Role of the hydrophobicity on the thermodynamic and kinetic acidity of Fischer thiocarbene complexes†‡

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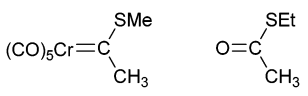
Rate constants for the reversible deprotonation of $(CO)_5W{=}C(SR)CH_3$ (**W-SR**) by OH^-, water and a number of primary aliphatic and secondary alicyclic amines, have been determined in 50% MeCN:50% water at 25 °C. In addition, solvation energy and proton affinities values for **M-SR** (M = Cr and W) in the gas phase and in acetonitrile have been computed at DFT level. Although there is not a linear correlation between the calculated proton affinities and the measured pK_as, the calculations reveal that when solvent effects are taken into account the substituted compounds studied show differences in their proton affinities. There is a good correlation between the change in cavitation energy (ΔG_{cav}) for the Fischer carbene complexes and log *P* of the thioalkyl substituents. In proton transfer reactions with amines, steric effects are more important for W complexes with respect to their Cr analogues as a consequence of differences in transition state progress. On the other hand, in reactions with OH^-, hydrophobicity of the R substituent is responsible for the observed changes in intrinsic kinetic acidities, which is supported by the good correlation obtained between log k_0 and log *P*. W complexes are more sensitive to hydrophobic effects due to the tighter solvation sphere with respect to their Cr counterparts. However, in the limit of log *P* = 0, *the energy involved in the solvent reorganization process is the same regardless of the metal.*

Introduction

The proton transfer from carbon acids is an important reaction from either a chemical or a biochemical point of view. Many enzymes catalyze the heterolytic abstraction of the α-proton from a carbon acid substrate to initiate, for example, 1,1-, 1,2-, 1,3-migrations of protons, aldol and Claisen condensations, and β-elimination reactions.[1] The rates of racemization of naturally occurring L-aminoacids, a spontaneous process that has been related to aging and loss of tissue functions,[2] depend on the acidity of α-C–H protons.[3] Carbon acids are also of great importance in chemical synthesis. Deprotonation of α-carbonyl protons of ketones and aldehydes leads to carbanions that are routinely used in nucleophilic substitution reactions forming carbon–carbon bonds. For instance, it has recently been shown that diazoacetoacetate derivatives—a family of useful intermediates in organic synthesis[4]—can be obtained in an efficient one-pot process from an initial DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)-promoted aldol condensation between ethyl diazoacetate with aldehydes followed by *in situ* oxidation with iodoxy benzoic acid.[5]

Fischer carbene complexes are a family of organometallic compounds that have proved to be extremely valuable intermediates in organic synthesis.[6] One of the most important features of Fischer carbenes is the pronounced electron deficiency of the carbene carbon due to the strongly electron-withdrawing metallic moiety. This enhances the acidity of protons in a carbon adjacent to the carbene carbon even beyond that of α-C–H protons in carbonyl compounds. For example, the thiomethyl carbene complex **Cr-SMe** has a pK_a value of 9.05 in an aqueous solvent,[7] whereas the structurally similar thiolester **O-SEt** has a pK_a value of ~21.0.[8]



Cr-SMe **O-SEt**

As it is typical for other carbon acids, the rate of proton abstraction from acidic Fischer carbenes is slower than the rate of proton abstraction from heteroatom or normal acids of equal acidity.[9] This has been related to the fact that the anions that are formed by deprotonation of these complexes are stabilized by delocalization of the negative charge into the metallic moiety. A large body of evidence accumulated so far indicates that charge delocalization *lags behind* the main bond

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† Dedicated to Prof. Pelayo Camps García, Facultad de Farmacia, Universidad de Barcelona, on the occasion of his 65th birthday

‡ Electronic supplementary information (ESI) available: Fig. S1, UV–vis spectra showing the recovery of the Fischer carbene **W–Sc-Hex** upon acidification of its anion; Fig. S2 and S3, showing the correlation of ΔG_{cav} *vs.* pK_a^{CH} and log *P*; Tables S1–S40, kinetic data for the reactions of **W-SR** with KOH and amines; Table S41, contributions of the solvation free energy for Fischer carbene complexes in acetonitrile; spectroscopic characterization (NMR, IR, HRMS and UV–vis) of **W-SR**. See DOI: 10.1039/c000141d

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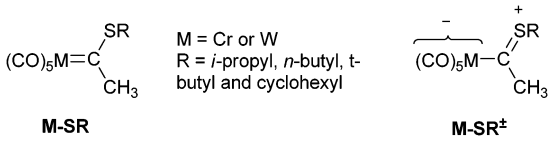
formation/breakage process in these type of reactions.[9c,10] This leads to an *imbalanced transition state*,[9c,10] with a high *intrinsic barrier*, $\Delta G_0^{\dagger}$.§ The study of how different factors, such as charge delocalization, aromaticity development, *etc*. affect the intrinsic reactivity of activated carbon acids is a topic of current interest.[11] This also includes Fischer carbene complexes as prototypical substrates.[12] However, most of these studies have been focused on either alkoxy or amino carbene complexes. This is probably due to the fact that these types of Fischer carbenes are prominent with respect to their synthetic applications. Fischer thiocarbenes, on the other hand, have received much less attention. One of the reasons might have been that it appeared that thiocarbene complexes would react following the same patterns of the isostructural alkoxycarbenes. It was not until recently that some fundamental differences in reactivity of ionizable thiocarbene and alkoxycarbene complexes were found in condensation reactions with acid amide [13] and imidoyl chlorides.[14] Although in recent years much effort has been put into gaining a detailed understanding of the chemical bonding and reactivity of these complexes by means of modern quantum-mechanical methods,[15] Fischer thiocarbenes are also conspicuously absent from these studies.

