, it is known that the volume of an alkyl substituent in this position can alter the preferred conformation of these complexes,[21] and that can also affect significantly the reactivity of these compounds against OH^- or water as nucleophiles,[22] but how it can influence the thermodynamic and kinetic acidities of ionizable Fischer carbenes has not yet been explored.

In this paper we report on the study of the proton transfer reaction from the Fischer thiocarbene complexes **5-M-R$_1$** to KOH and a series of primary aliphatic and secondary alicyclic amines in order to assess how a change in the volume of the alkyl substituent can affect the thermodynamic and kinetic acidities of these compounds. The results obtained provide a new insight into how an alkyl substituent can influence the acidity of these compounds and suggest that the thermodynamic acidity is mainly affected by the hydrophobicity of the substituent, whereas the kinetic acidity is influenced by its steric effect.



5-M-R$_1$

5-Cr-*n*Bu (M = Cr, R$_1$ = *n*-butyl)
5-Cr-*i*Pr (M = Cr, R$_1$ = *i*-propyl)
5-Cr-*t*Bu (M = Cr, R$_1$ = *t*-butyl)
5-Cr-cHex (M = Cr, R$_1$ = ciclohexyl)
5-W-*n*Bu (M = W, R$_1$ = *n*-butyl)
5-W-*i*Pr (M = W, R$_1$ = *i*-propyl)
5-W-*t*Bu (M = W, R$_1$ = *t*-butyl)
5-W-cHex (M = W, R$_1$ = cyclohexyl)

Experimental

Materials

The Fischer carbene complexes were synthesized according to the procedure of Yamashita *et al.*[23] The products were characterized by NMR spectroscopy (200 MHz and 400 MHz, $CDCl_3$), FT-IR (KBr), HRMS (FAB) and UV-Vis spectrophotometry (see ESI for the full spectroscopic characterization of the Fischer carbenes **5-M-R$_1$**†).

Acetonitrile was reagent grade and was used without further purification. Water was taken from a Milli-Q water purification system. The liquid amines were refluxed over Na and freshly distilled before use. TRIS was recrystallized from ethanol. Reagent grade potassium chloride was used as received. Stock solutions of KOH were prepared from solid KOH, reagent for analysis, with CO_2-free water. These solutions were titrated and used to prepare the KOH solutions for the kinetic runs.

Kinetics and spectra

Stock solutions of the carbene complexes were prepared in pure acetonitrile, a medium in which they were relatively stable, and were used to make appropriate solutions in 50% MeCN–50% water prior to use. Typical concentrations of **5-M-R$_1$** were (1.0–1.2) × 10^{-4} M. All kinetic experiments were performed on a stopped-flow spectrophotometer. The ionic strength was maintained at 0.1 M with KCl. Kinetic runs were monitored at the λ_{max} of the carbene complexes. For the reactions run in the reverse direction, the anion was first generated in a solution containing 0.004 M KOH outside the stopped-flow apparatus and then immediately injected into one of the stopped-flow syringes for a subsequent stopped-flow experiment. For these experiments, solutions were prepared in a manner that they would neutralize the KOH used to generate the anions, and the remaining buffer is what we informed as reacting with the anions. The k_1^{OH} values were obtained from 10 kinetic runs at [KOH] between 0.001–0.015 M. For the reactions with morpholine buffers, ten runs at total buffer concentrations ranging from 0.01 to 0.2 M were conducted at seven different pH values. The reactions with the other amines were run at only one pH, with 6–7 different total buffer concentrations ranging from 0.01 to 0.2 M.

The absorption spectra were recorded on a diode array UV-Vis spectrophotometer.

pH and pK_a measurements

The pH in 50% MeCN–50% water was calculated by adding 0.18 to the measured pH, according to Allen and Tidwell.[24] The pK_a^{BH} values for the amines used were determined by measuring the pH of various buffer ratios and plotting log([B]/[BH^+]) *vs.* pH according to the Henderson–Hasselbach equation, where the intercept is the pK_a and the slope is unity. The pH of the reaction solutions for stopped-flow experiments were measured in mock-mixing experiments that mimicked the stopped-flow runs.

