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Graphical Abstract



Nucleophilic Reactivities of Schiff Base Derivatives of Amino Acids

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Dedicated to Professor Léon Ghosez in recognition of his great contributions to chemistry

Abstract

Treatment of α -imino esters derived from glycine esters and benzophenone or benzaldehydes with potassium *tert*.butoxide in DMSO gave persistent solutions of carbanions at 20 °C. The kinetics of their reactions with quinone methides and benzylidene malonates (reference electrophiles) have been followed photometrically under pseudo-first order conditions. The reactions followed second-order rate laws. Since addition of 18-crown-6 ether did not affect the reaction rates, the measured rate constants correspond to the reactions of the non-paired carbanions. Plots of the second-order rate constants against the electrophilicity parameters *E* of the electrophiles are linear, which allowed us to derive the nucleophile-specific parameters *N* and s_N , according to the linear Gibbs energy relationship lg $k_2(20^\circ\text{C}) = s_N(N + E)$. The Ph₂C=N- and PhCH=N- groups act as very weak electron acceptors with the consequence that Ph₂C=N-CH⁻-CO₂R and PhCH=N-CH⁻-CO₂R have a similar nucleophilicity as Ph-CH⁻-CO₂Et, the anion of ethyl phenylacetate.

Keywords: α-amino acids / carbanions / nucleophilicity / kinetics / linear free-energy relationships / Michael addition

1. Introduction

 α -Imino esters have become frequently used building blocks for synthesizing racemic and optically active α -amino acids and derivatives, which are of great importance in pharmaceutical, biological and synthetic chemistry.¹ The benzophenone-derived imines of glycine alkyl esters were introduced by O'Donnell in 1978,² and in the last 30 years these substrates have been used for the synthesis of α -amino acids via a wide variety of synthetic routes, including phase transfer catalyzed alkylations³⁻⁵, Michael,⁶⁻¹¹ aldol,^{12,13} and Mannich¹⁴⁻¹⁷ reactions (Scheme 1).



Scheme 1. Amino acids from benzophenone imines of glycine esters.

During the last decades our research group has developed comprehensive nucleophilicity and electrophilicity scales, which afford a direct comparison of the reactivities of different classes of compounds.¹⁸ We have shown that the rates of the reactions of π -, n- and σ -nucleophiles with C_{sp2}-centered electrophiles can be described by the linear Gibbs energy relationship (1), where k_2 (20 °C) [L mol⁻¹ s⁻¹] is a second-order rate constant, N and s_N are solvent-dependent nucleophile-specific parameters and *E* is an electrophile-specific parameter.¹⁹

$$\lg k_2(20^{\circ}C) = s_N(N+E)$$
 (1)

This method has already been employed to determine the reactivity of various carbanions,²⁰ including nitronate anions,^{20b} alkoxycarbonyl-,^{20f} cyano-,^{19b,20d} phosphoryl-,^{20e} and sulfonyl-stabilized^{20g} carbanions and revealed that pK_a values of the conjugate acids do not serve as reliable measure of relative reactivities.^{20b,c,d,f}



Scheme 2. UV-Vis absorption maxima and pK_{aH} values in DMSO of Schiff base derivatives of amino acids investigated in this work. Counterion K⁺. ^a From Ref. 21.

We now report on the kinetics of the reactions of the potassium salts of different glycine- and alanine-derived imino esters **1a-e** and imino acetonitrile **1f** (Scheme 2) with the Michael acceptors **2a-e** (reference electrophiles, Table 1) in DMSO solution. The resulting second-order rate constants will then be used to determine the nucleophilicities of the title compounds according to Eq. (1).

Table 1. Quinone methides and benzylidene malonates as reference electrophiles employed in this work.

	Electrophile		E^{a}	$\lambda_{\max}^{\ b}$
	NC COOEt	2a	-18.06	283
	N tBu	2b	-17.90	521
Ċ	O ₂ N COOEt	2c	-17.67	302
	Me ₂ N <i>t</i> Bu	2d	-17.29	486
_	MeO <i>t</i> Bu	2e	-16.11	393

^a From Refs. 19b, 22. ^b In DMSO solution, given in nm.

2. Results and Discussions

2.1. Products of the Reactions of the Carbanions 1 with Reference Electrophiles 2

In order to examine the course of the reactions studied kinetically, we have characterized the products of representative combinations of the carbanions 1 with benzylidene malonate 2c or quinone methide 2d.



Scheme 3. Reactions of *tert*-butyl imino ester 1b-H with the reference electrophiles 2c and 2d in DMSO at 20 °C. ^a Determined from ¹H NMR spectra of the crude product.