In a recently published work, we studied the thermodynamic and kinetic acidity of a series of chromium Fischer thiocarbenes (**Cr-SR**) in which we assessed the effect of the bulkiness of the alkyl substituent bonded directly to the sulfur atom.[16] In that work we concluded that the hydrophobicity of the R group plays a significant role in determining the thermodynamic acidity of Fischer carbenes while the steric bulkiness of the substituent was a major factor affecting the kinetic acidity. In order to gain further understanding of the effect of the R substituent we have studied the kinetic and thermodynamic acidity of tungsten derivatives **W-SR** and we complemented the experimental results with a DFT study of the thermodynamic acidity of the Fischer carbenes **M-SR** (M = Cr and W, R = methyl, *i*-propyl, *n*-butyl, *t*-butyl and cyclohexyl). Given the higher electronegativity of W with respect to Cr,[17] it was our expectation that such a modification in the metallic centre would induce a larger effect of the alkyl group on the carbene acidity. This assertion was based on the fact that for a more electronegative metallic atom, the Fischer carbene would have a larger contribution of the zwitterionic resonance structure **M-SR**$^{\pm}$ to the resonance hybrid. This, in turn, should result in a higher positive charge on the sulfur atom and hence a tighter solvation sphere that would be more affected by the hydrophobicity of R. The enhanced reactivity of W Fischer thiocarbenes with respect to their Cr counterparts is well documented for nucleophilic substitution reactions with OH^-, water,[18] primary aliphatic[19] and secondary alicyclic amines[20] in aqueous acetonitrile, and is explained in terms of the higher electronegativity of W which makes the carbene carbon more electrophilic. The results obtained here clearly show, for the first time, that the main factor controlling the acidity of these complexes is the hydrophobicity of R. When this effect, as measured by log *P*, becomes less pronounced, the energy involved in the solvent reorganization is the same regardless of the metal (W or Cr).



M-SR **M-SR$^{\pm}$**

Experimental section

Materials

Fischer carbene complexes were synthesized according to the procedure of Yamashita *et al*.[21] The products were characterized by NMR (400 MHz, $CDCl_3$), FT-IR (KBr), HRMS (FAB) and UV–vis spectrophotometry (see the ESI for the full spectroscopic characterization‡).

Acetonitrile was reagent grade and was used without further purification. Water was taken from a Milli-Q water purification system. It was boiled and purged with dry N_2 before use. The liquid amines were refluxed over Na and freshly distilled before use. 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 dry 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 **M-SR** were (1.0–1.2) $\times$ 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} (*ca*. 435–440 nm) 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 would neutralize the KOH used to generate the anions, and the remaining buffer reacted with the anions. The k_1^{OH} values were obtained from 10 kinetic runs at [KOH] between 0.001–0.0375 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 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^{CH} measurements

The pH in 50% MeCN:50% water was calculated by adding 0.18 to the measured pH, according to Allen and Tidwell.[22] The pK_a^{BH} values for the amines used were determined

§ The intrinsic barrier of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $\Delta G_0^{\dagger} = \Delta G_1^{\dagger} = \Delta G_{-1}^{\dagger}$ when $\Delta G^{\circ} = 0$; similarly the intrinsic rate constant is defined as $k_0 = k_1 = k_{-1}$ when $K_1 = 1$.

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.

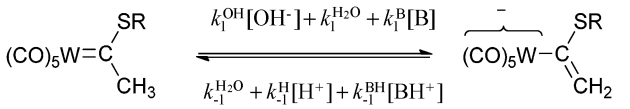
Computational details

All the calculations reported in this paper were obtained with the *Gaussian 03* suite of programs.[23] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[24] and the standard 6-31 + G* basis set for hydrogen, carbon, oxygen, and sulfur and the Hay–Wadt small core effective core potential (ECP) including a double-ζ valence basis set[25] for chromium and tungsten (LanL2DZ keyword). The validity of this method for these types of complexes has been tested in previous studies.[15f,i,26] Zero-point vibrational energy (ZPVE) corrections were computed at the B3LYP/LANL2DZ&6-31 + G* level and were not scaled. Fischer carbene complexes were taken in their more stable *syn*-geometry.[15i] Reactants and products were characterized by frequency calculations[27] and have positive definite Hessian matrices. The solvent was implemented as described in the CPCM model.[28] UAKS cavities and 250 tesserae per sphere with an average area of 0.3 Å^2 were used. The geometries were fully optimized in solvent using the keyword *loose* (RMS force of 0.0017 au) to achieve convergence in the solvated optimization. For the anion of **Cr-SMe**, the optimized structure in the condensed phase presented an imaginary frequency corresponding to the rotation around the Cr–C_{carb} bond with a value of −22 cm^{-1}. The torsion angle (O=)C–Cr–C_{carb}–C(H_3) was systematically modified, but an imaginary frequency was always obtained for all the optimized structures. Nonetheless, the difference in energy between all these rotamers was less than 0.5 kcal mol^{-1}, so this structure could be safely assumed as a minimum stationary point.[29]

