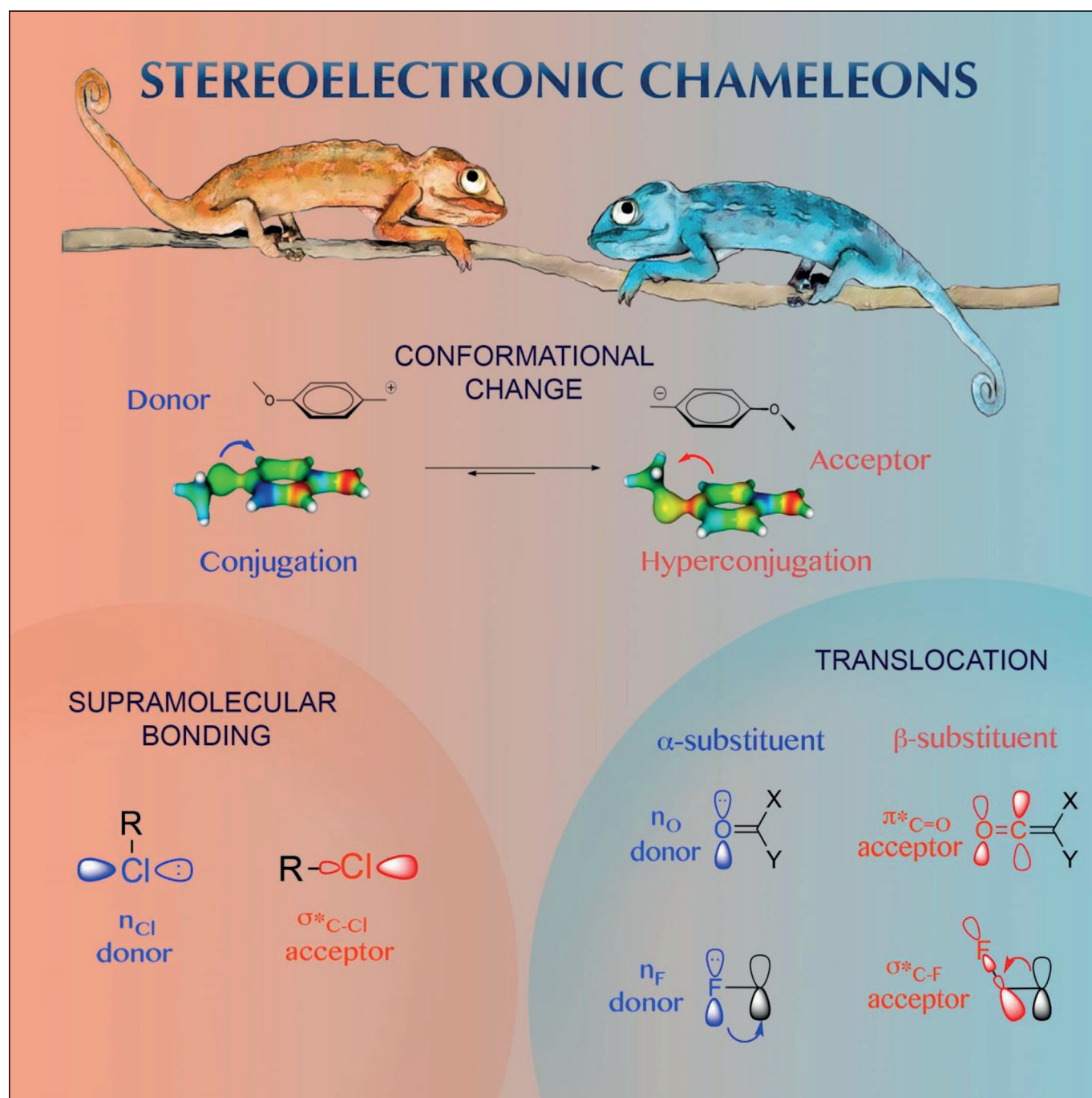


Stereolectronics

Stereolectronic Chameleons: The Donor–Acceptor Dichotomy of Functional Groups

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Abstract: Stereoelectronic factors account for the apparent reversal of donor–acceptor properties of a variety of functional groups by a simple change of their orientation in

space. The new reactivity patterns that arise from spatial anisotropy are associated with chameleonic behavior of common organic functionalities.