Results

General features

The reactions were carried out in 50% MeCN–50% water at 25 °C. The primary amines employed were *n*-butylamine, furfurylamine, benzylamine, and 2-amino-2-(hydroxymethyl)-propane-1,3-diol (TRIS), while the secondary amines were piperidine, piperazine, pyrrolidine and morpholine. When any of the thiocarbenes **5-M-R$_1$** is placed into a KOH or amine buffer solution, a rapid conversion to the corresponding anion is observed. After the addition of a few drops of a concentrated HCl solution, the Fischer carbene is recovered. When this addition was done within 1–2 min after formation of the anion, recoveries were virtually quantitative, which indicates good reversibility of the proton transfer reaction (Fig. 1 is illustrative).

The reaction scheme for the reversible proton transfer from **5-M-R$_1$** to a series of amine buffers and KOH consistent with the experiments described below is shown in Scheme 1.

The kinetic experiments were all carried out under pseudo-first order conditions with the Fischer carbenes as minor components. Hence, the general expression for the pseudo-first order rate constants is given by eqn (1).

$$k_{obsd} = k_1^{OH}[OH^-] + k_{-1}^{H_2O} + k_1^{H_2O} + k_{-1}^{H}a_{H^+} + k_1^{B}[B] + k_{-1}^{BH}[BH^+] \quad (1)$$

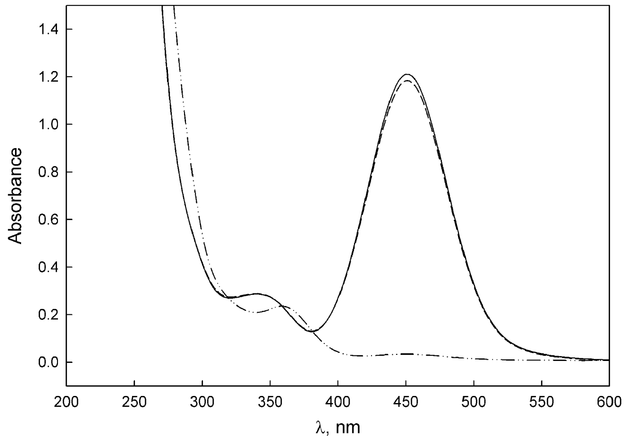
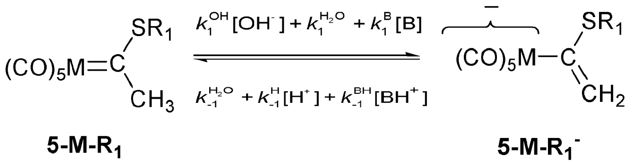


Fig. 1 UV-Vis spectra of (—) 1 × 10^{-4} M **5-Cr-*i*Pr** in 50% MeCN–50% water at 25 °C, (-· · ·-) the corresponding anion obtained in 5 × 10^{-4} M KOH and (--) recovery after addition of acid.



Scheme 1 Reversible proton transfer for the carbene complexes **5-M-R$_1$**.

Spectrophotometric determination of the pK_a^{CH} values

For the chromium derivatives, various phosphate and borate buffers were used to measure the absorbances of mixtures of **5-Cr-R$_1$** and **5-Cr-R$_1$**$^-$ in a pH range of 7–12. An illustrative example of the spectra obtained is shown in Fig. 2.

pK_a^{CH} (K_a^{CH} being the acidity constants of the Fischer carbene complexes studied) values were determined according to eqn (2), with A^{CH} being the absorbance at pH ≪ pK_a^{CH}, A the absorbance at pH ∼ pK_a^{CH} and A^{C^-} the absorbance at pH ≫ pK_a^{CH}. Plots according to eqn (2) (not shown) were linear and yielded the pK_a^{CH} (spec) values summarized in Table 1.

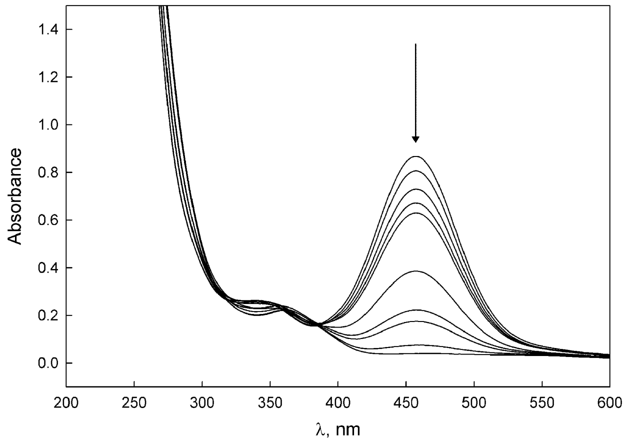


Fig. 2 Spectra obtained for **5-Cr-*t*Bu** at different pH values. The arrow indicates the sense of increasing pH: 7.00, 8.00, 8.50, 8.75, 9.00, 9.75, 10.00, 10.50, 11.00, and 12.00.

