Inherent Reactivity of Spiro-Activated Electrophilic Cyclopropanes

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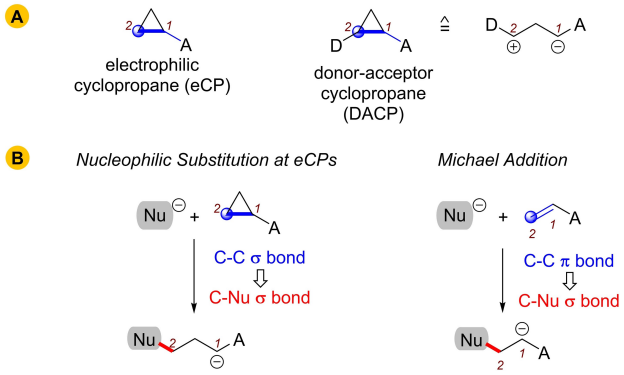
Dedicated to the memory of Professor Klaus Hafner

Abstract: The kinetics of the ring-opening reactions of thiophenolates with geminal bis(acceptor)-substituted cyclopropanes in DMSO at 20 °C was monitored by photometric methods. The determined second-order rate constants of the S_N2 reactions followed linear relationships with Mayr nucleophilicity parameters (N/s_N) and Brønsted basicities (pK_{aH}) of the thiophenolates as well as with Hammett substituent parameters (σ) for groups attached to the thiophenolates. Phenyl-substituted cyclopropanes reacted by up to a factor of 15 faster than their unsubstituted analogues, in accord with the known activating effect of adjacent π-systems in S_N2 reactions. Variation of the electronic properties of substituents at the phenyl groups of the cyclopropanes gave rise to parabolic Hammett relationships. Thus, the inherent S_N2 reactivity of electrophilic cyclopropanes is activated by electron-rich π-systems because of the more advanced C1–C2 bond polarization in the transition state. On the other hand, electron-poor π-systems also lower the energetic barriers for the attack of anionic nucleophiles owing to attractive electrostatic interactions.

Introduction

Cyclopropanes are unique building blocks for organic synthesis that react as electrophiles in polar reactions when substituted with electron-withdrawing groups.[1,2] In particular, spiro-activated cyclopropanes have been shown to react with nucleophiles under relatively mild conditions because the orthogonal orientation of the cyclopropane moiety and the plane of activating carbonyl groups facilitates delocalization of negative charge in the transition state (TS).[3] The synthetic versatility of electrophilic cyclopropanes (eCPs) was further enhanced by installing electron-donating groups at C2 (Scheme 1A). In this way, difunctionalized products can be synthesized from so-called donor–acceptor cyclopropanes (DACPs, Scheme 1A).[4,5] The polarization of the C1–C2 bond in the DACPs not only favorably enhances reactivity toward nucleophiles but also steers regioselectivity of nucleophilic attack toward the already substituted C2 position.[1]

Nowadays eCPs are regularly employed as precursors for carbo-[6] and heterocycles,[7,8] and asymmetric cyclopropanations have made DACPs useful tools for the synthetic chemist.[9,10]



Scheme 1. A) General structures for electrophilic and donor–acceptor cyclopropanes. B) Reactions of nucleophiles with electrophilic cyclopropanes generate methylene-extended Michael adducts.

Ring opening,[5e] (3+2), (3+3), and (4+3) cycloadditions[11] as well as rearrangements[12] of functionalized cyclopropanes offer access to a multitude of building blocks.[13]

Our interest was triggered, however, by the simple ring-opening reactions of nucleophiles with electrophilic cyclopropanes because of their relation to Michael additions to electron-deficient olefins and nucleophilic substitutions at sp^3-hybridized carbon centers (Scheme 1B). It can be anticipated that kinetic studies will provide fundamental insights into the factors that control polar cyclopropane reactivity.

Though the synthetic potential of electrophilic cyclopropanes has widely been explored, kinetic studies to characterize their reactivities are limited to a few solitary reactions of dimedone- and Meldrum's acid derived cyclopropanes with pyridines.[14,15] Lately, the Werz group systematically investigated substituent effects on the reactivity of $SnCl_4$-complexed 1,1-

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di(alkoxycarbonyl)-substituted cyclopropanes in (3+2)-cycloadditions with *p*-fluorobenzaldehyde by in situ NMR kinetics.[16] It is not straightforwardly possible to derive information on the inherent reactivity of electrophilic cyclopropanes from these kinetic studies, however, because cyclopropane reactivity is dominated by Lewis acid activation and the (3+2)-cycloadditions follow a complex mechanism.[17]

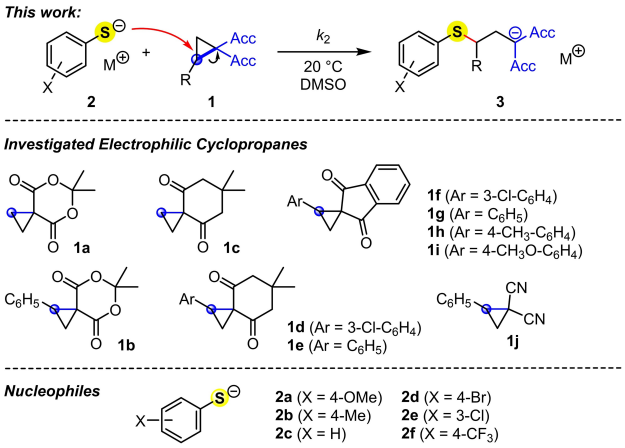
The currently most comprehensive reactivity scales for electrophile-nucleophile reactions have been constructed by Mayr. Within this framework, the electrophilic property of an electron-deficient substrate is described by the electrophilicity parameter *E* in the Mayr–Patz equation (1).[18]