The benzophenone-derived *tert*-butyl glycine imino ester anion **1b** (1.1 equiv.), which was generated from **1b**-H by treatment with KOtBu in DMSO, reacted with the reference electrophiles **2c** and **2d** to afford the adducts **3bc** and **3bd**, respectively, as a mixture of two diastereomers after aqueous work up (Scheme 3). The products were isolated in moderate yields after purification by column chromatography and characterized by mass spectrometry and ¹H and ¹³C NMR spectroscopy. Analogous products have recently been reported by Deng and coworkers via enantioselective copper-catalyzed additions of glycine Schiff bases to *para*-quinone methides.¹¹ The conjugate additions of glycine imino esters to arylidene malonates catalyzed by AgOAc/ThioClick Ferrosphos complexes have been reported to give the corresponding adducts in good yields with high enantioselectivities.¹⁰

As shown in Scheme 4, the imino acetonitrile anion **1f** was obtained by deprotonation of the corresponding CH acid with 1.05 equivalents of KO*t*Bu. Addition to the quinone methide **2b**, followed by aqueous workup, gave the product **3fb** in 82% yield as mixture of two diastereoisomers.



Scheme 4. Reaction of imino acetonitrile **1f**-H with the quinone methide **2b** in DMSO at 20 °C. ^a Determined from the ¹H NMR spectrum of the crude product.

When 1.1 equivalents of the potassium salt of **1e**-H, derived from alanine ester and benzaldehyde, was combined with quinone methide **2d**, only a small degree of conversion was observed, probably due to the reversibility of these reactions. When this reaction was carried out with 5 equivalents of **1e**, a higher degree of conversion of **2d** was observed. However, as the corresponding adduct **3ed** could not be separated from the crude reaction mixture, it was hydrolyzed to provide 12 % of the amino ester **4ed** (*dr* 2:3) after column chromatography (Scheme 5).



Scheme 5. Reaction of 1e-H with the quinone methide 2d in DMSO at 20 °C.

A fair yield of **4cb** was obtained when **2b** was combined with 2 equivalents of **1c**-H and 1 equivalent of KOtBu and the resulting imino ester **3cb** was hydrolyzed with 2 M HCl (Scheme 6).



Scheme 6. Reaction of 1c-H with the quinone methide 2b in DMSO at 20 °C.

2.2. Kinetic Investigations

The reactions of the 2-aza-allyl anions **1a-f** with the quinone methides **2b,d,e** and the benzylidene malonates **2a** and **2c** were performed in DMSO solution at 20 °C and monitored by UV-vis spectroscopy at or close to the absorption maxima of the electrophiles **2** (Table 1) using stopped-flow techniques. The potassium salts (**1a-f**)-K were not isolated because of their low stability but were generated in solution by deprotonation of the corresponding CH acids (**1a-f**)-H with KO*t*Bu (typically 1.05 equivalents) in DMSO directly before the kinetic experiments. In order to simplify the evaluation of the kinetic experiments, the nucleophiles **1a-f** were employed in large excess (\geq 10 equiv.) over the electrophiles **2**. Therefore, the concentrations of **1** can be considered almost constant throughout the reactions, resulting in pseudo-first-order kinetics in all runs (Eq. 2).

$$-d[\mathbf{2}]/dt = k_2[\mathbf{1}][\mathbf{2}];$$

for $[1] >> [2] => -d[2]/dt = k_{obs}[2]$ with $k_{obs} = k_2[1]$ (2)

As a consequence, monoexponential decays of the concentrations of the UV/Vis-active electrophiles were observed. The first-order rate constants k_{obs} [s⁻¹] were derived by least-squares fitting of the exponential function $A_t = A_0 \exp(-k_{obs}t) + C$ to the time-dependent absorbances A_t of the electrophiles (Fig. 1). Plots of k_{obs} against the concentrations of the nucleophiles [1] were linear as illustrated in Fig. 1 (insert); the small negative intercepts may be due to partial decomposition of the carbanions 1. Second-order rate constants k_2 [L mol⁻¹ s⁻¹] (Table 2) for the reactions of carbanions 1a-f with the reference electrophiles **2a-e** were derived from the slopes of these plots.



Fig. 1. Exponential decay of the absorbance of **1a** ($[\mathbf{1a}]_0 = 4.52 \times 10^{-5} \text{ mol } \text{L}^{-1}$) at 425 nm during its reaction with **2d** ($[\mathbf{2d}]_0 = 5.15 \times 10^{-4} \text{ mol } \text{L}^{-1}$) at 20 °C in DMSO solution. Inset: Correlation of the rate constants k_{obs} with $[\mathbf{1a}]$ in DMSO at 20 °C. The tagged data point refers to the depicted absorption-time trace. Open circles: In the presence of 18-crown-6 ether (1.1 equiv. with respect to **1a**-K). Filled circles: Without 18-crown-6 ether.