$$\log\left(\frac{A^{\mathrm{CH}}-A}{A-A^{\mathrm{C}^-}}\right)=\mathrm{pH}-\mathrm{p}K_a^{\mathrm{CH}} \qquad (2)$$

Reactions with morpholine buffers. Kinetic determination of pK_a^{CH}

Rates of the reaction with morpholine buffers were determined in the pH range of 7.80–9.60. Most of the experiments were performed in the reverse direction, *i.e.* the anion was first generated in 0.004 M KOH, then these solutions were mixed with various morpholine buffers. Plots of k_{obsd} *vs.* morpholinium ion concentration ([BH$^+$]) were all linear with negligible intercepts (Fig. 3). This means that eqn (1) can be approximated by eqn (3), with K_a^{BH} being the acidity constant of BH$^+$.

$$\begin{aligned}k_{\mathrm{obsd}}&=k_1^{\mathrm{B}}[\mathrm{B}]+k_{-1}^{\mathrm{BH}}[\mathrm{BH}^+]\\&=\left(\left(k_1^{\mathrm{B}}K_a^{\mathrm{BH}}/a_{\mathrm{H}^+}\right)+k_{-1}^{\mathrm{BH}}\right)[\mathrm{BH}^+]\\&=k_{-1}^{\mathrm{BH}}\left(\left(K_a^{\mathrm{CH}}/a_{\mathrm{H}^+}\right)+1\right)[\mathrm{BH}^+]\end{aligned} \qquad (3)$$

The slopes of the plots of k_{obsd} *vs.* [BH$^+$] are thus given by eqn (4). Fig. 4 shows representative plots of these slopes *vs.* $1/a_H{}^+$, from which the kinetic acidity constants for the carbene complexes **5-M-R$_1$** were obtained (pK_a^{CH} (kin) in Table 1). These plots also yield the k_{-1}^{BH} values reported in Table 2; k_1^B values were obtained as $k_{-1}^{BH}K_a^{CH}/K_a^{BH}$.

$$\mathrm{slope}=k_{-1}^{\mathrm{BH}}\left(\frac{K_a^{\mathrm{CH}}}{a_{\mathrm{H}^+}}+1\right) \qquad (4)$$

Reaction with KOH and various amine buffers

For the chromium derivatives, rates of deprotonation by OH$^-$ and a series of primary aliphatic and secondary alicyclic amines were also determined.

In KOH, rates were determined in the range [KOH] = 0.001–0.015 M. Plots of k_{obsd} *vs.* [KOH] were linear with negligible intercepts (Fig. S1 in the ESI†). From the slopes k_1^{OH} values were obtained and are reported in Table 3; whereas $k_{-1}{}^{H_2O}$ values were obtained as $k_1^{OH}K_w/K_a^{CH}$; where K_w is the solvent ionization constant. For the solvent used in this study pK_w = 15.19.[24]

In amine buffer solutions, depending on the pK_a^{BH}, reactions were either run in the forward direction (for pK_a^{BH} > pK_a^{CH}) or in the reverse direction (for pK_a^{BH} < pK_a^{CH}). For any given amine, reactions were run at only one pH value. In all cases, the plots of k_{obsd} *vs.* [B] or k_{obsd} *vs.* [BH$^+$] were linear, with slopes given by eqn (5) (plots *vs.* [B]) or eqn (4) (plots *vs.* [BH$^+$]). The values of k_1^B and k_{-1}^{BH} were obtained from the slopes and the known pK_a^{CH} (kin) values.

$$\mathrm{slope}=k_1^{\mathrm{B}}\left(\frac{a_{\mathrm{H}^+}}{K_a^{\mathrm{CH}}}+1\right) \qquad (5)$$

Table 1 Spectrophotometric and kinetic pK_a^{CH} values for the Fischer carbene complexes **5-M-R$_1$** determined in 50% MeCN–50% water at 25 °C,[a] and substituent parameters for inductive/field + resonance effects (F + R), hydrophobicity (log P) and steric effects (ν_{CH_2R})