1. Introduction

It is in the nature of scientists to classify objects of study into well-defined categories. This habit is even more common for educators who have to simplify the inherent complexity of their subjects to help their students to master their craft. Organic chemistry instructors, in particular, classify substituents as either “acceptors” or “donors”. Later, these terms were more accurately defined, as in σ -donors or π -acceptors, to explain how the same functionality may be a donor and an acceptor at the same time. For example, the distinction of p-donor and σ -acceptor ability of halogens in electrophilic substitution reactions helps to explain their *ortho/para*-directing character that coexists with their deactivating effect.

If one needs to change a donor into an acceptor, a chemical transformation is usually required—from something as simple and potentially reversible as protonation,^[1] or coordination with a Lewis acid etc. to chemical transformations, that is, reductions and oxidations. The utility of such thinking is illustrated by such concepts as in “umpolung”, which is based on switching of reactant polarity for the design of new synthetic transformations.

However, subtler and interesting situations exist in which the donor/acceptor properties of substituents and, hence, chemical reactivity is controlled by using groups that can be either donors or acceptors depending on their orientation in space with respect to the rest of a molecule. The focus of this review will be on a more nuanced stereoelectronic conversion of donors into acceptors (and vice versa) caused by either a conformational change or insertion of an additional atom between two functional groups. Such changes can lead to interesting consequences in stability, reactivity, and spectroscopy, among others. We illustrate a few of these changes in Figure 1.

The selection of examples discussed here spans from high energy reactive intermediates, both charged and neutral, to relatively stable molecules. For intramolecular substituent effects, the variety of their manifestations can be broadly characterized within two general scenarios: a) transforming a donor into an acceptor by rotation and b) converting a donor into an acceptor by translocation. The common stereoelectronic rea-

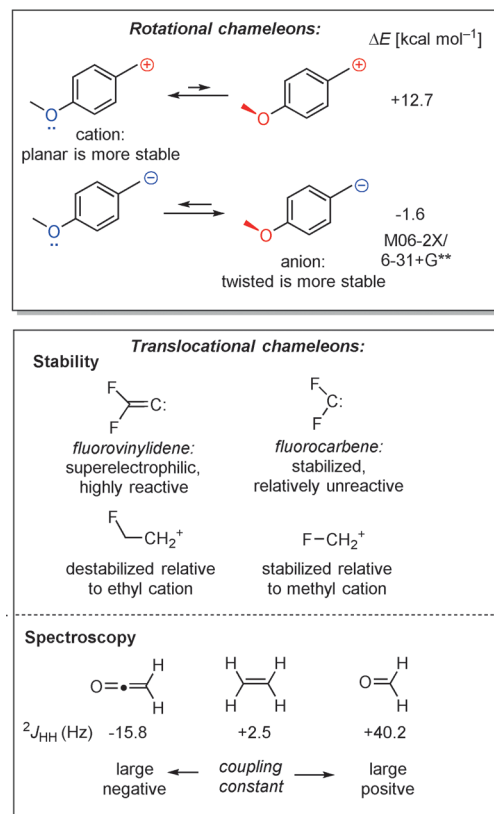


Figure 1. Contrasting intramolecular effects of the same functionality on stability, reactivity and spectroscopic values as a function of geometry that correspond to rotational and translocational “chameleons” (vide infra).

sons for chameleonic behavior in these two situations are summarized in Figure 2.

Conceptually, the combination of structural features that can result in chameleonic behavior logically follows from the electronic requirements. An atom connecting chameleonic functionality to the rest of the molecule should have a donor and an acceptor orbital with non-identical location in space. The donors can be either lone pairs or high energy bonding orbitals (σ or π). The acceptors can be low energy antibonding (again, σ or π) or empty non-bonding orbitals.