Results

General features

Reactions were carried out in 50% MeCN:50% water at 25 °C. The bases utilized were a series of primary aliphatic amines (*n*-butylamine, methoxiethylamine, benzylamine, furfurylamine, and glycine ethyl ester), a series of secondary alicyclic secondary amines (piperidine, piperazine, 1-(2-hydroxyethyl) piperazine (HEPA) and morpholine) and KOH. When any of the thiocarbenes **W-SR** were placed into a KOH or amine buffer solution, a rapid decrease of the MLCT absorption band was observed. After the addition of a few drops of a concentrated HCl solution, this absorption band, characteristic of the carbene complex, was recovered. When this addition was done within 1–2 min after formation of the anion, recoveries were in average *ca.* 80–90% (see Fig. S1 of the ESI‡). This indicates good reversibility of the proton transfer reaction. The reaction scheme for the reversible proton transfer from **W-SR** to a series of amine buffers and KOH consistent with the experiments is shown below (Scheme 1).



Scheme 1 Reversible proton transfer reaction for the carbene complexes **W-SR**.

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 constant is given by eqn (1).

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

Thermodynamic acidities

The pK_a^{CH} values for the Fischer carbenes **M-SR** (M = Cr and W) were determined in a previous work.[16] Those values were obtained from the kinetic experiments with morpholine in the pH range 7.80-9.60. For **Cr-SR** the pK_a^{CH} values were also determined spectrophotometrically, in good agreement with those determined kinetically. Fast decomposition of the conjugated anions precluded a spectrophotometric determination of the pK_a^{CH} values for **W-SR**. We performed DFT calculations to determine the minimum energy structures for the carbene complexes **M-SR** and their respective anions. Proton affinity[30] values were computed as the difference in Gibbs free energy between the aforementioned structures in the gas phase and in acetonitrile as solvent, for which the CPCM solvation model was used.[28] No attempt to calculate actual pK_a values was made, so the contribution of the proton solvation in acetonitrile was not taken into account. The results are summarized in Table 1.

Reaction with KOH and various amine buffers

The rates of deprotonation by OH^- were determined for **W-SR** using KOH in a concentration range of 0.001–0.037 M. Under these experimental conditions eqn (1) reduces to eqn (2). Plots of k_{obsd} *vs.* [KOH] were linear with negligible intercepts (Fig. 1). From the slopes k_1^{OH} values were obtained, whereas $k_{-1}^{H_2O}$ were obtained indirectly as $k_1^{OH}\,K_w/K_a^{CH}$, where K_w is the solvent ionization constant. For 50% MeCN:50% water pK_w = 15.19.[22] These values are summarized in Table 2.

$$k_{obsd} = k_1^{OH}[OH^-] + k_{-1}^{H_2O} \quad (2)$$

For the amine buffers, depending on the pK_a^{BH}, reactions were either run in the forward direction (for pK_a^{BH} ≥ pK_a^{CH}, in which situation k_1^B is determined directly) or in the reverse direction (for pK_a^{BH} ≤ pK_a^{CH}, where k_{-1}^{BH} is determined directly). For any given amine, reactions were run at only one pH value. Under these conditions eqn (1) can be simplified to eqn (3) or eqn (4). In all cases, the plots of k_{obsd} *vs.* [B] (when pK_a^{BH} ≥ pK_a^{CH}) or k_{obsd} *vs.* [BH^+] (when pK_a^{BH} ≤ pK_a^{CH}) were linear. The slopes of the plots of k_{obsd} *vs.* [BH^+] are given by eqn (5), whereas the slopes of the plots of k_{obsd} *vs.* [B] are given by eqn (6). Combining these equations with the known pK_a^{CH}, value k_1^B and

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Table 1 Experimental pK_a^{CH} values, calculated proton affinities (ΔG_{calc} in kcal mol^{-1}) for the Fischer carbene complexes **M-SR** and hydrophobicity parameter log *P* for the thioalkyl substituents studied