	M = Cr		M = W					
Carbene complex	pK_a^{CH} (spec)	pK_a^{CH} (kin)	pK_a^{CH} (kin)	F + R[c]	log P[d]	$\frac{\log P^{R_1}}{\log P^{Me}}$	ν_{CH_2R} [e]	$\frac{\nu_{CH_2R}^{R1}}{\nu_{CH_2R}^{Me}}$
5-M-Me[b]	9.00 ± 0.21	9.05 ± 0.03	8.37 ± 0.06	−0.17	0.56	1.0	0.56	1.0
5-M-*t*Bu	9.33 ± 0.03	9.17 ± 0.02	8.60 ± 0.05	−0.20	1.43	2.6	1.34	2.4
5-M-*i*Pr	9.29 ± 0.03	9.18 ± 0.01	8.79 ± 0.05	−0.15	1.21	2.2	0.98	1.8
5-M-*n*Bu	9.46 ± 0.04	9.24 ± 0.03	8.65 ± 0.01	−0.16	1.80	3.2	0.68	1.2
5-M-*c*Hex	9.46 ± 0.04	9.35 ± 0.03	8.81 ± 0.08	−0.15	2.10	3.8	0.97	1.7

[a] The error reported is that of the linear fit, which underestimates the actual value. [b] Values taken from ref. 19. [c] Values taken for the alkyl substituent from ref. 25. [d] Calculated for the thiols R$_1$SH according to Crippen and Ghose's fragmentation method, see ref. 26. [e] Values taken from ref. 27.

Discussion

Mechanism

We attribute the observed reaction to the proton transfer from the carbene complex to the various bases used, as depicted in Scheme 1 for several reasons: (i) nucleophilic substitution can be discarded in view of the virtually quantitative recovery of **5-M-R$_1$** upon acidification. Nucleophilic substitution with amines is actually observed, but it occurs on a slower time scale. A detailed study of these reactions will be the subject of a future report; (ii) reversible nucleophilic addition to form tetrahedral adducts can also be excluded as the source of the observed kinetic process because these are intermediates in the substitution reactions and no accumulation of such intermediates is observed in the substitution reactions of **5-M-Me** (M = Cr or W).[28] Therefore, there is no reason to support the formation of a stable tetrahedral intermediate in the reactions reported here; (iii) there is great similarity in the behavior of the substrates **5-M-R$_1$** with that of the previously studied carbene complexes **5-Cr-Me** (M = Cr, R$_1$ = methyl) and **5-W-Me** (M = W, R$_1$ = methyl).[19]

Effects of R$_1$ and the metal on the thermodynamic acidity

For the purpose of this discussion we will use the acidity constants determined from the kinetic experiments (labeled as pK_a^{CH} (kin) in Table 1) as they are not influenced by the decomposition of the conjugate base of the substrates, making them more reliable than the values determined spectrophotometrically. Nevertheless, it should be noted that the trends are the same whichever set is used for comparison purposes.[29]

In principle the structural modification introduced can affect the stability of either the carbene complex, the corresponding anion or both.

Although the difference in pK_a^{CH} is not large (0.30 pK units for M = Cr and 0.44 pK units for M = W), there is a clear trend of decreasing acidity in the sense R$_1$ = methyl > *tert*-butyl ~ isopropyl ~ *n*-butyl > cyclohexyl. The magnitude of the errors involved in the determination of the pK_a^{CH} values preclude a more clear-cut distinction in the order for the substrates that lie in the middle of the range, but the difference between the extremes is quite clear and beyond experimental uncertainties.

Since the resonance structure **5-M-R$_1$**$^{\pm}$ appears to play a dominant role in the stabilization of carbene complexes,[30] the contribution from the combined inductive/field and resonance effects (F + R in Table 1) is expected to mostly stabilize **5-M-R$_1$**$^{\pm}$ and would not affect the anions, in which the negative charge is delocalized into the CO ligands relatively far away from the SR$_1$ group.

This was the argument used to explain the difference in acidity between **6-Cr-Me** (pK_a^{CH} = 12.50) and **6-Cr-Et** (12.98).[20]