1.1 Intramolecular effects

Transforming donor to acceptor by rotation: When both donor and acceptor orbitals are present on the same atom and are projected to different directions, rotation around bonds connecting such an atom with the rest of the molecule can turn the donor/acceptor effects on and off, inverting the apparent electronic nature of the substituent (Figure 2A). This is a truly

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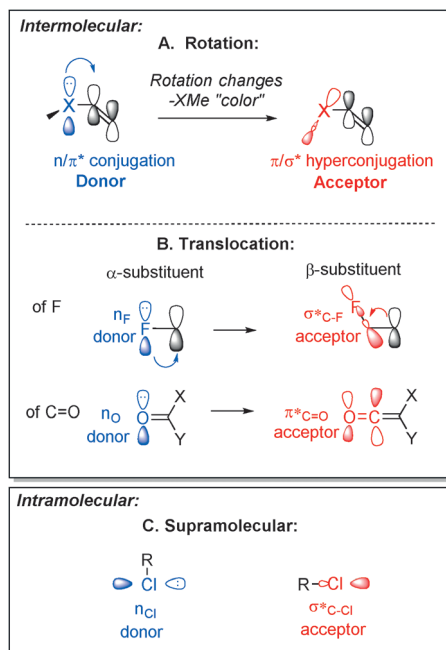


Figure 2. Two types of intramolecular "chameleonic" behavior for a functional group (top: rotational, center: translocational) and chameleonic potential for intermolecular interactions (bottom).

dynamic feature that manifests itself in those cases in which the distribution of electron density changes significantly in a chemical reaction. In these situations, changes in electronic demand can dictate a change in the preferred delocalizing stabilization mode.

Converting donor to acceptor by translocation: A conceptually distinct situation is often observed when a substituent is moved one atom away from the original (reference) position. There are many cases when such a change converts a donor into an acceptor. This means that the same group can be an α -donor and then a β -acceptor, or vice versa. Such changes, that is, the difference between carbenes and vinylidenes, or ketones and ketenes, can be dramatic. Unlike dynamic chameleons that "change their color" through a conformational change, the chameleonic nature of a substituent in this case is generally apparent when different molecules are compared (Figure 2). However, it can also be important for the reactivity of two different positions relative to a functional group in the same molecule.

1.2 Intermolecular effects

For intermolecular interactions, in which the two partners are free from the preexisting constraints (i.e., chemical connections), the target functionality can change from a donor to an acceptor when a different direction of approach to the molecule is chosen by supramolecular constraints. Such effects manifest themselves in non-covalent interactions and transition states for bimolecular reactions.

We suggest referring to functional groups that are capable of switching their donor/acceptor properties as "stereoelec-

tronic chameleons," a concept that will be introduced in the following sections. We will provide examples of intramolecular chameleonic behavior of common functional groups that can

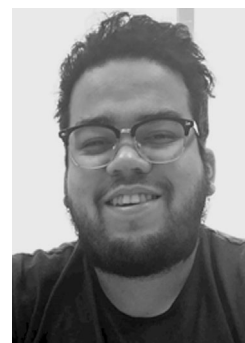
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be either donors or acceptors depending on their position and orientation relative to the rest of the molecule. We will also illustrate that interesting features of non-covalent complexes originate from their supramolecular chameleonic behavior (Figure 2C) and show how chameleonic properties can be beneficial at different stages of chemical reactions.