	M = Cr			M = W			
Carbene Complex	pK_a^{CH} (exp)	ΔG_{calc} (gas), kcal mol^{-1}[b]	ΔG_{calc} (MeCN), kcal mol^{-1}[b]	pK_a^{CH} (exp)	ΔG_{calc} (gas), kcal mol^{-1}[b]	ΔG_{calc} (MeCN), kcal mol^{-1}[b]	log *P* (RSH)[c]
M-SMe	9.05 ± 0.03[a]	317.30	295.15	8.37 ± 0.06[a]	316.55	293.58	0.56
M-Si–Pr	9.17 ± 0.02	318.03	294.09	8.72 ± 0.04	316.40	296.48	1.21
M-St-Bu	9.18 ± 0.01	317.63	296.00	8.60 ± 0.02	316.21	294.92	1.43
M-Sn-Bu	9.24 ± 0.03	318.17	296.29	8.62 ± 0.02	317.19	295.37	1.80
M-Sc-Hex	9.35 ± 0.03	317.48	299.27	8.80 ± 0.03	317.40	294.94	2.10

[a] Taken from ref. 7. [b] Calculated as *G*(anion)—*G*(carbene complex). All values were calculated at the B3LYP/LANL2DZ&6-31+G* level. [c] Calculated for the thiols RSH according to Crippen and Ghose's fragmentation method, see ref. 31.

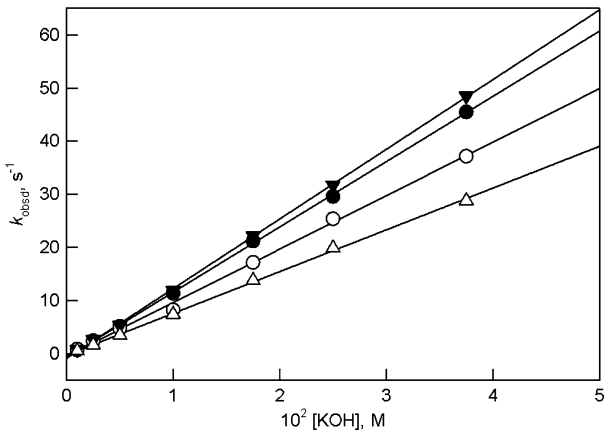

Fig. 1 Plot for the proton transfer reaction of W–S*t*Bu (▼), W–S*i*Pr (●), W–S*n*Bu (○) and W–S*c*Hex (△) with KOH in 50% MeCN:50% water at 25 °C.

k_{-1}^{BH} were obtained for all the substrates and are summarized in Table 2.

$$k_{obsd} = k_1^B[B] + k_{-1}^{BH}[BH^+] = \left(\left(\frac{k_1^B K_a^{BH}}{a_{H^+}}\right) + k_{-1}^{BH}\right)[BH^+] = k_{-1}^{BH}\left(\left(\frac{K_a^{CH}}{a_{H^+}}\right) + 1\right)[BH^+] \quad (3)$$

$$k_{obsd} = k_1^B\left(\left(\frac{a_{H^+}}{K_a^{CH}}\right) + 1\right)[B] \quad (4)$$

$$\text{slope} = k_{-1}^{BH}\left(\frac{K_a^{CH}}{a_{H^+}} + 1\right) \quad (5)$$

$$\text{slope} = k_1^B\left(\frac{a_{H^+}}{K_a^{CH}} + 1\right) \quad (6)$$

Discussion

Mechanism

The spectrophotometric changes observed in the time scale studied were attributed to the proton transfer reaction from the Fischer carbenes **W-SR** to the various bases used, as depicted in Scheme 1, for the following reasons: (i) Although the recoveries of the Fischer carbenes **W-SR** upon acidification were not quantitative, they were on average *ca.* 80–90%. This indicates a good reversibility of the reaction observed which rules out nucleophilic substitution. With amines, a second process, in a longer time scale, was observed. This could be attributed to the corresponding nucleophilic substitution reaction as described by Ali *et al.*;[20] (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 **M-SMe** (M = Cr or W);[20] (iii) there is great similarity in the kinetic behavior observed for **W-SR** with that of the previously studied carbene complexes **M-SMe** (M = Cr and W)[7] and **Cr-SR** (R = *iso*-propyl, *tert*-butyl, *n*-butyl and *c*-hexyl).[16]

Effects of R and the metal on the thermodynamic acidity: DFT calculations

Notwithstanding the relatively small effect of the alkyl substituent R for both series of carbene complexes on their acidity, the observed differences among the highest and the lowest pK_a^{CH} are well outside experimental error. It is interesting to note that ΔpK_a^{CH} (*c*-Hex–Me) is 0.30 and 0.43 for the Cr and W derivatives, respectively. The calculated proton affinities in the gas phase change very little among the series and do not correlate with the changes in the ΔpK_a^{CH}s determined experimentally. For instance, the lowest and highest proton affinities are obtained for Me and *n*-Bu for the Cr series with a difference of only 0.87 kcal mol^{-1}, whereas for the W series the lowest and highest values correspond to *t*-Bu and *c*-Hex respectively, differing by 1.2 kcal mol^{-1}. From these results, we conclude that in the gas phase the proton affinities are nearly independent of the R group in the Fischer carbene. The difference in proton affinity values between the different compounds is larger when the solvent effects are considered. However, they do not correlate with the observed ΔpK_a^{CH} values. It can be seen in Table 1 that the lowest proton affinities correspond to *i*-Pr and Me while the highest proton affinities correspond to *c*-Hex and *i*-Pr in the Cr and W series, respectively. It should be noted that a greater solvent effect should be expected in a mixture 50% MeCN:50% water, but modeling the effects of water is particularly difficult in implicit solvation models, mainly due to their failure in accounting for H-bonds.