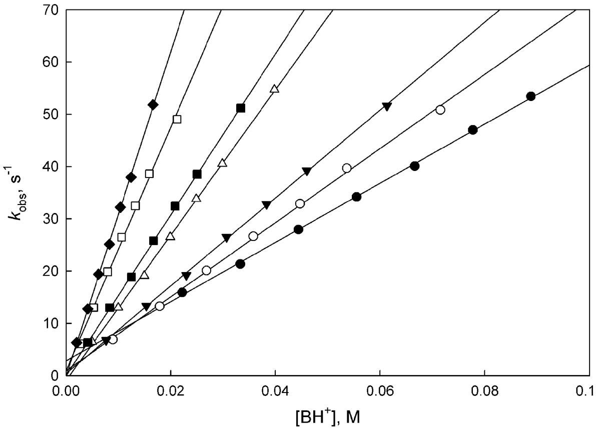


Fig. 3 Representative plots for the proton transfer reaction of **5-W-*i*Pr** with morpholine buffers in 50% MeCN–50% water at 25 °C. (●) pH = 7.80, (○) pH = 8.30, (▼) pH = 8.50, (△) pH = 8.88, (■) pH = 9.00, (□) pH = 9.27, (◆) pH = 9.40.

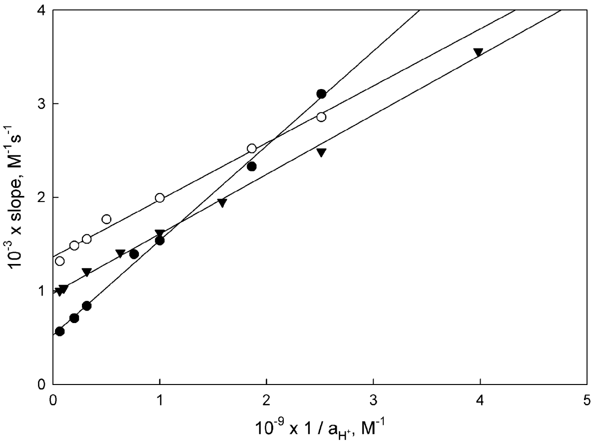


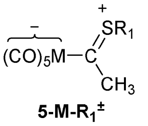
Fig. 4 Slopes *vs.* $1/a_{H^+}$ according to eqn (4) for the reactions of **5-Cr-*c*Hex** (○), **5-Cr-*i*Pr** (▼) and **5-W-*i*Pr** (●) with morpholine buffers.

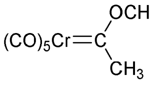
Table 2 Rate constants for the proton transfer reaction of **5-M-R$_1$** in morpholine buffers (50% MeCN–50% water, 25 °C)[a]

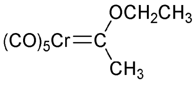
M	R$_1$	k_1^B/M^{-1} s^{-1}	k_{-1}^{BH}/M^{-1} s^{-1}
Cr	Methyl[b]	441	946 ± 30
	tert-Butyl	260	820 ± 20
	Isopropyl	320	970 ± 20
	n-Butyl	370	1320 ± 30
	Cyclohexyl	300	1400 ± 30
W	Methyl[b]	927	414 ± 55
	tert-Butyl	471	373 ± 23
	Isopropyl	476	592 ± 40
	n-Butyl	630	564 ± 5
	Cyclohexyl	500	641 ± 49

[a] Standard deviation given for rate constants determined directly. [b] Values taken from ref. 19.

Considering the sum F + R as a measure of the electronic effect of R$_1$, we can see in Table 1 that there is not a significant difference in the values for the series studied. So, from this point of view, all of the pK_a^{CH} values should be about the same. If there were any difference, **5-M-*t*Bu** should be the least acidic, but this does not correlate with the experimental findings.


5-M-R$_1$$^\pm$


6-Cr-Me


6-Cr-Et

One other factor that should not be set aside is the steric effect of SR$_1$. In the resonance structure **5-M-R$_1$$^\pm$** a planar conformation is required for optimum overlap of the sulfur d orbitals and the empty p$_z$ orbital in the carbene carbon. A bulkier R$_1$ group will make this conformation less favorable, thus causing a less efficient π-donation by the heteroatom and destabilizing the carbene complex. This reduced π-overlap efficiency has been observed for a series of Fischer aminocarbene complexes by ^{53}Cr-NMR studies, in which it was demonstrated that a bulkier substituent on the heteroatom causes a decrease in the charge density on the chromium atom.[31] This steric interference on π-overlap also manifests itself in reduced C–O and C–N bond orders obtained from X-ray crystallography.[30a] For the carbene complexes **5-Cr-R$_1$**, there is a noticeable shift in λ_{max} for the metal–ligand charge transfer band in the UV-Vis spectra. A ~10 nm shift to the red is observed from R$_1$ = methyl (448 nm) to R$_1$ = *tert*-butyl (457 nm). A shift to longer wavelengths of this band is usually attributed to a lower bond order between the heteroatom and the carbene carbon.[32] Thus, the steric effect of the bulkier isopropyl, cyclohexyl and *tert*-butyl substituents (ν_{CH_2R} in Table 1) is expected to enhance the acidity of the corresponding carbene complexes.