We also investigated the effect of ion-pairing on the measured rate constants by using 18crown-6 ether as an additive. As depicted by the open symbols in Fig. 1, the pseudo-firstorder rate constants k_{obs} , measured in the presence and in the absence of 18-crown-6 ether (1.1 equiv. with respect to **1a**), were on the same plots of k_{obs} versus concentration [**1**], indicating that interaction of the carbanion with K⁺ does not play a significant role, and the rate constants listed in Table 2 refer to the reactivities of the free carbanions **1a-f**.

Carbanion ^a	$\frac{N}{(s_{\rm N})^{\rm b}}$	Electrophile ^c	$\frac{k_2}{L \text{ mol}^{-1} \text{ s}^{-1}}$
1a	26.95	2a	3.16×10^{4}
	(0.52)		$2.69 imes 10^{4 d}$
		2b	4.92×10^4
		2c	$8.01 imes 10^4$
			$6.78 imes 10^{4 d}$
		2d	8.97×10^{4} e
		2e	3.84×10^{5} e
1b	27.77	2b	4.88×10^4
	(0.47)	2c	7.13×10^{4}
		2d	7.71×10^{4}
		2e	$3.59 \times 10^{5} e$
1c	$\approx 29.1^{\mathrm{f}}$	2b	3.82×10^{5}
1d	29.02	2b	2.79×10^{5}
	(0.49)	2d	5.55×10^{5}
1e	30.82	2b	2.22×10^{5}
	(0.41)	2d	3.97×10^{5}
1f	$\approx 29.5^{\mathrm{f}}$	2 b	6.65×10^{5}

Table 2. Second-order rate constants k_2 for the reactions of the carbanions **1a-f** with the reference electrophiles **2a-e** in DMSO at 20 °C.

^a Counterion K⁺. ^b The nucleophilicity parameters *N* and s_N were determined by correlation analysis using Eq. (1); see text. ^c Minor component in the pseudo-first order kinetics. ^d Pseudo-first order kinetics measured with **1a** as a minor component. ^e The decays of absorbances were not strictly monoexponential; therefore, only the initial 50% of the decays were used for evaluation of the pseudo-first-order rate constants k_{obs} . ^f For an estimated $s_N =$ 0.50.

As the 2-aza-allyl anions 1 are colored, we have also conducted kinetic experiments, where diethyl benzylidene malonates 2a and 2c were employed in excess (≥ 10 equiv.) over the anion 1a and monitored the exponential decays of the UV/Vis-absorbances of 1a. In these cases second-order rate constants k_2 were obtained from the slopes of the plots of k_{obs} against the concentrations of 2a and 2c. The resulting second-order rate constants differed by a factor of 1.2 from those determined with an excess of carbanion, indicating the error limits of the measured rate constants.

2.3. Correlation analysis

As shown in Fig. 2, plots of $\lg k_2$ for the reactions of the anions **1a** and **1b** with the reference electrophiles **2** versus the electrophilicity parameters *E* of **2** are linear. The slopes of these correlations equal the nucleophile-specific parameters s_N , and the negative intercepts on the

abscissa (lg $k_2 = 0$) correspond to the nucleophilicity parameters *N*, which are listed in Table 2.



Fig. 2. Correlations of $\lg k_2$ for the reactions of the carbanions 1 with reference electrophiles **2a–e** at 20 °C in DMSO with their electrophilicity parameters *E*.

Since similar slopes s_N have also been found for the 2-point correlations for **1e** and **1d** (0.42 and 0.52, Table 2), one can conclude that the relative reactivities of these carbanions depend only slightly on the electrophilicity of the reaction partners. The relative rate constants towards electrophile **2b**, which are depicted in Fig. 3, can, therefore, be considered to be representative for the relative reactivities.

Fig. 3 shows that the nature of the ester group (*tert*-butyl or ethyl) has no effect on the reactivity of the benzophenone derived Schiff bases **1a,b**. Removal of one phenyl group to give the benzaldehyde derivative **1c** increases nucleophilicity by a factor of 7.8, and the *p*-Cl substitution in **1d** reduces reactivity by a factor of 1.4. In analogy to previously reported relative reactivities of secondary and tertiary carbanions,^{20a} the comparison of **1c** and **1e** shows that an extra methyl group at the carbanionic center has only a slight effect on nucleophilic reactivity. The cyano-substituted carbanion **1f** is 13.5 times more reactive than the corresponding ester derivative **1a**.