$$\log k_2(20\,^{\circ}\mathrm{C}) = s_N(N+E) \quad (1)$$

The nucleophilicity parameter *N* and the nucleophile-specific slope s_N are specific for the nucleophile in a certain solvent and calibrated towards benzhydrylium ions and structurally related quinone methides (reference electrophiles). In this way, electrophilic and nucleophilic reactivities in the Mayr scales refer to reactions, in which only one new σ-bond is formed.[18d] With this constraint, it has been demonstrated that Equation (1) usually predicts rate constants with an accuracy better than a factor of 10^2 for structurally diverse electrophile-nucleophile combinations.[19] It cannot be expected that S_N2 reactions, in which bond formation and bond breaking are coupled events, follow the simple three-parameter Equation (1). Nevertheless, several examples show that the relative reactivity ordering of nucleophiles, originally calibrated towards one-bond reference electrophiles, also holds for reactions with electrophilic substrates of S_N2 reactions, in particular if the type of atom at the nucleophilic center is kept constant.[20]

Advantageously for the intended kinetic studies at 20 °C, sodium thiophenolate was reported to react with the Meldrum's acid derived spirocyclopropane already at room temperature.[3] In general, thiophenolates are potent nucleophiles that can be fine-tuned in reactivity by electronic effects but allow maintaining a constant steric demand in the vicinity of the nucleophilic sulfur atom. Because we recently determined the Mayr nucleophilicity parameters *N* and s_N of several UV-light absorbing ArS^- ions in DMSO,[21] the scene was set to use thiophenolates as the nucleophiles for investigating the reactivity of electrophilic cyclopropanes by photometric methods (Scheme 2).

In this work, we show that the inherent electrophilicity of 1,1-bis(acceptor)-substituted cyclopropanes **1a–j** can be assessed through kinetic data for reactions of **1** with thiophenolates **2**. The experimentally determined second-order rate constants (k_2) correlated linearly with physicochemical properties of the nucleophiles **2** but parabolic Hammett plots revealed so far undiscovered electrophile-dependent effects on the stabilization of the transition states of ring-opening reactions at electrophilic cyclopropanes.



Scheme 2. Ring-opening reaction of cyclopropanes **1** with thiophenolates **2** (counterion $M^+ = Na^+$ or K^+).

Results and Discussion

Preparation of cyclopropanes 1

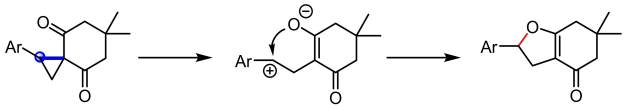
The Meldrum's acid derived spirocyclopropane **1a** was purchased. Corey-Chaykovsky cyclopropanations of active methylene compounds furnished **1c–e**, **1g**, and **1j** in yields of 36–84% according to described procedures.[22] When we applied the analogous synthetic protocol to prepare *p*-methyl or *p*-methoxy-substituted derivatives of **1e**, spontaneous Cloke–Wilson rearrangements yielded either solely the corresponding dihydrofuran or mixtures of cyclopropanes and dihydrofurans, which could not be used for subsequent kinetic studies (Scheme 3).[23]

As reported in ref. [24], light induced, NIS-initiated cyclizations that start from styrenes and cyclic 1,3-dicarbonyl compounds yielded the spirocyclopropanes **1b**, **1f**, **1h**, and **1i** (in 59–92% yields).

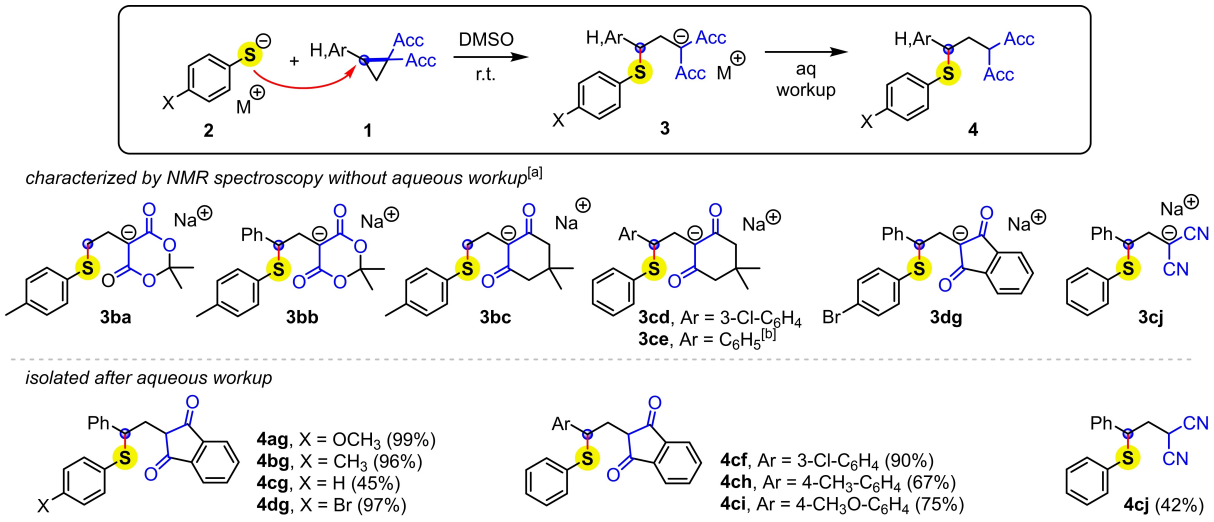
For details of the synthetic procedures and the spectroscopic characterization of cyclopropanes **1**, see the Supporting Information.