Another factor that should be considered is the hydrophobicity of R$_1$ (log *P* in Table 1). The more hydrophobic R$_1$ becomes, the more disrupted would be the solvation sphere of the carbene complex and that of the corresponding anion. Since the latter bears a full charge, it is expected to be the most affected by this structural modification, hence making the carbene complex less acidic with increasing hydrophobicity.

We can see from the values listed in Table 1 that there is a significant change in log *P* for the series studied, with R$_1$ = cyclohexyl being about four times more hydrophobic than R$_1$ = methyl. While this and the other factors discussed above (steric and electronic effects) appear to compensate each other for R$_1$ = *tert*-butyl, *n*-butyl and isopropyl, it seems to be the predominant factor decreasing the acidity for R$_1$ = cyclohexyl.

Tungsten carbene complexes are slightly more acidic than the corresponding chromium analogs. This is reminiscent of previous observations for alkoxy[20] as well as for thiocarbene complexes.[19] The difference in pK_a^{CH} values is slightly higher for M = W (0.44 units) than for M = Cr (0.30 units).

Table 3 Rate constants determined in the various amine buffers and KOH for the proton transfer reaction of **5-Cr-R$_1$** in 50% MeCN–50% water at 25 °C[a]

B	pK_a^{BH}	k_1^B/M^{-1} s^{-1}	k_{-1}^{BH}/M^{-1} s^{-1}	k_1^B/M^{-1} s^{-1}	k_{-1}^{BH}/M^{-1} s^{-1}
		5-Cr-*i*Pr		**5-Cr-*t*Bu**	
OH$^-$	16.64	872 ± 4	8.5 × 10^{-4} [c]	809 ± 7	8.2 × 10^{-4} [c]
Pyrrolidine	11.19	6814 ± 347	67	7261 ± 556	73
Piperidine	11.01	3273 ± 167	48	2937 ± 232	45
Piperazine	9.97	1035 ± 41	168	753 ± 58	126 ± 19
n-BuNH$_2$	10.40	927 ± 45	56	1007 ± 79	63
Benzylamine	9.12	346	403 ± 19	346 ± 53	420 ± 35
Furfurylamine	8.58	156	623 ± 33	156 ± 24	639 ± 56
TRIS[b]	8.32	4.4	32 ± 2	2.8 ± 0.5	21 ± 2
		5-Cr-*n*Bu		**5-Cr-*c*Hex**	
OH$^-$	16.64	739 ± 10	8.7 × 10^{-4} [c]	559 ± 8	8.6 × 10^{-4} [c]
Pyrrolidine	11.19	7618 ± 624	89	6599 ± 482	101
Piperidine	11.01	4174 ± 324	74	3508 ± 230	82
Piperazine	9.97	1073 ± 78	209	805 ± 53	205
n-BuNH$_2$	10.40	1118 ± 81	81 ± 11	959 ± 62	91 ± 11
Benzylamine	9.12	395 ± 54	552 ± 41	335 ± 39	612 ± 39
Furfurylamine	8.58	163 ± 22	778 ± 57	141 ± 18	885 ± 64
TRIS[b]	8.32	4.1 ± 0.6	36 ± 3	3.5 ± 0.5	40 ± 3

[a] Standard deviation given for rate constants determined directly. [b] TRIS, 2-amino-2-(hydroxymethyl)propane-1,3-diol. [c] Rate constant values in s^{-1}.

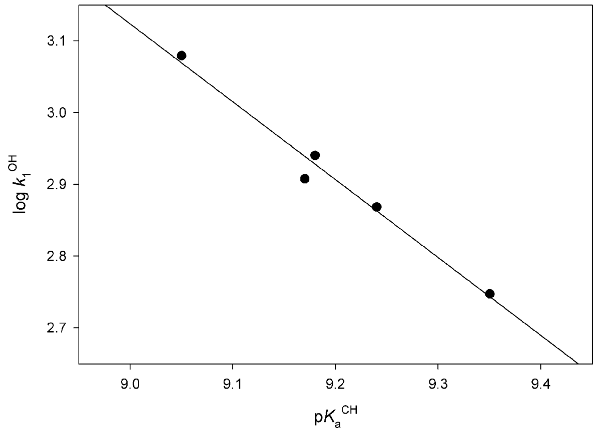


Fig. 5 Correlation between the kinetic acidity in KOH ($k_1^{OH} = k_1^{B}$ for OH^- entry in Table 3) and the thermodynamic acidity for the chromium carbene complexes studied.

