Metal Enolates – Enamines – Enol Ethers: How Do Enolate Equivalents Differ in Nucleophilic Reactivity?

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Abstract The kinetics of the reactions of trimethylsilyl enol ethers and enamines (derived from deoxybenzoin, indane-1-one, and α-tetralone) with reference electrophiles (p-quinone methides, benzhydrylium and indolylbenzylium ions) were measured by conventional and stopped-flow photometry in acetonitrile at 20 °C. The resulting second-order rate constants were subjected to a least-squares minimization based on the correlation equation \( \lg k = s_N(N + E) \) for determining the reactivity descriptors \( N \) and \( s_N \) of the silyl enol ethers and enamines. The relative reactivities of structurally analogous silyl enol ethers, enamines, and enolate anions towards carbon-centered electrophiles are determined as \( 10^7 \), \( 10^1 \), and \( 10^{14} \), respectively. A survey of synthetic applications of enolate ions and their synthetic equivalents shows that their behavior can be properly described by their nucleophilicity parameters, which therefore can be used for designing novel synthetic transformations.

Key words alkylation, enols, kinetics, linear free energy relationship, reactivity scales

Enolate equivalents are among the most important reagents in organic and biochemistry. In organic synthesis, they are commonly employed as metal enolates or as their synthetic equivalents, enamines or enol ethers, depending on the electrophilicity of the corresponding reaction partners. The qualitative ranking of reactivity — metal enolate > enamine > enol ether — is well known. A quantitative comparison has been hampered by the fact, however, that electrophiles, which are suitable for kinetic studies with enolate ions, have such low electrophilicities that they do not react with enamines and enol ethers. On the other hand, electrophiles, suitable for studying the kinetics of their reactions with enamines or enol ethers, are so reactive that they will generally undergo unselective diffusion-controlled reactions with alkali enolates. How can this dilemma be overcome?

In previous years, we have established a series of colored reference electrophiles covering a reactivity range of 32 orders of magnitude, which are suitable for studying the reactivities of nucleophiles of widely differing reactivity. By using equation 1, in which electrophiles are characterized by one parameter \( E \), and nucleophiles are characterized by the solvent-dependent nucleophilicity parameter \( N \) and susceptibility \( s_N \), we have so far parameterized more than 300 electrophiles and 1100 nucleophiles.

\[
\lg k_{20 \, \degree C} = s_N(E + N) \tag{1}
\]

Equation 1

We now report on the reactivities of the enolate equivalents depicted in Figure 1, which allow us to quantitatively compare the previously reported nucleophilicities of potassium enolates with those of structurally analogous enamines and enol ethers. We will furthermore demonstrate that the combination of nucleophilicity parameters for enolates, enamines, and silyl enol ethers with the reactivity parameters \( E \) of electrophiles provides an ordering principle for enolate chemistry.

Figure 1 Structures of silyl enol ethers 1a–d and enamines 2a,b investigated as enolate equivalents in this work
Table 1 lists the indolylbenzylium ions 3a–c, benzhydrylium ions 3d–l, and quinone methides 3m–o, which were employed as reference electrophiles for the kinetic measurements.

**Product Studies**

The reactions of the silyl enol ethers 1a, 1c, and 1d with benzhydrylium or indolylbenzylium tetrafluoroborates initially yielded siloxy-substituted carbenium ions 4. Fast subsequent desilylation then afforded ketones 5a–c (Scheme 1), which were purified by column chromatography and characterized by NMR spectroscopy and mass spectrometry. Electrophilic attack of the prochiral carbocation 3a led to a mixture of two diastereomers of 5c in a ratio of ca. 1:1.33 (determined by NMR spectroscopy).

Electrophilic attack of the benzhydrylium tetrafluoroborate 3g on the enamine 2b led to formation of the iminium salt 6. Its hydrolysis gave the ketone 5d, which was purified by column chromatography and isolated in moderate yield (Scheme 2).

