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Methyl Anion Affinities of the Canonical Organic Functional Groups

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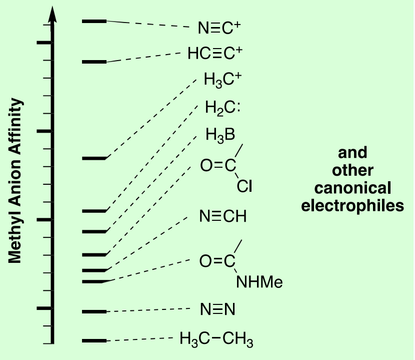
ABSTRACT: Calculated methyl anion affinities are known to correlate with experimentally determined Mayr *E* parameters for individual organic functional group classes but not between neutral and cationic organic electrophiles. We demonstrate that methyl anion affinities calculated with a solvation model (MAA*) give a linear correlation with Mayr *E* parameters for a broad range of functional groups. Methyl anion affinities (MAA*), plotted on the log scale of Mayr *E*, provide insights into the full range of electrophilicity of organic functional groups. On the Mayr *E* scale, the electrophilicity toward the methyl anion spans 180 orders of magnitude.



INTRODUCTION

Organic chemistry is taught using a canonical set of functional groups. To a first order approximation, prediction of polar chemical reactivity rests on the deceptively simple act of quantifying the nucleophilicity and electrophilicity of every functional group that is present in the reactants. The ability to independently quantify nucleophilicity and electrophilicity largely eluded organic chemists until the pioneering work of Mayr and coworkers.[1] In a heroic body of work, Mayr's team has shown that solution-phase nucleophilicity and electrophilicity can be independently quantified using a log scale, allowing useful predictions of reaction rate constants using the equation $\log k_{20°} = s_N\, s_E\, (E + N)$, where E and N are electrophilicity and nucleophilicity parameters, respectively, which quantify log-scale electrophilicity and nucleophilicity.[2,3] The variable s_N is a nucleophile-specific sensitivity parameter and s_E is close to unity.

The success of the Mayr equation centers around a focus on reactions that form bonds to carbon atoms, not, for example, Cs−O or F−Ge bonds, but a focus on carbon is not a significant limitation in the field of organic chemistry. The current set of electrophilicity parameters spans about 33 orders of magnitude and does not encompass highly reactive nor unreactive groups that serve as the pedagogical foundation for the field of organic chemistry, for example, *t*-butyl carbocation, ester carbonyls, amide carbonyls, acid chlorides, imines, alkyl halides, and carbon−carbon bonds.

Methyl anion affinity (MAA, Figure 1A) is related to the Mayr *E* parameter: $-\Delta E \propto$ Mayr *E* and is proportional to log *k* from the Mayr equation when s_E is 1. In early work, Mayr and Houk showed that calculated methyl anion affinity (AM1 H_f, gas phase) gives a good linear correlation with the Mayr

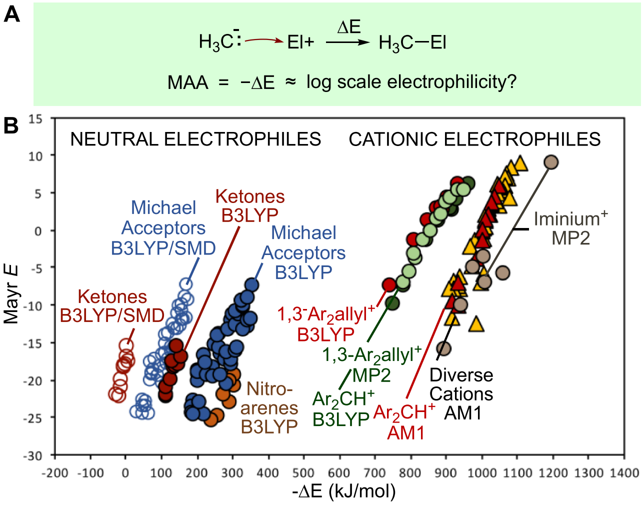


Figure 1. Previous correlations of MAA with Mayr *E*. (A) MAA is defined as the negative of the energy change for reaction of H_3C^- with electrophiles so that higher affinity correlates intuitively with higher energy, and higher kinetic electrophilicity. (B) Calculated MAA vs Mayr *E* generated lines that were dramatically different for neutral and cationic electrophiles. At higher levels of theory, different functional groups give different linear correlations.