However, this difference is relatively small with respect to the experimental errors, so no interpretation of this small metal dependence will be attempted.

Effects of R_1 and the metal on the kinetic acidity

There is a very good linear correlation between the catalytic rate constants for the deprotonation in KOH (see k_1^{B} values for OH^- entry in Table 3) of the substrates with M = Cr and their acidity constants (Fig. 5). The linear plot yields a slope of 1.09 ± 0.09.

Since these reactions have fairly large equilibrium constants, a relatively early transition state is expected according to the Hammond–Leffler postulate.[33] The large value of the slope in the correlation of $\log k_1^{OH}$ *vs.* $\log K_a^{CH}$, seems to contradict this assumption. The transition state seems to be affected by the change in the R_1 substituent to the same extent as the corresponding carbanion. This is reflected in the unchanging $k_{-1}{}^{H_2O}$ values obtained for all the substrates.

This apparent contradiction is the result of the base bearing a negative charge. The transition state of these proton transfer reactions also has a full negative charge, so the hydrophobicity effect exerted by R_1 will be 'felt' by the transition state to about the same extent as the carbanion that results from the reaction.

The steric effect of R_1 seems to play an important role in the kinetic acidity of this series of carbene complexes in the reactions with amines. This is evidenced, on the one hand, by the abnormal reactivity of TRIS and pyrrolidine. TRIS is *less* reactive, whereas pyrrolidine is *more* reactive than expected from their pK_a^{BH} values. The fact that the relative reactivity between a relatively unhindered amine such as *n*-butylamine and TRIS is higher for the substrate with R_1 = *tert*-butyl (360-fold) than for the substrate with R_1 = *n*-butyl (270-fold), supports the notion that steric effects are important.

Unlike the other primary amines, TRIS has three bulky substituents on the carbon directly bonded to the nitrogen. So, in all of its possible conformations, one of the bulky hydroxymethylene substituents is placed towards the reaction center. Pyrrolidine is the only five-membered ring secondary amine used in this study. Its reduced size could contribute to a decreased steric hindrance in the transition state.

On the other hand, for the secondary 6-membered ring amines, **5-M-*t*Bu** are always *less* reactive than **5-M-*c*Hex**, although the former is more acidic and, hence, has a larger thermodynamic driving force. This fact points to a reduced intrinsic reactivity of the former substrates in these reactions.[34]

The steric effect seems to be more pronounced on the tungsten derivatives, as is evident from the comparison of the k_1^{B}(methyl)/k_1^{B}(*tert*-butyl) ratios. With B = morpholine, this ratio is 1.70 for M = Cr, while it increases to 1.97 with M = W. This could be explained in terms of a more advanced transition state, which is a consequence of a more favourable equilibrium constant towards deprotonation.

Intrinsic rate constants and transition states imbalances. Effects of R_1 and the metal

Intrinsic rate constants for the chromium derivatives were determined from the corresponding Eigen plots. Fig. 6 shows a representative plot of k_1^{B} and k_{-1}^{BH} *vs.* $pK_a^{BH} - pK_a^{CH} + \log(p/q)$.[36] The intrinsic rate constants are extracted as $\log k_0$ from the intercepts of these plots. The values for $\log k_0$ and the Brønsted coefficients are summarized in Table 4.

The Brønsted coefficient values are all within the usual range for the proton transfer from Fischer carbene complexes [17–19] and many other carbon acids,[37] so no further comments will be made regarding these parameters.

The intrinsic rate constants are slightly lower for the reactions with primary amines than with secondary amines. In proton transfer reactions secondary amines are usually more reactive than primary amines. This is mainly due to a higher solvation energy of the ammonium ion for the primary amines, combined with the fact that solvation is only incipiently developed at the transition state. This leads to differences of $\log k_0(R_2NH) - \log k_0(RNH_2)$ between 0.8–1.0 logarithmic units. Smaller differences imply the operation of steric effects.[16c] In the proton transfer reactions for the substrates **5-Cr-R₁** this difference is much smaller than the usual values. Furthermore, there is a decrease in the sense R_1 = methyl (0.52) ≫ *n*-butyl (0.21) ~ isopropyl (0.20) > cyclohexyl (0.17)