Table 2 Rate constants determined in the various amine buffers and KOH for the proton transfer reaction of **W-SR** in 50% MeCN:50% water at 25 °C[a]

		W–Si–Pr (pK_a^{CH} = 8.72)		**W-St-Bu** (pK_a^{CH} = 8.60)	
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}
OH^-	16.64	1229 ± 10	4.18 10^{-4}[b]	1311 ± 10	3.39 10^{-4}[b]
Piperidine	11.01	6990 ± 893	36	6480 ± 432	25.3
Piperazine	9.97	1802 ± 253	102	1411 ± 85	60.5
HEPA[c]	9.33	644 ± 77	158	475 ± 27	88.9
Morpholine	8.70	506[d]	526 ± 35[d]	471[d]	372 ± 12[d]
n-$BuNH_2$	10.40	2023 ± 270	42.4	2294 ± 134	36.5
$MeOCH_2CH_2NH_2$	9.39	438 ± 54	94	476 ± 28	77.6
Benzylamine	9.12	1016 ± 123	405	1112 ± 66	337
Furfurylamine	8.58	348 ± 43	481	421 ± 21	443
$EtOCOCH_2NH_2$	7.43	55.5	1085 ± 151	74.5	1107 ± 77
		W–Sn-Bu (pK_a^{CH} = 8.62)		**W–Sc-Hex** (pK_a^{CH} = 8.80)	
OH^-	16.64	1006 ± 22	4.06 10^{-4}[b]	786 ± 11	2.12 10^{-4}[b]
Piperidine	11.01	12917 ± 1250	52.6	9429 ± 1139	57.6
Piperazine	9.97	2110 ± 136	94.2	1676 ± 164	112
HEPA[c]	9.33	801 ± 43	156.1	627 ± 50	184
Morpholine	8.70	666[d]	549 ± 20[d]	508[d]	634 ± 27[d]
n-$BuNH_2$	10.40	2812 ± 164	46.7	2121 ± 182	53
$MeOCH_2CH_2NH_2$	9.39	518 ± 31	87.9	432 ± 34	110
Benzylamine	9.12	1436 ± 88	454	1062 ± 77	504
Furfurylamine	8.58	491 ± 24	539	336 ± 27	553
$EtOCOCH_2NH_2$	7.43	76.9	1190 ± 88	59.6	1385 ± 137

[a] The error reported represent the standard deviation of the plots of k_{obs} *vs.* [B] (for $pK_a^{BH} \geq pK_a^{CH}$) or k_{obs} *vs.* [BH^+] (for $pK_a^{BH} \leq pK_a^{CH}$), see text. [b] Rate constant values in s^{-1}. [c] HEPA, 1-(2-hydroxyethyl)piperazine. [d] The difference between these values and those reported before in ref. 16 lies in the fact that more experiments have been performed to improve them.

In the CPCM model, the Gibbs free energy change for solvating a solute can be expressed as the contribution of different terms as described in eqn (7) below:

$$\Delta G_{solv} = \Delta G_{el} + \Delta G_{cav} + \Delta G_{dis} + \Delta G_{rep} \quad (7)$$

ΔG_{el} is the electrostatic component, and is calculated using the CPCM self-consistent reaction field method. ΔG_{cav} is the energy required to create a cavity of vacuum into which is inserted the solute. ΔG_{dis} refers to the dispersion interaction that arises from induced dipoles in the cavity surface, and ΔG_{rep} is the repulsion energy. These contributions to the free energy of solvation for **M-SR** in acetonitrile are summarized in Table S41 of the ESI.‡

It can be noticed that there is a good linear correlation between the cavitation free energy and the experimental pK_a^{CH} values for the Cr series, for both the neutral and the anionic forms of the Fischer carbenes (Fig. S2 of the ESI‡). The plot of ΔG_{cav} *vs.* pK_a^{CH} gave a slope of 23 kcal mol^{-1} with correlation coefficient r^2 = 0.9 for both species. For the **W-SR** derivatives the correlation is poorer *i.e.* r^2 = 0.7, but it is remarkable that the slopes are also the same, namely 14 kcal mol^{-1}, for the neutral carbene and its anion. The fact that in both series the slopes obtained for the anionic and neutral forms are the same is a consequence of the fact that the cavitation energy depends mainly on the size of the compound. Even more remarkable is the fact that the ΔG_{cav} values for the neutral and anionic species of the W and Cr derivatives are linearly related to log *P*, with almost identical slopes (Fig. S3 of the ESI‡).