Reactions of the cyclopropanes 1 with thiophenolates 2

Products: Reactions of cyclopropanes **1** and sodium thiophenolates **2**, generated by deprotonation of thiophenols with sodium hydride, in [D_6]DMSO furnished the ionic adducts **3**, which were characterized directly by NMR spectroscopy and HRMS. Mixing thiophenols, potassium *tert*-butoxide, and the cyclopropanes **1**



Scheme 3. Cloke-Wilson rearrangement of Meldrum's acid-derived spirocyclopropanes with electron-rich aryl groups at C2 (Ar = *p*-tolyl or *p*-anisyl).



Scheme 4. Reactions of cyclopropanes **1** with sodium or potassium thiophenolates Na/K-**2** furnished ring-opened products **4** via the initial adducts **3** (yields are given for isolated products). [a] Reactions in [D_6]DMSO. [b] Counterion: K^+.

in DMSO yielded, after aqueous workup, methylene-extended Michael adducts **4**, which were isolated in moderate to excellent yields (Scheme 4). Consistently, product analysis showed that reactions of ArS^- (**2**) with cyclopropanes **1** occurred chemoselectively by nucleophilic attack of the thiophenolate at the cyclopropyl ring. Furthermore, all reactions of **2** with aryl-substituted cyclopropanes **1 b** and **1 d–j** proceeded regioselectively, and carbon-sulfur bond-formation was observed only at the already substituted cyclopropane carbon C2, irrespective of whether aryl groups with electron-withdrawing or electron-donating substituents were attached to this position.

Kinetics: The kinetics of the reactions of cyclopropanes **1 a–e** and **1 j** with thiophenolates **2** in DMSO at 20 °C were monitored photometrically by following the fading of the UV absorptions of the thiophenolates at or close to their absorption maximum (stopped-flow method, λ_{max} = 302–329 nm in DMSO),[21] To simplify the kinetic evaluation of the second-order reactions, we used the cyclopropanes **1 a–e** or **1 j** in at least tenfold excess relative to the initial thiophenolate concentrations $[\mathbf{2}]_0$. Under these conditions, the fading out of the thiophenolate absorptions could be fitted by the mono-exponential decay function $A = A_0 \exp(-k_{obs}t) + C$ to determine the (pseudo)-first-order rate constants k_{obs} [s^{-1}]. For each cyclopropane/thiophenolate pair k_{obs} was determined at four different concentrations of the (excess) cyclopropane, which allowed us to calculate the second-order rate constants k_2 [$M^{-1}s^{-1}$] from the slope of the linear correlation of k_{obs} with [**1**]. Figure 1 visualizes this procedure for the ring-opening reaction of **1 e** with the parent thiophenolate PhS^- (**2 c**).

Reactions of the 1,3-indandione-derived cyclopropanes **1 f–i** with the thiophenolates **2** generated stable solutions of enolate ions of structural type **3**, which absorb light at 390–396 nm. By obeying the same conditions for (pseudo)first-order kinetics as before, that is $[\mathbf{1}]_0/[\mathbf{2}]_0 > 10$, the increasing absorption of the ring-opened enolate ions could be fitted with the increasing mono-exponential function $A_t = A_0[1-\exp(-k_{obs}t)] + C$ to yield the rate constants k_{obs}. In analogy to the evaluation of the kinetics with decreasing absorptions, the experiments were repeated at four different concentrations of **1 f–i**. The resulting linear correlations of k_{obs} with [**1**] were of comparable quality as those obtained from absorption decay kinetics and, consequently, the determination of k_2 values for the absorption increase kinetics could be determined analogously, as exemplified in Figure 2.

Data of the individual kinetic measurements for the nucleophilic attack of thiophenolates **2** at the cyclopropanes **1** are given in the Supporting Information. The determined second-order rate constants k_2 are compiled in Table 1.

Phenyl effect in reactions of 1 with thiophenolates 2: A significant phenyl effect was reported for the kinetics of ring-opening reactions of **1 a,b** with pyridine. In acetonitrile at 25 °C, **1 b** reacted by a factor of 80 faster with pyridine than **1 a** (for

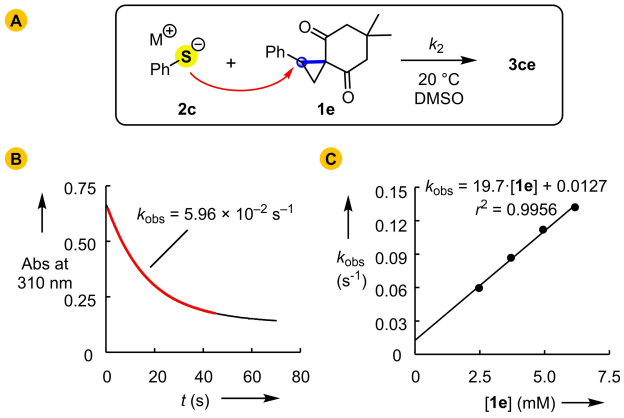


Figure 1. A) Kinetics of the reaction of **1 e** with **2 c**. B) Monoexponential decay of the absorbance *A* at 310 nm in the reaction of **2 c** (0.247 mM, $M^+ = K^+$) with **1 e** (2.47 mM). C) Linear correlation of the observed rate constants k_{obs} with the concentration of cyclopropane **1 e**.