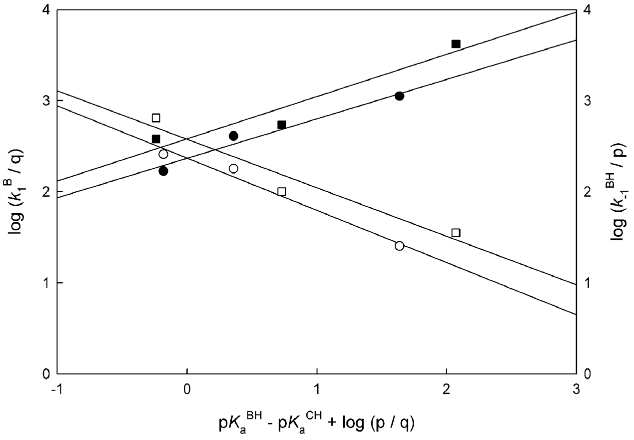


Fig. 6 Eigen plot for the proton transfer reaction of **5-Cr-*n*Bu**. Filled symbols for k_1^{B}; open symbols for k_{-1}^{BH}. (●, ○) Primary amines; (■, □) secondary amines.

Table 4 Summary of Brønsted α^B and β^B values and of log k_0 for the reactions of **5-Cr-R$_1$** with primary and secondary amines in 50% MeCN–50% water at 25 °C

Carbene complex	pK_a^{CH}	Base type	$\alpha^{B\ b}$	$\beta^{B\ c}$	log k_0 ^{d}
5-Cr-Me^a	9.05	RNH_2	0.52 ± 0.04	0.48 ± 0.04	2.09 ± 0.08
		R_2NH	0.55 ± 0.06	0.45 ± 0.06	2.61 ± 0.10
5-Cr-*t*Bu	9.17	RNH_2	0.58 ± 0.07	0.42 ± 0.07	2.31 ± 0.07
		R_2NH	0.54 ± 0.14	0.46 ± 0.14	2.39 ± 0.18
5-Cr-*i*Pr	9.18	RNH_2	0.59 ± 0.07	0.41 ± 0.07	2.30 ± 0.07
		R_2NH	0.56 ± 0.11	0.44 ± 0.11	2.50 ± 0.14
5-Cr-*n*Bu	9.24	RNH_2	0.57 ± 0.08	0.43 ± 0.08	2.37 ± 0.08
		R_2NH	0.53 ± 0.14	0.47 ± 0.14	2.58 ± 0.17
5-Cr-*c*Hex	9.35	RNH_2	0.57 ± 0.08	0.43 ± 0.08	2.36 ± 0.07
		R_2NH	0.52 ± 0.16	0.48 ± 0.16	2.53 ± 0.19

^{a} Values taken from ref. 19. ^{b} Obtained as the slopes of the plots of log K_{-1}^{BH} *vs.* $pK_a^{BH} - pK_a^{CH} + \log(p/q)$. ^{c} Obtained as the slopes of the plots of log K_1^B *vs.* $pK_a^{BH} - pK_a^{CH} + \log(p/q)$. ^{d} Obtained as the intercepts of the plots of log k_1^B or log k_{-1}^{BH} *vs.* $pK_a^{BH} - pK_a^{CH} + \log(p/q)$.

≫ *tert*-butyl (0.08). This finding is a clear indication that steric effects are operating in the transition state of the proton transfer reaction.

Conclusions

The hydrophobicity of the R$_1$ group plays a significant role in determining the thermodynamic acidity of the Fischer carbenes **5-M-R$_1$**, making these compounds slightly less acidic in the sense R$_1$ = methyl > *tert*-butyl ~ isopropyl ~ *n*-butyl > cyclohexyl.

On the other hand, the kinetic acidity is reduced in the following order: R$_1$ = methyl > *n*-butyl > isopropyl ~ cyclohexyl > *tert*-butyl. This result can be interpreted in terms of the steric effect exerted by the substituent, which is also manifested as a reduction in the intrinsic reactivity of secondary amines with respect to primary amines.

The greater stabilization of the negative charge by the $W(CO)_5$ moiety compared to the $Cr(CO)_5$ makes the former carbene complexes both thermodynamically and kinetically more acidic. With respect to the kinetic acidity, the steric bulkiness of R$_1$ is manifested slightly stronger in the W carbene complexes due to a more advanced transition state.

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