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electrophilicity (Mayr *E*) for various cations: carbenium, iminium, and oxonium ions (Figure 1B).[4,5] It is promising that diverse cationic electrophiles fall on the same line. Subsequent work focused on individual functional groups but no attempt was made to correlate MAA with Mayr *E* for both neutral and cationic electrophiles. At higher levels of theory (MP2 and B3LYP), calculated MAAs also correlate linearly with Mayr electrophilicity for other classes of electrophiles: diarylallyl[6,7] and azacarbenium ions.[8] Mayr and coworkers have also shown that neutral electrophiles such as ketones,[9] Michael acceptors,[10] and nitroarenes[11] give good linear correlation between calculated MAAs and Mayr *E*. In theory, the common slope of these lines should correlate with $1/s_N$ for a methyl anion.

At all levels of theory, the correlation between MAA and Mayr *E* are linear with similar slopes but it is sobering to see that, even at high levels of theory, different classes of functional groups such as ketones, Michael acceptors, nitroarenes, benzhydryl cations, allyl cations, and azacarbenium ions, fall on different lines, suggesting that it may be impossible to broadly correlate MAA with Mayr *E* across all of the canonical functional groups in organic chemistry. The SMD solvation model [dimethyl sulfoxide (DMSO)] improves the linear correlation but did not lead to convergence of the lines for ketones and enones (Figure 1B). It is unclear if any theoretical treatment can be used to correlate the calculated methyl anion affinity with the solution phase electrophilicity of canonical organic functional groups.

■ RESULTS AND DISCUSSION

Solvation Improves Correlation of MAA* with Electrophilicity. We set out to compare the COSMO(∞) solvation model with SMD(DMSO) for calculation of MAAs that would correlate with electrophilicity. For this study, we chose a functionally diverse test set of electrophilic species that span almost the entire range of experimentally determined Mayr *E* parameters (Figure 2A): pentan-2-one,[9] acrylonitrile,[10] butanal,[12] methyl vinyl ketone,[10] maleic anhydride,[13] dimethylmethyleneammonium cation,[14] tropylium cation,[14] methoxyphenylmethylium cation,[14] benzhydryl cation,[15] and cumyl cation.[16] We restricted the product geometries to idealized transition state-like conformations by locking the newly formed H_3C-C bond 90° to the pi system being attacked for cumyl cation, methyl vinyl ketone, and acrylonitrile (Supporting Information). For example, methyl vinyl ketone was constrained to the *S*-cis conformation and newly formed H_3C-C bond in the product was constrained to be 90° to the original enone pi system, instead of the lower energy gauche conformation that minimizes the $A_{1,3}$ strain (Figure 2B). For most electrophiles, the minimized product geometries tend to be geometrically and energetically similar to the transition state-like geometries.

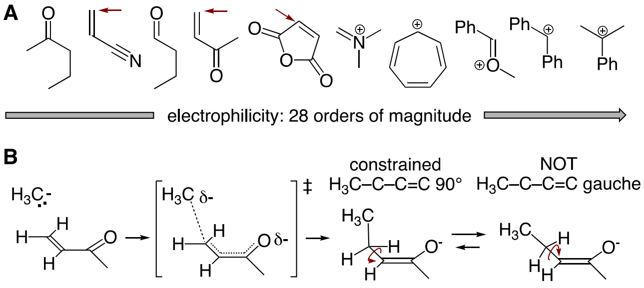


Figure 2. (A) Test set of electrophiles for which Mayr has reported experimental *E* parameters. Arrows show sites of attack. (B) MAAs were calculated by restricting products to transition state-like geometries.

The correlation between MAA and Mayr *E* is particularly poor when both neutral and cationic electrophiles are compared (Figure 3). When COSMO(∞) was used in the calculation of methyl anion affinity, the MAA gave surprisingly good linear correlation with Mayr *E* across both cationic and neutral electrophiles. Unexpectedly, on the full scale of measured Mayr *E* parameters, the SMD(DMSO) solvation was about as good as COSMO(∞) (R^2 0.95 vs 0.97, respectively) for calculation of MAAs that correlate with experimental electrophilicity although the correlation was not quite as good for ketones. Going forward, we define MAA* as a methyl anion affinity calculated with a solvation model to distinguish it from the traditional notion of a gas phase methyl anion affinity (MAA). MAA*s calculated with PBE0(disp)/def2-TZVP[17] gave about the same or better (R^2 0.97 vs 0.96) linear correlation with Mayr electrophilicity compared to B3LYP/6-311++G(3df,2pd), but was significantly faster and was used for all subsequent calculations of MAA*s.