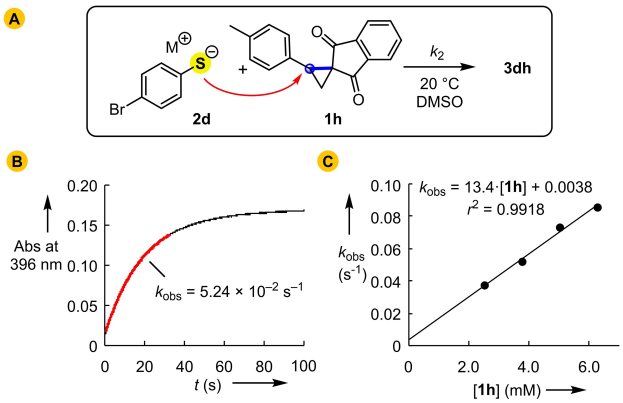


Figure 2. A) Kinetics of the reaction of **1 h** with **2 d**. B) Monoexponential increase of the absorbance *A* at 396 nm in the reaction of **2 d** (0.250 mM, $M^+ = K^+$) with **1 h** (3.75 mM). C) Linear correlation of the observed rate constants k_{obs} with the concentration of cyclopropane **1 h**.

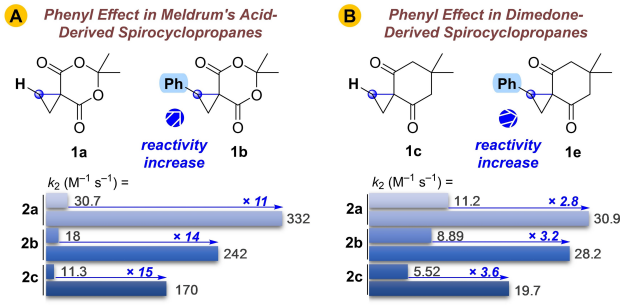


Figure 3. Phenyl effect on the reactivities of A) Meldrum's acid- and B) dimedone-derived spriocyclopropanes in reactions with thiophenolates (k_2 in DMSO at 20 °C from Table 1).

1 a + pyridine: $k_2 = 1.04 \times 10^{-5}\,M^{-1}\,s^{-1}$; for **1 b** + pyridine: $k_2 = 8.27 \times 10^{-4}\,M^{-1}\,s^{-1}$).[14]

In this work, the second-order rate constants k_2 in Table 1 enable a comparison of the reactivities of the parent spirocyclopropanes **1 a** and **1 c** with those of the 2-phenyl-substituted analogues **1 b** and **1 e**, respectively, which are DACPs (Figure 3). The thiophenolates **2 a–c** underwent by a factor of 11 to 15 faster reactions with the Meldrum's acid-derived 2-phenylcyclopropane **1 b** than with the unsubstituted **1 a** (Figure 3A), in accord with the known rate enhancing 'benzyl effect' on S_N2 reactivity.[25] Analogous additions of thiophenolates **2 a–c** to the dimedone-derived **1 e** were by a factor of 3–4 faster than for the unsubstituted **1 c** (Figure 3B).

In both series of reactions, a consistent trend towards a stronger phenyl effect for the slower reactions was observed, which may explain the phenyl effect of 80 reported by McKinney and colleagues for the reactions of pyridine with **1 a**,**b**,[14] which are more than 5000-fold slower than the reactions studied in this work.

Comparison of electrophilic cyclopropanes with Michael acceptors: The activating phenyl effect on electrophilic cyclopropanes (Figure 3) is in obvious contrast to the significant deactivation of olefinic Michael acceptors by β-phenyl groups. For comparison, Figure 4A illustrates that the reactivities of typical Michael acceptors towards neutral and anionic nucleophiles are significantly retarded, as expressed by the 5 to 6 units difference in the logarithmic Mayr *E* parameters, when β-hydrogen is replaced by a phenyl group.[26]

Nevertheless, when electrophilic cyclopropanes and Michael acceptors with identical acceptor groups are compared, relative rate constants for the reactions with the parent thiophenolate **2 c** show that Michael acceptors are still by 8 to 9 orders of magnitude stronger electrophiles than the related cyclopropanes (Figure 4B). Thus, breaking a carbon–carbon σ-bond in the reactions of the cyclopropanes causes systematically higher activation barriers than breaking a weaker carbon–carbon π-bond in structurally related Michael acceptors.

Spiro activation: Proper orientation of the electron-withdrawing carbonyl groups is assumed to enhance the electrophilicity of the spiro compounds **1 a–f** compared to analogous non-spirocyclopropanes. Interestingly, cyclopropane **1 j** is only slightly less electrophilic than **1 b**, **1 e**, or **1 g** (Figure 5A). This observation demonstrates that spiro-activation can conceptually be replaced by activation through rod-like EWGs, such as cyano groups, whose electron-withdrawing effect does not require optimum orientation of the electron-poor π-system to the σ-bonds of the cyclopropane moiety to become effective.