The change in free energy of solvation when the neutral carbene is ionized, *i.e.* ΔG_{solv}(anion)–ΔG_{solv}(neutral), does not follow a regular trend and the maximum differences along the series are 0.49 and 0.53 kcal mol^{-1} for the Cr and W derivatives, respectively. It is noteworthy that the solvation energy for the neutral methyl derivatives has the lowest positive value while in the anion it has the highest negative value. This result is consistent with the fact that the methyl group is the smallest and the less hydrophobic of all the substituents considered in this study.

Effect of R and the metal on the kinetic acidity

Table 2 summarizes the catalytic rate constants for the proton transfer reaction from the Fischer carbenes **W-SR** to the bases studied here. Intrinsic rate constants (k_0) for each series of amines are extracted as log k_0 from the corresponding Eigen plots (Fig. 2) and are summarized, in Table 3. Likewise, the intrinsic rate constants for the reactions with KOH were estimated according to eqn (8), where $K_1^{OH} = k_1^{OH}/k_{-1}^{H_2O}$ and are also summarized in Table 3. The values for the Cr complexes from our previous work are also included for comparison purposes.

$$\log k_0 = \log k_1^{OH} - 0.5 \log K_1^{OH} \quad (8)$$

The discussion that follows has been separated in two parts, one dealing with the reactions in the presence of amine buffers and other dealing with the reactions in alkaline conditions:

Reactions with amine buffers

More enlightening than comparing logk_0 values themselves is the difference $\Delta\log k_0$ = logk_0 (R_2NH)–logk_0 (RNH_2) for each carbene complex. The fact that secondary amines are intrinsically more reactive than primary amines is well known in

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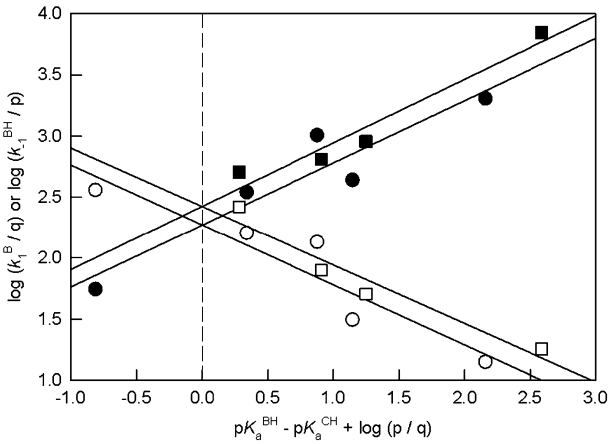

Fig. 2 Eigen plot for the proton transfer reaction of **W–Si-Pr** with amine buffers. Filled symbols are for k_1^B and opened symbols are for k_{-1}^{BH}: (●,○) primary amines; (■, □) secondary amines.

proton transfer reactions. It is caused by differences in the solvation energies of the respective protonated amines and the fact that at the transition state solvation of the incipient protonated amine lags behind proton transfer.[9c,32] Differences of $\Delta\log k_0$ between 0.8–1.0 are typical, whereas smaller differences, like those observed for the carbene complexes **M-SR**, are usually attributed to *steric effects*.[10a] It is noteworthy that $\Delta\log k_0$ becomes smaller for W complexes when compared with their Cr analogues. This is a consequence of a more favorable equilibrium constant towards deprotonation, which leads to less advanced transition state in the case of the W complexes. This is consistent with the Hammond–Leffer postulate.[33]

As is well known, the transition state of a proton transfer reaction from these type of complexes is imbalanced.[12a] The negative charge that develops is largely localized on the α-carbon. A more advanced transition state for the Cr derivatives implies that the charge on this carbon should be higher than for the W complexes. This results in a more pronounced electrostatic repulsion with the lone pairs on the nitrogen bases. Hence, the proton transfer takes place at a larger distance between the carbene complex and the base, leading to a *smaller* steric effect of the R substituent for the Cr complexes.

Reactions with KOH

Although **W-SMe** is less reactive than **Cr-SMe** towards OH^- as reported by Bernasconi *et al.*,[7] in this study we found that for the carbene complexes with bulkier R substituents the W analogues have a higher kinetic acidity than their Cr counterparts. This result is in agreement with the general notion that W carbenes are more reactive than Cr carbenes.[34] Nonetheless, the intrinsic reactivity, as approximated by eqn (8), is lower for the W complexes, following the same trend shown for the reactions with amines.

The order of reactivity towards OH^- decreases in the same sense as the thermodynamic acidity decreases, *i.e.* S*t*-Bu > S*i*-Pr > S*n*-Bu > S*c*-Hex. This constitutes a marked contrast with the reactions with amines, where the order of reactivity is dictated by the steric bulkiness of the substituent. This is related to the fact that the thermodynamic driving force is larger for the reaction with OH^- and, hence, an earlier transition state is expected. As is shown in Fig. 3 there is a good correlation between log k_1^{OH} and the hydrophobicity parameter of the R substituent as measured by log *P*. There is a slight increase (~20%) of this effect for the W derivatives which can be well correlated with the effect of the hydrophobicity on the acidity constants.