**Biographical Sketches**

**Artem I. Leonov** obtained a diploma in chemical engineering at the Mendeleev University of Chemical Technology of Russia (Moscow) before moving to Ludwig-Maximilians-Universität München (LMU) (Germany) in 2013, where he received his doctoral degree in the group of Dr. Ofial on physical organic chemistry. His research focused on kinetic and mechanistic studies of carbon nucleophiles such as Grignard reagents, carbanions, enol ethers and enamines for the further development of the Munich reactivity scale. In 2018, he joined the group of Prof. Lee Cronin in Glasgow (UK) to work on an automatic synthetic platform and the implementation of kinetic analysis for reaction optimization.

**Daria S. Timofeeva** received her diploma in chemical engineering at the Mendeleev University of Chemical Technology of Russia (Moscow), with her final research project on pheromone total synthesis conducted at the All-Russian Plant Quarantine Center. In 2014, she started her doctoral studies in the group of Prof. Herbert Mayr at the LMU München (Germany), where her work has focused on the study of the reactivity of enamines and electrophilic fluorinating reagents.

**Armin R. Ofial** studied chemistry at the Technical University of Darmstadt (Germany), where he graduated with Prof. Alarich Weiss in 1991 (diploma) and received his doctoral degree with Prof. Herbert Mayr in 1996. In 1997, he moved as a research associate to the Ludwig-Maximilians-Universität München (Germany). In 2009, he established his research group at the LMU München and habilitated in 2013. Armin’s research interests include reactions of iminium ions, kinetics, and selective C–H bond functionalizations. He received the Thieme Chemistry Journals Award in 2012.

**Herbert Mayr** obtained his Ph.D. in 1974 (Prof. R. Huisgen, LMU München). After postdoctoral studies (Prof. G. A. Olah, Cleveland, USA), he completed his habilitation in 1980 (Prof. P. von R. Schleyer, Erlangen). After professorships in Lübeck and Darmstadt, he returned to the LMU München in 1996. He received the Alexander von Humboldt Honorary Fellowship of the Foundation for Polish Science (2004) and the Liebig Denkmünze (GDCh, 2006). He is a member of the Bavarian Academy of Sciences and the Leopoldina - National Academy of Sciences. His research interests comprise quantitative approaches to organic reactivity including mechanisms of organocatalytic reactions and the theory of polar organic reactions.
The reaction of the enamine 2a with the quinone methide 3m furnished the zwitterion 7, which tautomerized, and within 30 minutes, quantitatively yielded the product 8 as determined by NMR spectroscopy (Scheme 3).

Table 1  Indolylbenzylium Ions 3a–c, Benzhydrylium Ions 3d–l and Quinone Methides 3m–o Employed as Reference Electrophiles in this Study

| Electrophile | £ | 
|--------------|---|---|
| ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) |
| ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) |
| ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) |

*Electrophilicity parameters £ were taken from refs 12, 13, 17, and 18.

Scheme 1  Reactions of silyl enol ethers 1a, 1c, and 1d with reference electrophiles. Yields refer to isolated products.
Kinetic Investigations

The reactions of the silyl enol ethers 1a–d and enamines 2a,b with the reference electrophiles 3a–n were investigated in either acetonitrile or dichloromethane at 20 °C and monitored by UV–Vis spectroscopy at or close to the absorption maxima of the electrophiles (Table 2). To simplify the evaluation of the kinetic experiments, the nucleophiles were used in large excess (usually 8 equiv or more) to keep their concentrations almost constant throughout the reactions. The first-order rate constants \(k_{\text{obs}}\) were derived by least-squares fitting of the exponential function \(A_t = A_0 \exp(-k_{\text{obs}}t) + C\) to the time-dependent absorbances \(A_t\) of the electrophile. The second-order rate constants \(k_2\), listed in Table 2, were obtained as the slopes of the linear correlations between \(k_{\text{obs}}\) and the concentrations of the nucleophiles as exemplified in Figure 2 for the reaction of the silyl enol ether 1a with the indolylbenzylium ion 3a.