Table 1. Second-order rate constants k_2 for the reactions of cyclopropanes **1** with thiophenolates **2** (counterion: K^+) in DMSO (20 °C).

	k_2 [M^{-1} s^{-1}]					
	2 a	**2 b**	**2 c**	**2 d**	**2 e**	**2 f**
	$N = 24.97$	$N = 24.35$	$N = 23.36$	$N = 22.80$	$N = 22.50$	$N = 21.30$
Electrophile	$s_N = 0.68$	$s_N = 0.69$	$s_N = 0.74$	$s_N = 0.78$	$s_N = 0.78$	$s_N = 0.86$
1 a	30.7[a]	18.0[a]	11.3[a]	n.d.	n.d.	n.d.
1 b	332[a]	242[a]	170[a]	n.d.	n.d.	n.d.
1 c	11.2[a]	8.89[a]	5.52[a]	n.d.	n.d.	n.d.
1 d	84.7	59.2	40.3	25.7	n.d.	n.d.
1 e	30.9	28.2	19.7	16.6	14.3	7.74
1 f	47.7	32.9	20.5	12.3	n.d.	n.d.
1 g	31.5	21.9	15.0	8.38	6.90	3.68
1 h	33.7	26.1	20.3	13.4	n.d.	n.d.
1 i	93.9	65.3	44.9	33.6	n.d.	n.d.
1 j	17.4	11.3	8.54	4.30	n.d.	n.d.

[a] Sodium instead of potassium used as counterion for the thiophenolate **2**.

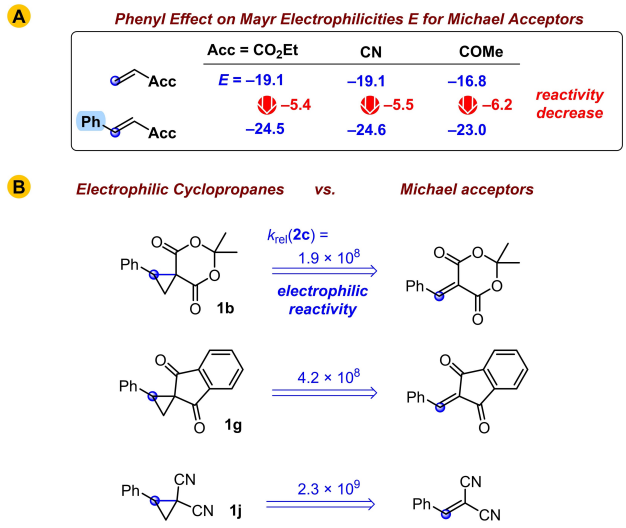


Figure 4. A) Phenyl effect on Michael acceptors expressed by the decrease in electrophilicities *E*. B) Relative rate constants k_{rel} for reactions of the thiophenolate ion (**2c**) with cyclopropanes **1** and structurally related Michael acceptors (20 °C, DMSO, with kinetic data for **1b**, **g**, and **j** from Table 1; rate constants for Michael acceptors calculated by applying *N* and s_N for **2c** from Table 1 and *E* parameters from ref. [18d] in Equation (1)).

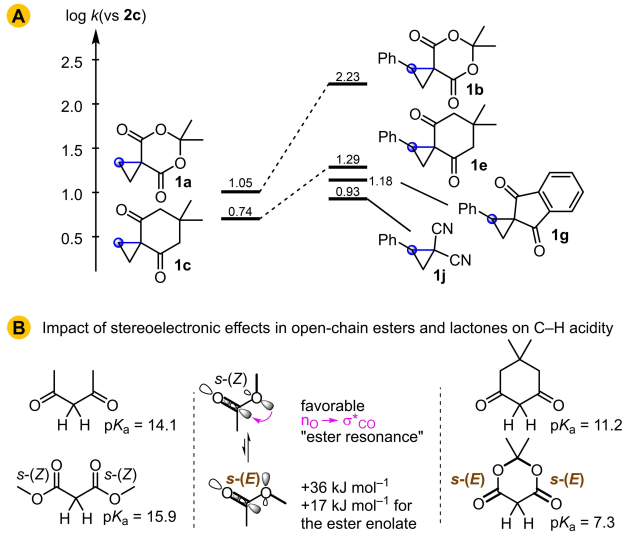


Figure 5. A) Relative reactivities of cyclopropanes **1** towards the thiophenolate ion **2c** (in DMSO, 20 °C). B) Meldrum's acid with two unfavorable *s*-(*E*) ester conformations is more acidic than dimedone (pK_a in DMSO, from ref. [27a]).

Reactivity of dimedone- versus Meldrum's acid-derived cyclopropanes: Furthermore, the comparison in Figure 5A illustrates that the Meldrum's acid-derived cyclopropanes **1a**/**1b** are more electrophilic towards the thiophenolates **2** than the dimedone-derived **1c**/**1e**. This observation is counterintuitive, because ketones are known to be more C–H acidic than their ester analogues. For example, $pK_a = 14.1$ of pentan-2,4-dione is almost two orders of magnitude lower than the $pK_a = 15.9$ of dimethyl malonate (Figure 5B, left).[27a,b] An inverse ordering is found, however, when the acidity of a cyclic ketone is compared with that of a structurally analogous lactone (Figure 5B, right): Meldrum's acid ($pK_a = 7.3$) is the stronger C–H acid than dimedone ($pK_a = 11.2$).[27a,b]