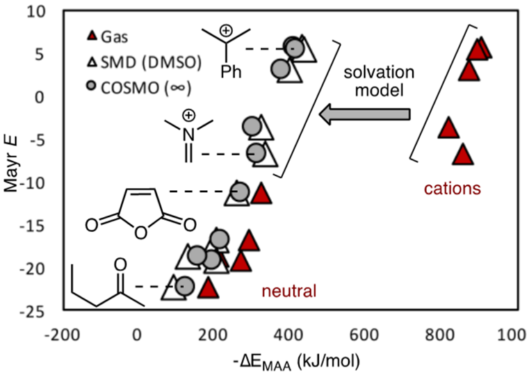


Figure 3. Solvation models lead to the correlation of MAA with Mayr *E*. Inclusion of a solvation model like SMD or COSMO leads to a good linear correlation between calculated MAA and Mayr *E* for both cationic and neutral functional groups.

MAA* Correlates with Mayr *E* Across a Broad Range of Electrophiles. Having shown that MAA*s correlate well with the Mayr *E* parameters for the test set of ten electrophiles, we set out to extend that analysis to a much fuller set of structurally diverse electrophiles. To date, Mayr and Ofial have reported Mayr *E* parameters for over 319 electrophiles.[18] The set includes molecules from over 30 different classes of functional groups: (i) empty p orbitals with π conjugation: benzylic cations,[14−16,19−23] allyl cations,[6,14] and the tropylium ion;[14] (ii) empty π^* orbitals: ketones,[9] iminium ions,[14,24] oxacarbenium ions,[14] sulfacarbenium ions,[14] acyl imines,[25] tosyl imines,[25] phosphoryl imines,[25] quinone methides,[26,27] indolylmethylium ions,[28,29] alpha, beta-unsaturated ketones,[10,12,30−32] acrylates,[10] acrylamides,[10] cinnamates,[10] acrylonitriles,[10] alkylidenemalonates and related compounds,[33−35] maleates and related compounds,[13] alkylidene malonitriles,[13] nitrostyrenes,[36] cinnamyliminium ion derivatives,[37−41] benzylidene malonitriles,[42] quinones,[43,44] sulfonyl substituted ethylenes,[10,45,46] electrophilic arenes,[47−50] and azocarboxylates;[51,52] and (iii) empty σ^* orbitals: chlorinating agents ($\sigma^*_{\text{C−Cl}}$),[53] electrophilic fluorinating agents ($\sigma^*_{\text{N−F}}$),[54] and electrophilic trifluoromethylsulfenylating agents (σ^{*}_{X-S}).[55] Cationic pi-metal complexes[14,19,56,57] can be represented as empty p orbitals or empty σ^*. We selected 75 of the 319 molecules (28 out of 32 functional groups) in the Mayr−Ofial database in an attempt to capture as many of the common canonical functional groups in organic chemistry as possible, excluding cationic π-metal complexes, chlorinating, fluorinating, and sulfenylating reagents that react through S_N2-like processes as-discussed below. MAA* was found to correlate linearly with the Mayr E parameters for nearly all of the functional groups, including the most reactive electrophiles (e.g., 1-(mesityl)ethenium ion, E = 6.04) and the least reactive electrophiles (e.g., cinnamonitrile, E = −24.60). Ultimately, it was found that MAA* based on calculated free energies (G_{298}) of unconstrained products gave the same correlation as MAA offering a more reproducible procedure (Figure 4, see the Supporting Information). As discussed below, ketones are a notable exception to this linear correlation and were not used in the linear regression (R^2 0.96); the mean absolute error for Mayr E was ±1.2. Inclusion of an additional term for $(E_{HOMO}-E_{LUMO})^{-1}$ did not change R^2, using E_{HOMO} for a typical nucleophile, methylamine (Supporting Information).