Correlation Analysis

The rate constants (lg \(k_2\)) for the reactions of the silyl enol ethers 1 and enamines 2 with indolylbenzylium ions 3a–c, benzhydrylium ions 3e–l, and quinone methides 3m–n correlate linearly with the electrophilicity parameters \(E\) of 3a–n (Figure 3). Therefore, equation 1 is applicable, and the \(N\) and \(s_p\) parameters for the nucleophiles 1 and 2 (Table 2) were derived from the intercepts and slopes of these correlations.

Structure–Reactivity Relationships

The narrow range of the nucleophile-specific susceptibilities (0.82 < \(s_N\) < 0.94) for the silyl enol ethers 1 indicates that the relative reactivities of these \(\pi\)-systems depend only slightly on the nature of the attacking electrophiles. Therefore, the reactivities towards any of the carbenium ions 3a–l reflect general structure–reactivity trends.

Table 2 shows that the reactions of 1a with 3a and 3c proceed only 1.3 times faster in dichloromethane than in acetonitrile. Because of this small difference, solvent effects will be neglected in the following discussions.

![Figure 2](image-url) Exponential decay of the absorbance \(A\) (at 425 nm) during the reaction of 3a (9.27 × 10–5 M) with 1a (8.82 × 10–4 M) in acetonitrile at 20 °C. (b) Correlation of the first-order rate constants \(k_{\text{obs}}\) with the concentrations of the nucleophile 1a.

![Figure 3](image-url) Correlations of the second-order rate constants (lg \(k_2\)) for the reactions of the enolate equivalents 1 and 2 with the electrophiles 3 in acetonitrile at 20 °C with the electrophilicity parameters \(E\) of 3.
Figure 4 compares the reactivities of the silyl enol ethers 1a and 1b towards indolylbenzylium ion 3b with the previously reported reactivity of the acetophenone-derived silyl enol ether 9a towards the same electrophile.12 Introduction of a methyl group at the site of electrophilic attack (9a → 1b) decreases the reactivity by a factor of 10, whereas introduction of a phenyl group at this position (9a → 1a) reduces nucleophilic reactivity by three orders of magnitude.

Benzoannulation of the cyclic enol ether 9b increases its reactivity towards 3g by a factor of 3.9 (9b → 1c) (Figure 5), whereas benzoannulation of 1-(trimethylsiloxy)cyclohexene (9c) does not have a significant effect on the reactivity of the enolate ion (9c → 1d). As a consequence, the previously reported reactivity preference of the cyclopentenyl over the cyclohexenyl silyl enol ether by a factor of 20 increases to almost two orders of magnitude for the benzoannulated analogs (1c vs 1d). As mentioned above, the small reactivity difference of 1a in acetonitrile and dichloromethane (Table 2) allows us to neglect the fact that the data for 9b and 9c in Figure 5 refer to dichloromethane whereas those for 1c and 1d refer to acetonitrile solutions.

Figure 6 compares the nucleophilic reactivities of enamines at 20 °C.4 Second-order rate constant (in dichloromethane) from ref 19. b Second-order rate constant (in MeCN) from Table 2. c Second-order rate constant (in MeCN) from ref 21.

With the newly determined nucleophilicity parameters, it is now possible to compare directly the nucleophilic reactivity of the enolate ion 1122 with the reactivities of its structurally related equivalents 1a and 10c23 (Figure 7). When the N and S0 parameters of 1a and 10c are used to calculate the rate constants of their reactions with quinone methide 3o (E = −13.39), the most reactive electrophile used for the characterization of the enolate ion 11, one finds that the enamine 10c is 107 times less reactive than 11 and that the enol ether 1a is another 103 times less reactive than the enamine 10c. In a dilute solution, in which the reaction of the enolate ion 11 would proceed within one second, the corresponding reaction of the enamine 10c would require one year, and the silyl enol ether 1a would reach the same degree of conversion after ten million years.