In an ester group with *s*-(*Z*) conformation, favorable $n_O \rightarrow \sigma^*$-(CO) interaction (known as 'ester resonance') transfers electron density from the oxygen lone pair into the antiperiplanar antibonding orbital.[27b] As a consequence, *s*-(*Z*) methyl acetate is preferred by 36 kJ mol^{-1} if compared to *s*-(*E*) methyl acetate. In the corresponding ester enolate structures, the *s*-(*Z*) geometry remains preferred by 17 kJ mol^{-1} over the *s*-(*E*) form (Figure 5B, center).[27c] Both ester groups in Meldrum's acid are locked in the *s*-(*E*) geometry and $n_O \rightarrow \sigma^*$(CO) interactions are ineffective. Besides the impact of the locked *s*-(*E*) geometry of ester groups in lactones on C–H acidity (Figure 5B) and nucleophilicities,[27d] also the electrophilic reactivities of lactones are affected. The lack of $n_O \rightarrow \sigma^*$(CO) donation gives rise, for example, to enhanced hydrolysis rates of lactones with four to eight ring members.[27e] Furthermore, lactone-derived Michael acceptors react faster with pyridinium and sulfonium ylides than structurally related open-chain α,β-unsaturated esters or cyclic enones.[27f] The observed reactivity ordering of **1a**/**1b** being more electrophilic than **1c**/**1e** is, thus, in accord with previous observations and can be explained by stereoelectronic effects.[27b–f]

Correlation Analysis for the Reactions of 1 with Thiophenolates 2

a) *Correlations with nucleophilicities N of thiophenolates*: Variation of the substituents in the thiophenolates **2a**–**f** modulated the second-order rate constants in reactions with **1** (Figure 6A) only moderately. For example, exchanging *p*-methoxy in **2a** for *p*-trifluoromethyl in **2f** reduced the second-order rate constants k_2 in the reactions with **1e** or **1g**, respectively, only within one order of magnitude (Table 1).
By using a rearranged form of Equation (1), a linear relationship of good quality is observed when the ratio $(\log k_2)/s_N$ is correlated with the recently reported nucleophilicity parameters *N* of the thiophenolates in DMSO,[21] as exemplified for the reactions of **1e** ($r^2 = 0.9907$) and **1g** ($r^2 = 0.9888$) in Figure 6B. However, reactivity parameters *N* and s_N for **2** were calibrated by utilizing kinetics of reactions, in which only one new σ-bond was generated.[18] As a consequence, it is expected that the slopes of the correlations in Figure 6B deviate from unity because S_N2-type ring-opening reactions of electrophilic cyclopropanes are comprised of coupled bond-breaking and bond-making processes. An assignment of Mayr *E* parameters to cyclopropanes **1** is, therefore, not possible at the moment. Nevertheless, linear correlations as shown in Figure 6B (and Section 5.11 in the Supporting Information) can be used to predict reaction times at least for the reactions of **1** with further thiophenolates in polar, aprotic solvents.

b) *Brønsted correlations*: Reported pK_{aH} values in DMSO show that the Brønsted basicity of thiophenolates **2** increases