Fig. 3. Relative reactivities of the nucleophiles **1a-f** towards the quinone methide **2b** (DMSO, 20 °C).

In previous work^{20a} we have shown that the nucleophilic reactivities of carbanions in water as well as in DMSO correlate only poorly with the corresponding pK_{aH} values in these solvents. O'Donnell and co-workers have systematically studied the pK_{aH} values of the Schiff base derivatives of amino acids and related compounds that were of interest for the synthesis of the amino acids by phase-transfer alkylations.²¹ The Brønsted correlation in Fig. 4, which plots the second-order rate constants for the reactions of various carbanions with quinone methide **2b** against the corresponding pK_{aH} values,^{21,23} is of low quality and again demonstrates the limitation of pK_a values for predicting nucleophilic reactivities. It is obvious, however, that the 2-aza-allyl anions **1** are more reactive than expected from the pK_a values of the conjugate CH-acids **1**-H. We have not examined whether the positive deviations of anions **1** from the Brønsted plots are due to lower intrinsic barriers for these reactions or due to the fact that the rate constants refer to reactions with a carbon center whereas the pK_{aH} values correspond to associations with the proton.²⁴



Fig. 4. Brønsted correlation for the reactions of the quinone methide **2b** with carbanions derived from amino acid derivatives **1** and related carbanions in DMSO at 20 °C. pK_{aH} from ref 21 (for anions **1**) and ref 23 (for other carbanions); second-order rate constants k_2 from Table 2 (for reactions of **2b** with anions **1**) and refs 20d,e,f and 25 (for reactions of **2b** with other carbanions).

3. Conclusion

The second-order rate constants of the reactions of the α -iminoesters **1a** and **1b**, derived from benzophenone and glycine esters, with quinone methides and arylidene malonates **2a**–e (reference electrophiles) correlate linearly with the electrophilicity parameters *E* of **2**, which allowed us to calculate the susceptibilities s_N (slopes in Fig. 2) and the nucleophilicities *N* (negative intercepts on the abscissa in Fig. 2) of **1a,b**. Since the corresponding two-point correlations for **1d** and **1e** yield similar susceptibilities s_N , we concluded that the relative reactivities of the carbanions **1a-f** are almost independent of the electrophilicity of their reaction partners. The structure-reactivity relationships derived from the reactivities toward the quinone methide **2b** were, therefore, considered to be representative for the reactivities of these carbanions. Comparison of **1a** and **1c** shows that the benzophenone-derived iminoester is 8 times less reactive than the benzaldehyde-derived iminoester and that the cyano derivative **1f** is 13 times more reactive than the ester derivative **1a**.

In line with earlier investigations of the kinetics of the reactions of carbanions with quinone methides and other Michael acceptors,²⁵ the rates of the reactions of the azaallyl anions **1** were independent of the nature of the counterions, which can be explained by complete dissociation of the ion pairs in dilute DMSO solution ([**1**] < 10^{-4} mol L⁻¹). Because of the low solubilities of the carbanion salts in nonpolar solvents, where ion pairing was shown to reduce

their reactivities significantly,²⁶ we have not been able to study kinetics of their reactions in toluene-CHCl₃ or CH_2Cl_2 solution, i.e., the organic solvents in which enantioselective alkylations of **1** under phase-transfer conditions were performed.¹

Since kinetics of the reactions of the quinone methide **2b** with other carbanions have previously been reported, we can also compare the nucleophilicities of the iminoesters **1** with those of other types of carbanions. Fig. 5, which compares the influence of various α -substituents on ethyl acetate anions, shows that the imino substituted carbanions have a similar nucleophilicity as the anion derived from ethyl phenylacetate. Even though the relative reactivities of the carbanions in Fig. 5 will somewhat vary with the nature of the electrophile because of the different magnitude of s_N , one can see that replacement of the imino group in **1a,c** by cyano, alkoxycarbonyl, acyl, phosphoryl, and sulfonyl groups leads to a significant reduction of nucleophilicity. One, therefore, can expect that all electrophiles known to react with these types of carbanions will also react with the corresponding imino-substituted carbanions **1**. More precise predictions of potential electrophilic reaction partners can be obtained by using Eq. (1), which combines the *N* and s_N parameters determined in this work with the electrophilicity parameters accessible through ref 19g.



Fig. 5. Comparison of second-order rate constants (lg k_2) for the reactions of the quinone methide **2b** with the carbanions derived from α -imino esters **1** and related carbanions. *N* and s_N are given below each nucleophile (reactivities refer to DMSO as solvent). ^a From ref 20f. ^b From ref 19b. ^c From ref 20e. ^d From ref 20g.

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