Applications

The nucleophilicity parameters determined in this investigation can now be combined with previously reported reactivity indices16 to rationalize the use of enolate ions and their synthetic equivalents in organic synthesis. Figure 8 depicts enolates, enamines, and silyl enol ethers with in-
Increasing nucleophilicity from bottom to top and electrophiles with increasing reactivities from top to bottom. Nucleophiles and electrophiles at the same level \((E + N = -3)\) react with a rate constant of ca. 0.004 M\(^{-1}\) s\(^{-1}\) at 20 °C (from equation 1 for a typical value of \(s_\text{N}\) = 0.8), which corresponds to a half reaction time of about 20 minutes for 0.2 M solutions. If enolate ions and enamines are intermediates of catalytic processes, their lower concentration has to be taken into account when estimating the reaction times.

Reactions of Enolate Ions

Reactions of enolate ions with C-centered electrophiles represent important methods for generating new carbon–carbon bonds.\(^2\)\(^{-11}\),\(^24\)\(^{-29}\) The non-stabilized enolate ions at the top of Figure 8 react with all electrophiles shown on the right. Due to their high reactivity, lithium enolates are useful reagents for cross-aldol reactions with ketones and aldehydes (as shown for 12 in Scheme 4a).\(^30\) In reactions with Michael acceptors (e.g., with 13), they may be used as preformed anions or may be generated in situ by treatment of the corresponding CH acids with catalytic amounts of Brønsted bases (Scheme 4b).\(^31\),\(^32\) Acceptor-substituted enolate ions, such as cyano-, acetyl-, alkoxycarbonyl- and phenyl-sulfonyl-substituted enolate ions, react at or slightly above room temperature with a large variety of Michael acceptors with \(E > -23\) (as exemplified for the combination 14 + 15 in Scheme 4c),\(^33\)\(^{-35}\) but we are not aware of reactions of such stabilized enolate ions with weak electrophiles, such as the cinnamic ester 16 (\(E = -24.5\)).

Pyridinium-substituted enolate ions (that is, acyl-substituted pyridinium ylides) readily react with Michael acceptors of \(E > -25\) to give zwitterions, which usually cyclize with formation of 1,2,3,8a-tetrahydroindolizines (Scheme 5a)\(^16\),\(^37\) or cyclopropanes.\(^38\),\(^39\)

Monitoring the reaction of equimolar amounts of a 4-(dimethylamino)-substituted pyridinium ylide with \(p\)-methoxybenzylidene malononitrile by NMR spectroscopy showed the quantitative formation of a betaine, which did not cyclize under the reaction conditions due to the stabilizing effect of the two cyano groups at the carbonionic center (Scheme 5b).\(^40\)

Reactions of Enamines

Pyrrolidine-derived enamines, such as 1-(cyclopent-1-en-1-yl)pyrrolidine (10a) or 10b, have been reported to react with a large variety of Michael acceptors with \(E > -20\) (Scheme 6a).\(^41\)\(^^{-43}\) Whereas the reaction with the weakly electrophilic acrylonitrile (19) required 12 hours refluxing in dioxane,\(^41\) the reactions with more electrophilic nitroalkenes\(^42\) and the strong electrophile 20 proceed rapidly at room temperature.\(^43\) The nucleophilic attack of enamines at the carbonyl group of aromatic and aliphatic aldehydes yields α,β-unsaturated ketones through condensation and subsequent aqueous workup (Scheme 6b).\(^44\)
Figure 8: Ranking of C-nucleophiles on the nucleophilicity scale and the scope of their reactions with electrophiles. Enolate ions and their synthetic equivalents (on the left-hand side) can be expected to react with all electrophiles (on the right-hand side) located at the same level of the respective nucleophile or below (nucleophilicity parameters \( N \) in acetonitrile if not mentioned otherwise, \( N \) and \( E \) were taken from ref 16).
Enamines (for example, 2b or 10b) react with preformed iminium salts such as 21a and 21b in high yields under mild conditions to give the Mannich bases of α-tetralone or cyclohexanone, respectively (Scheme 7).45,46