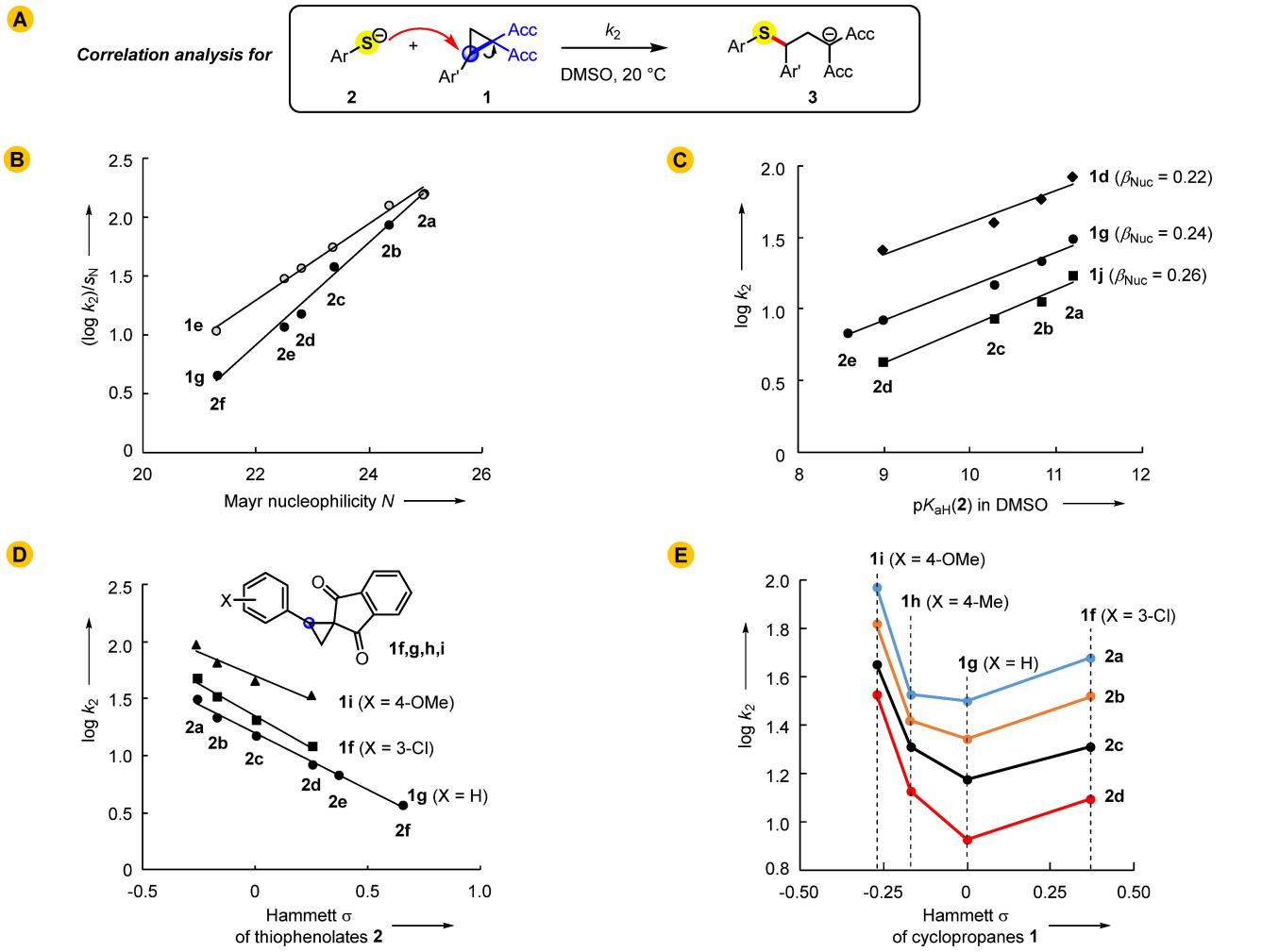


Figure 6. A) Nucleophilic attack of thiophenolates **2** at electrophilic cyclopropanes **1**. B) Applying the Mayr-Patz equation [Eq. (1)] to reactions of **1** with **2** results in a linear increase of (log k_2)/s_N with the nucleophilicity descriptors N of the thiophenolates **2** (with N, s_N from ref. [21]). C) Brønsted plots for the cyclopropanes **1 d**, **1 g**, and **1 j** show linear correlations of the second-order rate constants (log k_2) for the ring-opening reactions of **1** + **2** with the basicities of the thiophenolates **2 a**–**e** (pK_{aH} in DMSO, from ref. [28]). D) Linear correlation of the second-order rate constants (log k_2) for reactions of **1 f**–**i** + **2** with the Hammett substituent constants σ_p^- or σ_m of the nucleophiles **2 a**–**f**. For clarity, data for reactions of **2** with **1 h** are not shown. E) Curved relationship of the second-order rate constant (log k_2) for the reactions of **1 f**–**i** + **2** with the Hammett substituent constants σ of the electrophiles **1 f**–**i**.

when going from acceptor- to donor-substituted derivatives.[28] If substituents in **2** are varied in the *meta* and *para* positions, that is, remote from the reacting sulfur atom, the logarithmic second-order rate constants (log k_2) of the ring-opening reactions with the cyclopropanes **1** increase linearly with the increase of pK_{aH} of **2** (Figure 6C). Brønsted β_{Nuc} values, that is, the slope of the correlations in Figure 6C, do not show significant differences between the β_{Nuc} values of 0.22 and 0.24 for the spiro-activated cyclopropanes **1 d** and **1 g**, respectively, and that for the 1,1-dicyano-activated **1 j** (β_{Nuc} = 0.26), which is the only electrophilic cyclopropane in this study without a spiro motif. Similar β_{Nuc} values have been reported for the ring-opening reactions of pyridines (in MeCN) with **1 b** (β_{Nuc} = 0.26)[14] and a 1,2-di(dimedone)-substituted cyclopropane (β_{Nuc} = 0.24).[15]

c) *Hammett correlations for thiophenolates*: As shown for the kinetics of a series of ring-opening reactions of thiophenolates **2** with indandione-derived spirocyclopropanes **1 f**, **1 g**, and **1 i** (Figure 6D), the second-order rate constants log k_2 follow a linear correlation with Hammett substituent constants σ[29] of the thiophenolates **2**. The linear relationships in Figure 6D provide another possibility to straightforwardly predict rate constants for further thiophenolates that have not been included in this work.

d) *Hammett correlations for cyclopropanes*: The relative order of the correlation lines in Figure 6D readily indicates that indandione-derived cyclopropanes with substituents at the 2-phenyl ring undergo faster reactions with the thiophenolates **2** than the unsubstituted **1 g**. Accordingly, systematic variation of the substituents at the 2-phenyl group of **1 f**–**i** in reactions with a given thiophenolate **2** did not result in linear but in U-shaped correlations of log k_2 with Hammett σ constants (Figure 6E). In each reaction series, log k_2 goes through a minimum for the parent 2-phenyl-substituted

cyclopropane **1 g**. Both the installation of electron-donating (**1 h**, **1 i**) and electron-withdrawing substituents (**1 f**) at the 2-phenyl group in **1** increase the electrophilic reactivity of the cyclopropanes **1** relative to the parent **1 g**. Analogous parabolic Hammett plots were observed by Hudson and Klopman in reactions of lithium thiophenolates with benzyl bromides in methanol at 20 °C, which follow an S_N2 mechanism.[30]

The required high degree of organization in transition states of S_N2 reactions causes a mix of stabilizing effects, highly dependent on the participating electrophiles, nucleophiles, leaving groups and solvents. The mutual interactions of at minimum six atoms plus solvent molecules in the S_N2 TS leave enough freedom for the ensemble to use different effects to lower the energetic barrier.