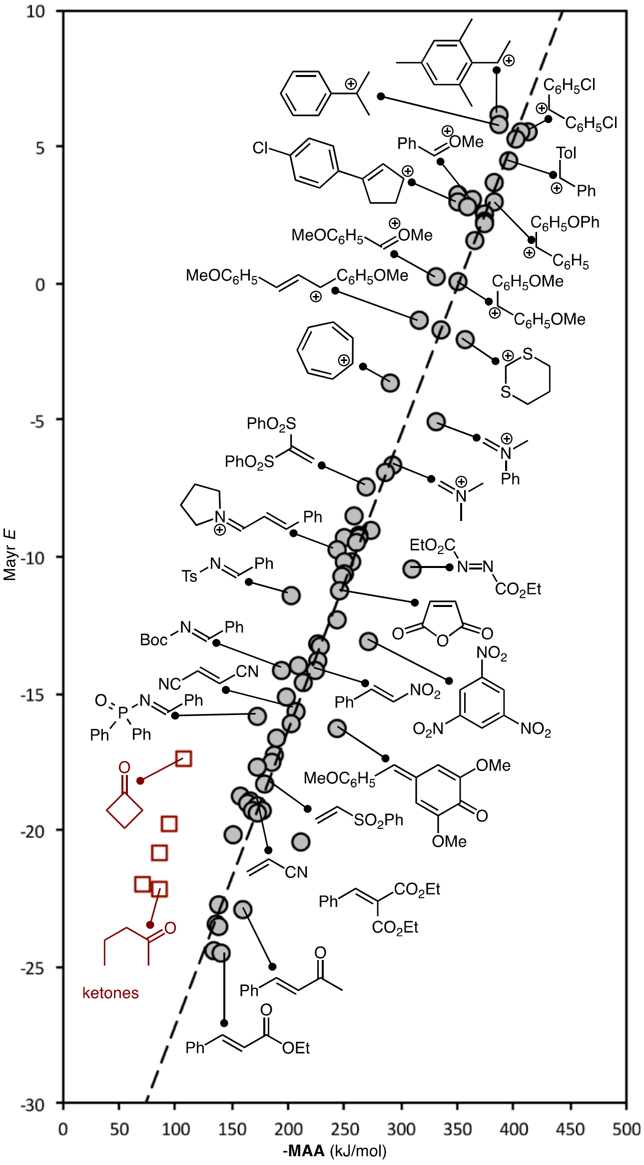


Figure 4. Correlation between experimental parameters and theory. There is good correlation between the calculated MAA* (PBE0/def2-TZVP COSMO(∞)) and Mayr E parameter across a broad range of organic electrophiles.