Fast F⁺ transfer reactions to colored enamines, such as 10c, were used to quantify the reactivity of electrophilic fluorinating N–F reagents with −10.5 < E < −5 [such as NSFI (22)] in Scheme 8a.47 The same types of enamines were used to characterize F₃CS⁺ and F₂CHS⁺ transfer agents, such as the saccharin derivative 23 (Scheme 8b).48

Enamine activation has emerged as a widely applicable organocatalytic method for the α-functionalization of carbonyl compounds.49–56 List et al. discovered that enantioselective aldol reactions between acetone and various aldehydes proceed through conversion of the ketone into the corresponding proline-derived enamine intermediate (Scheme 9a).57,58 Subsequently proline-catalyzed three-component Mannich reactions with N-arylimines59 and Michael additions to nitroolefins, such as 24 (Scheme 9b),60 were developed (at r.t., several hours of reaction time).
reoselectivity (Scheme 10a).64,65 The diphenylprolinol silyl ether-catalyzed reaction of 3-phenylpropanal with the less electrophilic methyl vinyl ketone (18) delivered only a moderate yield of the 1,5-dicarbonyl product with high enantioselectivity, even when a higher catalyst loading was used (Scheme 10b).64,66

Scheme 10 Michael additions via Hayashi–Jørgensen-catalyst-derived enamines (from ref 64)

Cozzi and coworkers rationally designed enantioselective α-alkylation reactions of aldehydes, in which in situ generated carbocations R’+ with electrophilicities E between –1.5 and –7 were intercepted by enamines (e.g., by 10e in Figure 8) derived from aldehydes and MacMillan’s imidazolidinone catalysts.67–70 The position of enamine 10e in Figure 8 is also in line with the observation that NFSI (22)71 and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (25) are suitable reagents for imidazolidinone-catalyzed α-halogenations of aldehydes (Scheme 11).72,73

Reactions of Enol Ethers

Alkyl enol ethers have similar nucleophilic reactivities as structurally analogous silyl enol ethers (Scheme 12a),74 but are considerably less nucleophilic than enamines (see Figure 8). The use of alkyl enol ethers as enolate anion equivalents is rather limited, however, because of their tendency to undergo polymerization. In an extensive review, Hall demonstrated that highly electrophilic ethylene derivatives can initiate the ionic polymerization of alkyl enol ethers.75 Polymerization is avoided when 1,4-zwitterions are formed, which cyclize with formation of cyclobutanes, as studied in detail by Huisgen (Scheme 12b).76

Lewis acid catalyzed additions of alkyl halides, acetics, and orthoesters to alkyl enol ethers only give 1:1 products when the reactants ionize more readily than the products.77–79 Though ZnCl₂-catalyzed additions of α,β-unsaturated acetics to ethyl vinyl ether are key steps in Isler’s technical β-carotin synthesis,80 the choice of reactants, which ionize faster than the resulting α-haloethers or acetics, is limited,81 as shown by the examples depicted in Scheme 13. Silyl enol ethers, which are readily accessible from carbonyl compounds with high regio- and stereoselectivity, are more versatile reagents.82 Since α-siloxy-carbenium ions generated by electrophilic attack at silyl enol ethers are
rapidly disilylated to give carbonyl compounds, the problem of polymerization encountered with alkyl enol ethers is largely eliminated. However, only highly electrophilic Michael acceptors, like the bis(benzenesulfonyl)-substituted ethylene \( \text{20} \), undergo uncatalyzed reactions with silylated enol ethers (Scheme 14).\(^{43}\)