2. Conformational Chameleons

2.1 Methoxy groups as stereoelectronic chameleons

The reputation of the OMe group as a donor substituent is based on its accelerating effect in electrophilic substitution of aromatics (up to 10^9 relative to benzene)^[2] and in electrophilic additions to vinyl ethers.^[3] Furthermore, in both cases, acceleration comes with high regioselectivity. The conformational profile of an OMe group attached to a π -system is consistent with the donor properties of oxygen. The lowest energy conformations in vinyl ether **1a,b**, ethenol, and methyl formate (**2a,b**) are planar because this geometry allows for the perfect alignment of the p-type lone pair at oxygen with the π -system (Figure 3).^[4,5] In this scenario, the dominant electronic interaction between oxygen and alkene is the $n_O \rightarrow \pi^*_{C=C/O}$ donation from oxygen to the alkene or the carbonyl.^[6]

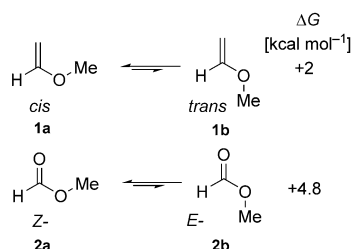


Figure 3. Preferred conformations of vinyl ether and methyl formate.

However, this preference can change under the conditions in which the importance of donation to the σ^*_{O-C} orbital increases and, hence, the acceptor properties of the ether group can contribute more to the overall molecular stability. Such increase comes from two alternative sources: a) introduction of electronegative atoms at the alkoxy carbon (e.g., change from OMe to OCF₃), or b) conversion of the π -system into a particularly strong donor (e.g., donor groups at the alkene/arene or electron injection and switch to a reductive process). An example of the first source of chameleonic behavior of an OR group is provided by a change in the preferred conformation in trifluoromethoxybenzene **4**. Unlike anisole **3**, the conformation of **4b**, in which the O–CF₃ bond is perpendicular to the phenyl plane, is favored (Figure 4).^[7,8]

A Cambridge Structural Database (CSD) search for methoxy-substituted aromatics provided 32 234 hits, of which there was a strong preference for the torsional angles [C_{aryl}–C_{aryl}–O–CH₃] of -180° , 0° , and 180° , as expected for the planar geometries (Figure 5A). This strong preference is consistent with the relatively

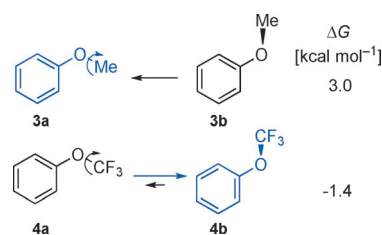


Figure 4. Calculated differences in the conformational preferences of anisole^[7] at B3LYP/6-31G* level and trifluoromethoxybenzene at MP2/6-31G** level^[8].

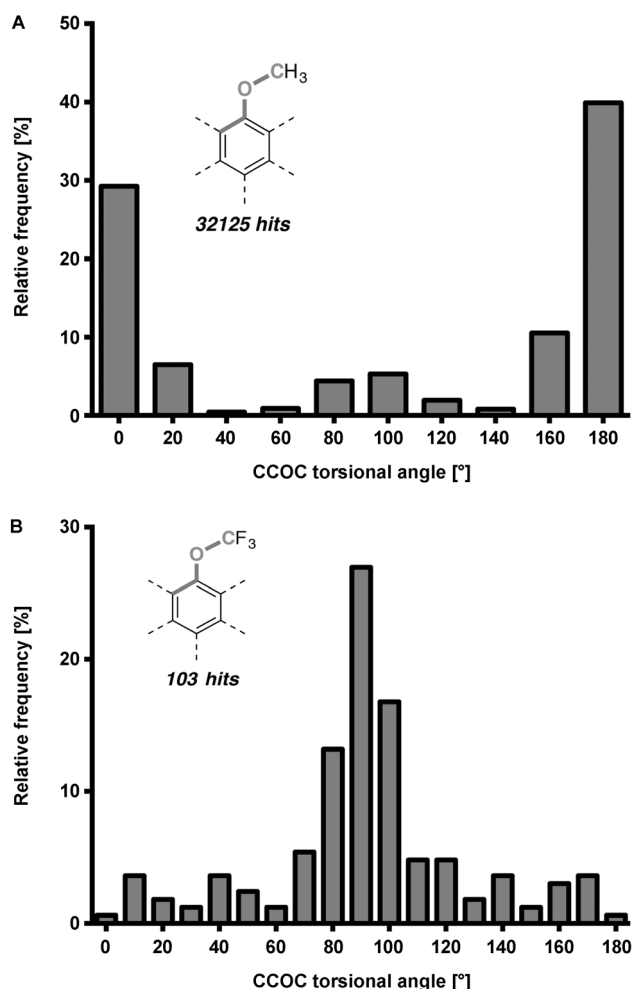


Figure 5. CSD analysis of torsional angles in substituted ArOCH_nF_m molecules. A) Substituted anisoles, B) OCF₃-substituted aromatics; vertical axis: % of search results.