The reduced reactivity of **W-SMe** with respect to its Cr analogue poses an interesting question. Bernasconi *et al.*[7] suggested that the strong solvation of OH^- could be a part of the explanation. In view of the above results we propose an alternative explanation. The three-step mechanism for proton transfers originally proposed by Eigen[35] involves the association of the reactants molecules, followed by the proton transfer itself and a subsequent dissociation step into the products, as shown in Scheme 2 below.For proton transfer reactions from carbon acids such as those studied here, the proton transfer step is rate determining, and the free energy barrier for the reaction is given by the Marcus equation [eqn (9)],

$$\Delta G^{\dagger} = W^{R} + \Delta G_0^{\dagger}\left[1 + \frac{\Delta G^0 - \Delta W}{4\Delta G_0^{\dagger}}\right]^2 \qquad (9)$$

where W^R is the work required to bring the reactants together, ΔW is the difference between W^R and the corresponding work required to separate the products (W^P), $\Delta G_0^{\dagger}$ is the intrinsic barrier for the reaction and ΔG^0 is the thermodynamic driving force. When rate constants correlate linearly with the thermodynamic driving force, as is the case for the reactions studied here, this equation can be approximated and rewritten as eqn (10) below.

$$\Delta G^{\dagger} = \frac{\Delta G^0}{2} + \frac{W^R + W^P}{2} + \Delta G_0^{\dagger} \qquad (10)$$

It should be noted that the work term $(W^R + W^P)/2$ refers to the solvent reorganization taking place during the proton

Table 3 Summary of $\log k_0$ values for the reactions of **M-SR** with primary and secondary amines, and hydroxide anion in 50% MeCN:50% water at 25 °C.

	M = Cr				M = W			
Carbene Complex	$\log k_0$ (OH^-)	$\log k_0$ (R_2NH)	$\log k_0$ (RNH_2)	$\Delta\log k_0$[a]	$\log k_0$ (OH^-)	$\log k_0$ (R_2NH)	$\log k_0$ (RNH_2)	$\Delta\log k_0$[a]
M-SMe[b]	0.01	2.61 ± 0.10	2.09 ± 0.08	0.52	−0.49	2.50 ± 0.18	2.17 ± 0.05	0.33
M-Si–Pr	−0.06[c]	2.50 ± 0.10[c]	2.30 ± 0.10[c]	0.20	−0.15	2.42 ± 0.13	2.27 ± 0.13	0.15
M-St-Bu	−0.10[c]	2.39 ± 0.10[c]	2.31 ± 0.10[c]	0.08	−0.18	2.27 ± 0.20	2.30 ± 0.30	−0.03
M-Sn-Bu	−0.11[c]	2.58 ± 0.10[c]	2.37 ± 0.10[b]	0.21	−0.28	2.41 ± 0.20	2.36 ± 0.15	0.05
M-Sc-Hex	−0.17[c]	2.53 ± 0.10[c]	2.36 ± 0.10[c]	0.18	−0.30	2.42 ± 0.17	2.32 ± 0.12	0.10

[a] Difference in $\log k_0$ between secondary and primary amines (R_2NH—RNH_2). [b] Ref. 7. [c] Ref. 16.

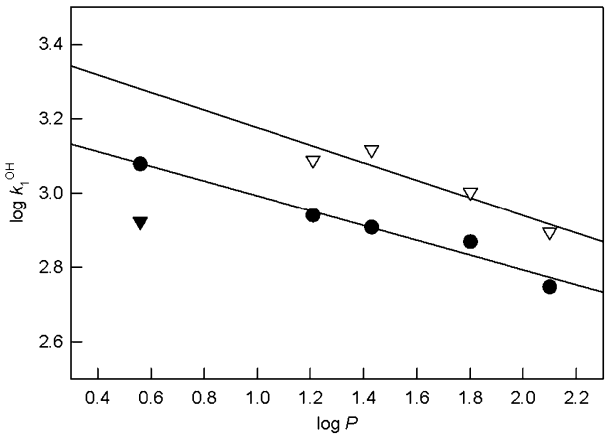

Fig. 3 Linear dependence between $\log k_1^{OH}$ and log P for the Cr carbene complexes (●, slope = −0.20, r^2 = 0.965) and for the W carbene complexes (▽, slope = −0.24, r^2 = 0.870). The thiomethyl W complex, **W-SMe**, is represented by ▼ and has not been taken into account for the linear correlation.