Reactions of silyl enol ethers with less reactive electrophiles, such as carbonyl compounds, \( \alpha,\beta \)-unsaturated ketones or alkyl acrylates, require activation.\(^{83}\) For example, Lewis acids can be employed to enhance the reactivity of carbonyl compounds for their reactions with silyl enol ethers. This concept is widely used in Mukaiyama-type cross-aldol\(^{84}\) and Michael reactions\(^ {85} \) of silyl enol ethers as shown for the reactions of \( \text{9b} \) in Scheme 15.\(^{86-88}\)

Alternatively, Lewis base catalysis\(^ {89} \) was used to activate the nucleophile in Mannich-type reactions of silyl enol ethers with Schiff bases, such as \( \text{PhCH=NTs} \) (\( \text{26} \)).\(^ {90,91} \) In these reactions, coordination of phthalimide or carboxylate anions at silicon is assumed to enhance the nucleophilicity of the silyl enol ether through the formation of hypervalent silicon species (Scheme 16a).\(^ {91-93} \) Similarly, acetate ions triggered the Michael reactions of \( \text{1b} \) and 1-(trimethylsiloxy)cyclohexene \( \text{9c} \) with chalcone \( \text{13} \) (Scheme 16b).\(^ {94-96} \)

As expected from their nucleophilicity parameters, silyl enol ethers react with iminium ions under mild conditions to give Mannich bases as illustrated in Scheme 18a.\(^ {100-103} \) Important variants of this reaction are chiral-imidazolidinone-catalyzed reactions of \( \alpha,\beta \)-unsaturated aldehydes with silyl enol ethers to give \( \delta \)-ketoaldehydes in high yields and enantioselectivities (Scheme 18b).\(^ {104,105} \)
Silyl enol ethers readily react with the (tricarbonyl)iron-complexed cyclohexadienylium (27) and the 2-phenyl-[1,3]-dithian-2-ylium ion (28), which are positioned below most enol ethers in Figure 8 (Scheme 19).106–108 Highly reactive Co2(CO)6-complexed propargyl cations (with E in the range of +1 to –116 generated from the corresponding propargyl methyl ethers or acetates by BF3·OEt2-mediated ionization) have been reported to react with the silyl enol ethers 1b and 9c even at 0 °C in dichloromethane to yield, after aqueous workup, α-substituted ketones.109

Silyl enol ethers have also been used for the synthesis of α-heteroatom-substituted carbonyl compounds. Slow reactions of silyl enol ethers 9a–c with diethyl diazocarboxylate (29) are predicted by equation 1. The observation that α-amino ketones formed slightly faster than predicted by equation 1 may be due to the fact that the electrophilic attack of the azodicarboxylate at the silylated enol ether is assisted by the interaction of the second nitrogen with silicon, thus giving rise to a concerted sila-Alder-ene reaction (Scheme 20).111,112

Reactions of the N-fluoropyridinium triflate with silyl enol ethers are sluggish at room temperature and deliver α-fluorinated products only after heating the reaction mixtures to reflux for several hours,113 in accord with the significantly lower nucleophilicities of silyl enol ethers compared to those of the structurally analogous enamines. The more electrophilic fluorinating and chlorinating reagents NFSI (22)114 and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (25),73 respectively, with E > –9, are effective for the α-halogenation of silyl enol ethers at ambient temperature (Scheme 21).

Conclusion

While studies on the chemistry of enolate anions started in the 19th century, it was only in the second half of the 20th century, particularly through the pioneering work of Stork and Mukaiyama, that the synthetic potential of enamines and silyl enol ethers became obvious. It was soon rec-
enamines, and silyl enol ethers have relative reactivities of
substituted stilbenes with C-centered electrophiles have
more than 300 reported electrophilicity parameters
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(81) The synthetic scope of the reactions of acetals with alkyl enol ethers is demonstrated in the articles quoted in ref 79.