large (3 kcal mol⁻¹ (B3LYP/6-31G*)) preference for the planar anisole conformation of **3a** in Figure 4.

In contrast, the structural search for OCF₃-substituted aromatic compounds in the CSD provided 103 hits with torsional angles [C_{aryl}–C_{aryl}–O–CF₃] equal or close to 90° , suggesting that such behavior is general (Figure 5B). The change in the preferred conformation likely plays a role in the pharmacological properties of molecules that incorporate the OCF₃ group. Although this preference was clearly pronounced, a noticeable

amount of cases with a relatively broad distribution of angles was also found. The weaker conformational preference was consistent with the smaller [ca. $1.4 \text{ kcal mol}^{-1}$ (MP2/6-31G**)] energy difference between the two conformations (**4a,b**) in the parent trifluoroanisole molecule (Figure 4).

This conformational change is due to the change in the dominating stereoelectronic effect. The presence of the three fluorine atoms in CF_3 has two complementary consequences: 1) it decreases the donor ability of the oxygen lone pair and 2) it increases the acceptor ability of the $\sigma^*_{\text{O-C}}$ orbital, so this orbital can benefit much more from the interaction with the aromatic π -system. The difference between planar and orthogonal conformations depends on the tug of war between two acceptors, the aromatic π -system and the CF_3 group for the p-type lone pair of the oxygen atom.

The CF_3 group wins this competition with a parent benzene ring. However, if acceptor ability of the π -system is increased by suitable substitution, the chameleonic OCF_3 group can "change its color" again. For example, presence of a carbonyl group at the *para*-position significantly decreases the difference between the planar and perpendicular conformations. This is well-illustrated by the curious molecule shown in Figure 6, in which each of the four chemically identical OCF_3 groups adopts different conformations depending on their crystal environment. Evidently, the conformational preferences are sufficiently small in these systems to be overridden by the crystal packing effects.^[9]

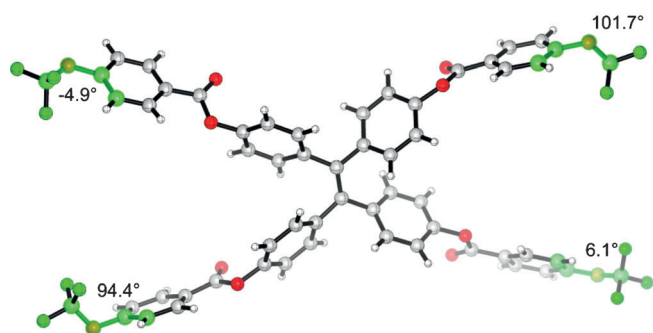


Figure 6. "Conformationally confused" OMe substituents in four electronically similar methoxyaryl groups in the same molecule constrained in a crystal.

For the same reasons, the preferred conformation of the OCF_3 group switches back to the planar geometry in electron-deficient heteroaromatic systems such as for 2-pyridines (Figure 7A). Sufficient crystallographic data is available for evaluating the conformational preference for the OCHF_2 group. For this weaker acceptor, the CSD search for torsional angles in the $[\text{C}_{\text{aryl}}-\text{C}_{\text{aryl}}-\text{O}-\text{CHF}_2]$ moiety revealed modest preference for the planar geometry among the 17 search results (Figure 7B). Unfortunately, not a single aromatic molecule with an OCHF_2 is present in the CSD and this additional comparison is not possible at this point.