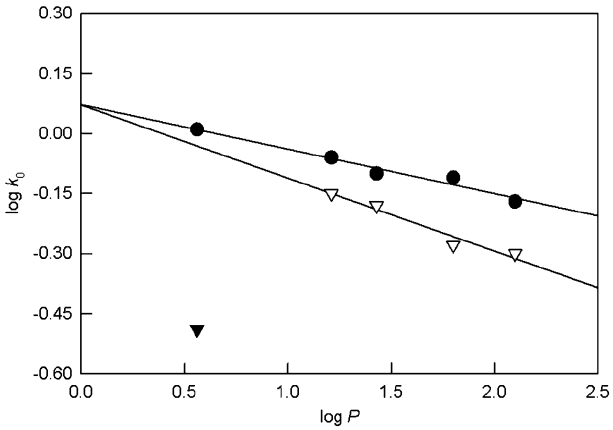

Fig. 4 Linear dependence shown by $\log k_0$ *vs.* log P for the Cr carbene (●, slope = −0.11, r^2 = 0.967) and W carbene (▽, slope = −0.18, r^2 = 0.954) complexes series. **W-SMe** is shown as ▼ and was not included in the correlation.

transfer process. Since the association process involves bringing the tightly solvated OH^- into a more hydrophobic environment, it is reasonable to suppose an increment of W^R along with log P. On the other hand, the expulsion of the water molecule after the proton transfer reaction has occurred should be less costly for a more hydrophobic R substituent, leading to a smaller W^P as log P becomes larger.

This counter effect of the hydrophobicity on the work term might be the source of the reduced reactivity of **W-SMe**, as compared with the other tungsten carbene complexes, if the amount by which W^R is reduced is not compensated by the increase in W^P. Note that the change in hydrophobicity is more significant when R = Me compared to any of the other bulkier R groups. The effect of the metal can be explained in terms of the solvation of the Fischer carbene. Due to the fact that $W(CO)_5$ is more electron withdrawing than the $Cr(CO)_5$ moiety, it is expected that the resonant structure **M-SR**$^{\pm}$ would contribute to a higher extent to the resonance hybrid in the tungsten derivatives. This should lead to a tighter solvation sphere around the carbene complex, making solvent reorganization more difficult and thus increasing both W^R and W^P. When R becomes bulkier, the hydrophobicity in the proximity of the alkyl group increases and the W^R term should increase.

Rearranging eqn (10) and combining it with eqn (8), eqn (11) is obtained:

$$\Delta G^{\dagger} - \frac{\Delta G^0}{2} = \frac{W^R + W^P}{2} + \Delta G_0^{\dagger} \propto \log k_0 \qquad (11)$$

Since $\Delta G_0^{\dagger}$ is assumed to be constant for a family of closely related compounds,[9c,10,36] the dependence of $\log k_0$ on log P is related to the influence of the hydrophobicity on the work term. It is expected that the largest effect would be given by the solvent reorganization term.

$$CH + B^v \leftrightarrows CH{\cdot\cdot}B^v \leftrightarrows C^-{\cdot\cdot}HB^{v+1} \leftrightarrows C^- + HB^{v+1}$$

Scheme 2 Three-step mechanism for a proton transfer reaction.

As is shown in Fig. 4, there is a good linear relationship between $\log k_0$ and log P. The negative slope could be attributed to the fact that the change in intrinsic reactivity for the different compounds is dominated by the term W^R. Again, for **W-SMe** it can be observed that its intrinsic reactivity is the lowest, explaining the reduced proton transfer rate overcoming the thermodynamic driving force. As stated before, this low reactivity could be explained in terms of higher energy cost for solvent reorganization deriving from a tighter solvation sphere with respect to the other carbene complexes.

The more pronounced effect of the W complexes can be attributed again to the contribution of **M-SR**$^{\pm}$ to the resonance hybrid. The effect of disrupting the solvation sphere is more dramatic for a more tightly bound solvation sphere around the carbene complex.

Note that the extrapolation to log P = 0 yields the same value for both series of carbene complexes. Thus, in this limit, *the energy involved in solvent reorganization is the same regardless of the metal.*

Conclusions

Hydrophobicity plays an important role in thermodynamic acidity of Fischer carbene complexes. DFT/CPCM calculations suggest that the change in pK_a^{CH} can be correlated with the change in cavitation energy but there is not a correlation with the total solvation free energy of the substrates. However, the data show that the span in proton affinity among the different compounds is greater when the solvent is considered. On the other hand, in the gas phase there is almost no effect of the R substituent on the proton affinities.

For proton transfer between amines and **M-SR**, the steric effect is more important for W complexes than for their Cr analogues. This is a consequence of a more favorable equilibrium constant towards deprotonation and an imbalanced transition state. For the Cr series proton transfer takes place at larger distances between the carbene complex and the base, leading to a *smaller* steric effect of the R substituent.

Tungsten Fischer carbene complexes with bulky R substituents have a higher kinetic acidity than their Cr counterparts.

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Interestingly, proton transfer reactions towards HO^- show an important role of the hydrophobicity of the R group, supported by a good correlation between log k_1^{OH} and the hydrophobicity parameter log *P*. The fact that $W(CO)_5$ is more electron withdrawing than $Cr(CO)_5$, leads to a tighter solvation sphere around the carbene complex, making solvent reorganization more difficult. When R becomes bulkier, its hydrophobicity disrupts the solvation sphere becoming the dominant factor. Nevertheless, when hydrophobic effects are less pronounced, for both series of carbene complexes (Cr and W) the amount of energy involved in solvent reorganization is the same regardless of the identity of the metal.

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