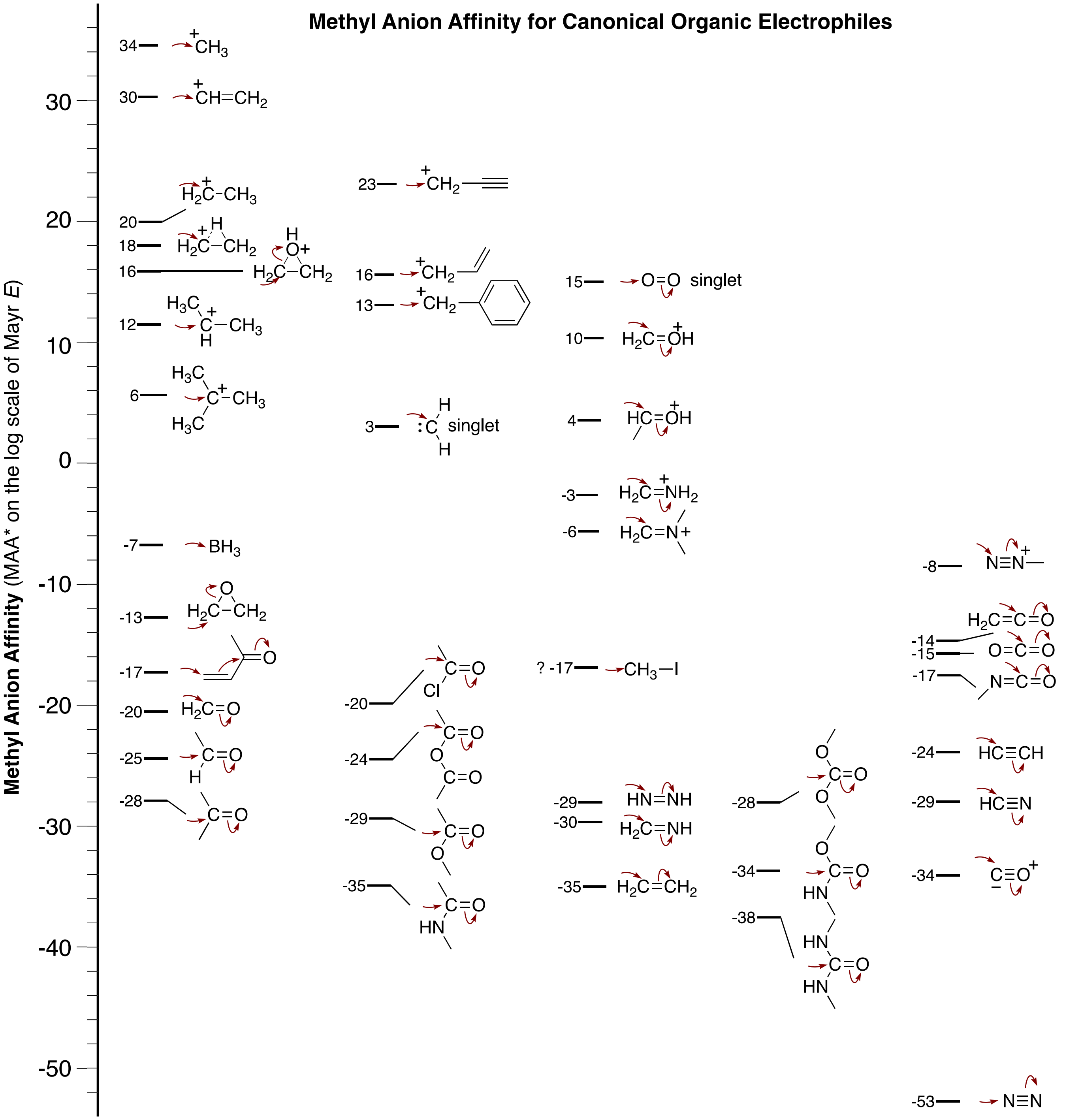
Acetyl chloride and acetic anhydride do not generate stable tetrahedral intermediates at the PBE0/def2-TZVP level of theory. Therefore, we constrained the C−Cl distance to 1.800 Å in the adduct of acetyl chloride and we constrained the C−OAc distance to 1.395 Å in the adduct of acetic anhydride.[58,59]

No Mayr E parameter has ever been reported for an S_N2 displacement reaction at carbon although Mayr has reported E parameters for electrophiles in three other types of displacement reactions: chlorination by attack on Cl−C bonds, fluorination by attack on F−N bonds, and (trifluoromethyl)-sulfenylation. Mayr has noted that "deviations are expected for S_N2 type reactions, where making one σ-bond is coupled with breaking another σ-bond."[14] E and s_E parameters can be estimated based on published kinetic data for S_N2 attack on $CH_3S^+R_2$ (E = −10),[2] CH_3I (E = −23),[2] and CH_3Br (E = −22)[60] in protic solvents and for CH_3I (E = −17),[61] in DMSO but the resulting E and s_E values are less reliable for calculation of rates than for other types of electrophiles.[61] Thus, it is not surprising that a plot of MAA* versus these renegade E parameters does not fall on the same line as the other types of electrophiles for which E parameters have been vetted, even after correction for translational entropy differences[62] and distortion energies.[63] It is ironic that the relative reactivity of S_N2 substrates, long studied with linear free energy relationships,[58] remains among the most pressing issues of our time in the field of physical organic chemistry.

Perhaps free carbenium ions and iminium ions give good agreement with MAA* because the experimental counter ions like BF_4^- do not interact strongly with the reactants or the transition state for nucleophilic attack. Naked carbonyl compounds may end up fitting a second parallel linear function that could easily be applied to canonical electrophiles, but we lack high quality Mayr E parameters for aldehydes and ketones at this lower end of the reactivity scale. The Mayr E parameters were determined in the presence of *t*-BuOH and K^+ (which were not included in calculation of MAA*) with careful control experiments involving 18-crown-6 and phosphazene bases. To explore the issue of carbonyl activation, we compared MAA*s calculated from electronic energies for various forms of cyclobutanone. The cyclobutanone·K^+·18-crown-6 adduct, modeled from the butanone crystal structure,[64] had an even lower MAA* than free cyclobutanone but the MAA* for cyclobutanone·K^+ was 31 kJ/mol higher than that for naked cyclobutanone. The MAA* for benzaldehyde·HO*t*-Bu was 21 kJ/mol higher than that of free cyclobutanone.