The other type of chameleonic behavior for an OR group is illustrated by the preferred geometry for fluorinated alkenyl ethers **5**. In a sharp contrast with the parent vinyl ether **6**,

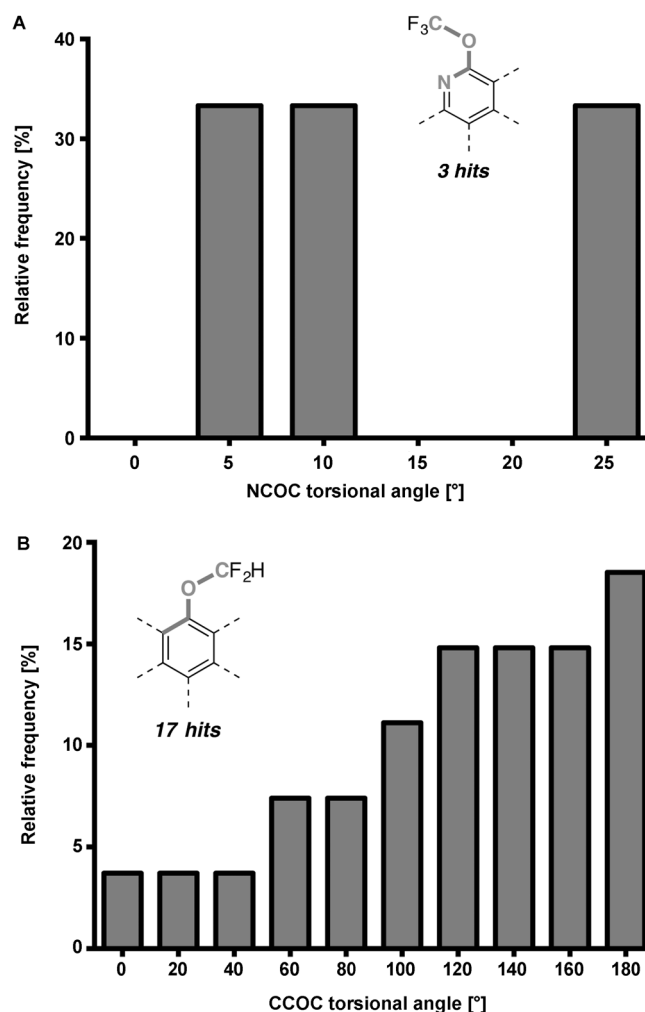


Figure 7. CSD analysis of torsional angles in undecided ArOCH_nF_m systems in which the donor/acceptor character of the aromatic system and the OR group are finely balanced. A) Substituted 2- OCF_3 pyridines, B) OCF_2H -substituted aromatics; vertical axis: % of search results.

these molecules adopt an anticlinal conformation in which the O-C bond is aligned with the π -system.^[10] This change results from two stereoelectronic components. Importantly, the lone pairs of the multiple fluorine atoms induce chameleonic behavior of the OMe group by making the π -system of alkene **5** quite electron rich and by strengthening the $\pi_{\text{C=C}} \rightarrow \sigma^*_{\text{O-C}}$ interaction, in which the methoxy moiety behaves as a σ -acceptor relative to the $\pi_{\text{C=C}}$ bond (Figure 8). In addition, the perpendicular geometry in **5** aligns the oxygen p-type lone pair with the vicinal $\sigma^*_{\text{C-F}}$ orbital, maximizing the $n_{\text{O}} \rightarrow \sigma^*_{\text{C-F}}$ interaction. Note that both the fluorine and the oxygen functionalities play two opposite roles: each of the heteroatoms can play the role of either a donor (through the lone pairs) or an acceptor (through the $\sigma^*_{\text{C-X}}$ antibonding orbitals). In the two effects shown in Figure 8, oxygen and fluorine exchange their relative roles. A similar conformational preference has been observed for the fluorinated thioethers^[11] and 2,3,5,6-tetrafluoroanisole.^[12]