Attractive electrostatic interactions between the electrophile, the incoming nucleophile, and the leaving group have been identified to be the main factors that influence the activation barriers of S_N2 reactions at electrophilic carbon centers with adjacent π-systems, that is, substitutions at benzylic or allylic substrates.[31,32,33] In the kinetics summarized in Figure 6E, nucleophile, leaving group, and solvents are kept constant. Hence, the TS are only influenced by the structural features of the electrophile.

In accord with previous interpretations,[31,32] we observed that EWGs (as in **1 f**) stabilize the TS in reactions with highly basic, negatively charged nucleophiles by favorable electrostatic interactions. With EDGs in para-position at the phenyl ring in (hyper)conjugation with the electrophilic carbon (as in **1 h** and **1 i**), however, cyclopropane C–C bond polarization is enhanced. This gives rise to a more electron-deficient electrophilic center and promotes a slightly more advanced bond-breaking in the TS.[25] In this way, also EDGs at the 2-phenyl ring lower the energetic barrier for nucleophilic attack. In short, EDGs and EWGs provoke a slight deviation from a synchronous S_N2 mechanism and both enable decreased activation barriers. The underlying reasons for the S_N2-accelerating effect of EWG- and that of EDG-substituted phenyls at the electrophilic center of cyclopropanes are different, however, as illustrated in the More O'Ferrall-Jencks diagram in Figure 7.

Variation of substituents in $SnCl_4$-catalyzed (3 + 2)-cycloadditions of 2-aryl-1,1-di(alkoxycarbonyl)cyclopropanes with *p*-fluorobenzaldehyde recently studied by the Werz group resulted in a linear Hammett relationship, in which EDG-substituted substrates reacted faster than EWG-substituted analogues.[16a] Accordingly, Werz reported that relaxed force constants calculated for the C1–C2 bonds, which undergo cleavage in the course of the reactions, correlated with the relative reaction rates: lower force constants for EDG-substituted cyclopropanes were associated with faster reactions. We assume that complexation with the Lewis acid $SnCl_4$ enhanced the electron-deficiency of the 1,1-di(alkoxycarbonyl)-substituted cyclopropanes such that their reactivity was entirely governed by the degree of the C–C bond polarization, consistent with the intimate ion pair mechanism suggested for this reaction by Johnson and coworkers.[17]

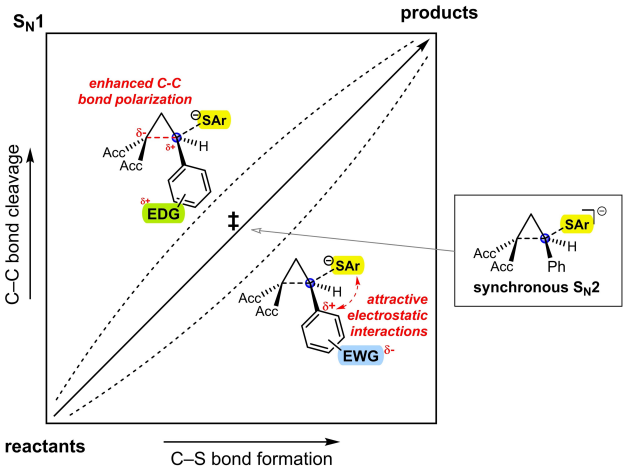


Figure 7. S_N2-accelerating effects in the TS of reactions of 2-aryl-substituted cyclopropanes with thiophenolates.

Conclusion

The kinetics of the S_N2-type ring-opening reactions of thiophenolates at Meldrum's acid-, dimedone-, and indandione-derived spiro-activated cyclopropanes were investigated by photometric methods. Product studies indicated selective nucleophilic substitutions at the C2 position of the cyclopropane ring, and kinetics revealed that S_N2 reactions occurred three to 15 times faster when the C2 carried an aryl group. Linear correlations of the determined second-order rate constants in DMSO with Mayr nucleophilicity parameters (N/s_N), Brønsted basicities (pK_{aH}), and Hammett substituent parameters (σ) of thiophenolates facilitate the rational prediction of reaction rates for so-far-unexplored cyclopropane–thiophenolate combinations.

When the reactivity of the electrophiles was varied by installing EWG and EDG groups at the phenyl rings attached to the 2-position of the cyclopropanes, a parabolic Hammett relationship was observed and rationalized by a gradual change from favorable electrostatic interactions (with EWGs) to an enhanced dissociative character of the C–C bond (with EDGs) in the transition states of the S_N2 reactions. Computations by the Aggarwal group showed that the rate-enhancing effect of EWG on S_N2 reactions might be limited to reactions with negatively charged nucleophiles.[32] It remains to be tested, therefore, whether the accelerating effect of EWGs at the electrophilic cyclopropanes vanishes when neutral nucleophiles are used instead of the anionic thiophenolates.

The kinetic studies in this work provide insight into the inherent reactivity of the cyclopropanes **1**, which is not shifted by complexation of the carbonyl groups with acids. The astonishing observation that reactions under neutral or basic conditions are accelerated by both EDGs and EWGs at the 2-phenyl groups of the cyclopropanes opens interesting perspectives to enhance the efficiency and synthetic versatility of ring-opening nucleophilic reactions at cyclopropanes. Not only vicinally donor–acceptor substituted cyclopropanes but also

those with the corresponding acceptor–acceptor motifs will facilitate nucleophilic attack.

Currently, we are investigating whether the ordering of electrophilic reactivity of the cyclopropanes, that we referenced toward thiophenolates in this work, also enables a rational design of reactions with other types of nucleophiles.

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Conflict of Interest

The authors declare no conflict of interest.

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