Which value best reveals the "electrophilicity" of a carbonyl group: the MAA*, which matches the naked arrow-pushing depiction or a Mayr E parameter determined in the presence of species that are not depicted? After philosophical reflection, the answer is probably: both.

Quantifying the Reactivity of the Canonical Electrophiles on the Mayr Scale. With good confidence in the linear correlation between MAA* (G_{298} from PBE0/def2-TZVP COSMO(∞)), we were then motivated to calculate MAA*s for unsubstituted canonical electrophiles (Figure 5) and convert them to the logarithmic Mayr E scale. On this scale, the C−C bond of ethane corresponding to the intrinsic



Methyl Anion Affinity

$$H_3\overset{-}{C}{:} \longrightarrow El+ \xrightarrow[\text{calcd}]{\Delta G^\circ} H_3C{-}El$$

MAA* = -ΔG°

level of theory: PBE0 (dis)/def2-TZVP COSMO(∞)

Log-scale Electrophilicity versus CH_3^-

$E^* = MAA^* \cdot 0.11 - 37.9$

Polar Reactivity Scales and Poster Format

- ■ Herbert Mayr and Armin R. Ofial "Kinetics of Electrophile-Nucleophile Combinations: A General Approach to Polar Organic Reactivity" *Pure Appl. Chem.* **2005**, *77*, 1807.
- ■ Herbert Mayr and Matthias Patz "Scales of Nucleophilicity and Electrophilicity: A System for Ordering Polar Organic and Organometallic Reactions" *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938.

Mayr/Ofial Database of experimental Mayr *E*, Mayr *N*, and Mayr s_N parameters

- ■ https://www.cup.uni-muenchen.de/oc/mayr/DBintro.html and references therein

Figure 5. MAA* for the Canonical Electrophiles in Organic Chemistry. Methyl anion affinity, calculated with a solvation model, and plotted on the logarithmic Mayr *E* scale offers insight into electrophilicity.

barrier for attack on σ^*_{CC} has a value of −70. The acetylide cation and cyanide cation have values of +87 and +111, respectively. To the extent that methyl anion affinity, calculated with solvation correlates with solution phase reactivity, we begin to glimpse the breathtaking range of electrophilicity for canonical organic functional groups, as commonly depicted with arrow-pushing representations on the scale of the Mayr *E* parameter.

Accuracy and Relevance of Methyl Anion Affinities. If the correlation between MAA* and Mayr *E* is linear and the distribution is normal, then the furthest reaches of predicted electrophilicity, from $H_3C{-}CH_3$ to $^{+}C{\equiv}N$ will range from MAA* of −70 (±3) to +111(±5) on the Mayr *E* scale at a 95% confidence level. The structure of the Mayr equation, log $k_{20°} = s_N\, s_E\, (E + N)$ suggests that a truly independent scale of nucleophilicity and electrophilicity may be out of reach for some classes of polar reactions such as S_N2. Approaches involving deep learning could allow us to make predictions based on complex nonlinear structure-reactivity relationships.[65−67]

What is the significance of electrophiles that cannot be studied in solution? Reactions of the simplest carbenium ion, methyl cation[68] (H_3C^+), and even the supremely reactive cyanide cation ($^{+}C{\equiv}N$)[69,70] have been studied in gas phase experiments. Singlet methylidene[71] and vinyl, ethyl, and propargyl cations have been identified in the atmosphere within our solar system and in interstellar environments.[72] Until there is a comprehensive database of *E* parameters that includes these gas phase species, it seems expedient to assess electrophilicity on the familiar Mayr scale. Allyl cation and less reactive carbenium ions have been studied in solution on our own planet under superacid conditions.[73] The ubiquitous C−C σ^* is at the bottom end of the electrophilicity scale. Understanding the kinetic electrophilicity of these species on a common scale inspires us to think about their potential reactivity on Earth and beyond.

CONCLUSIONS

MAA* is an economical tool for estimating the log scale electrophilicity of the canonical organic functional groups, covering a staggering range of 180 orders of magnitude. Moreover, such experimental determinations of Mayr *E* parameters are needed to explore the limits of the linear correlation with methyl anion affinity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03187.

Computational details and methods (PDF)

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Notes

The authors declare no competing financial interest.

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