The other source of chameleonic behavior is obvious in the conformation of the *p*-OMe substituted benzylic anion in which the usual planar conformation of non-crowded alkoxyar-

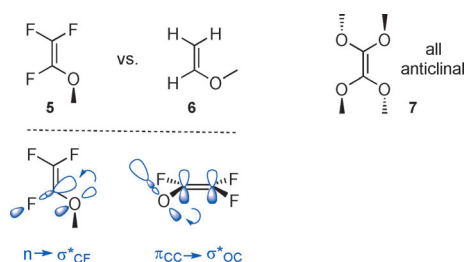


Figure 8. Preferred conformations in alkenes and fluoroalkenes.

omatics is changed to the perpendicular orientation. The conformational change “inverts” the electronic character of the OMe group, converting it from a π -donor to a hyperconjugative σ -acceptor. Figure 9 illustrates connection of such conformational preferences with electronic stabilization in the benzylic cation, radical, and anion.

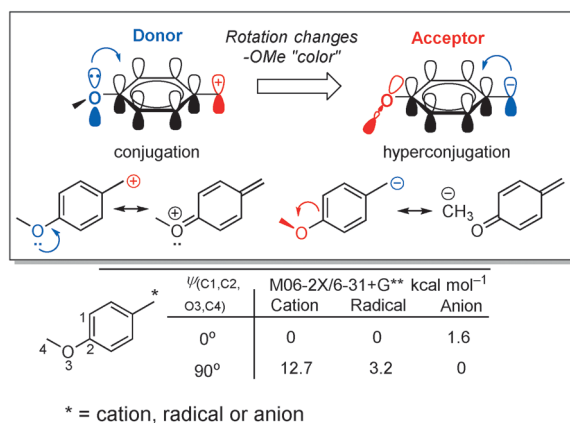


Figure 9. “Stereoelectronic chameleon”: the two faces of the OMe group. Methoxy serves as a donor in cationic and radical reactions, but behaves as an acceptor towards anionic species.

Rotation of the *p*-OMe substituent has profound stereoelectronic consequences for the regioselectivity of reductive C1-C5 cyclization of enediynes **8** (Figure 10).^[13] Reactions proceed via a transition state (TS) with a significant accumulation of negative charge at the internal carbon of one of the breaking triple bonds. The acceptor at the *para*-position can provide stabilization to this TS and control regioselectivity (**9** vs. **10**) of the ring closure.

Adler and co-workers have shown that the relative energies for the coplanar versus perpendicular conformation of the OR group can be controlled by the steric bulk of R. It was suggested that such conformational change can render the OTIPS (TIPS = triisopropyl silyl) groups electron withdrawing and, potentially, increase their hydrogen-bonding catalytic abilities (Figure 11).^[14]

The extent of electronic stabilization can be quantified using a sequence of isodesmic reactions. The two reactions in Figure 12 highlight the donor ability of the OMe group. Because communication between the cationic center of the benzylic cation and the lone pair of oxygen is stereoelectronically

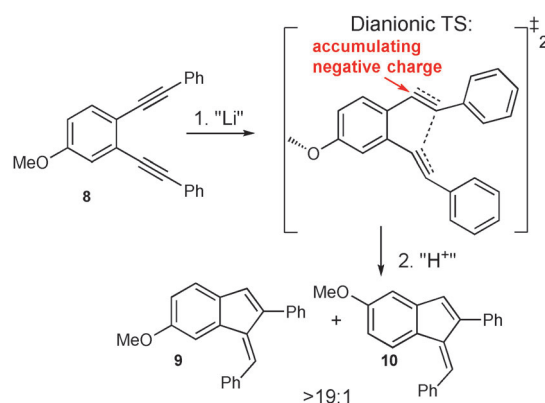


Figure 10. Chameleonic behavior of the methoxy group accounts for the observed regioselectivity of anionic C₁-C₅ cyclizations of methoxy-substituted enediynes in which the $\sigma^*_{\text{O-C}}$ orbital serves as a hyperconjugative acceptor and stabilizes negative charge accumulating in the TS.

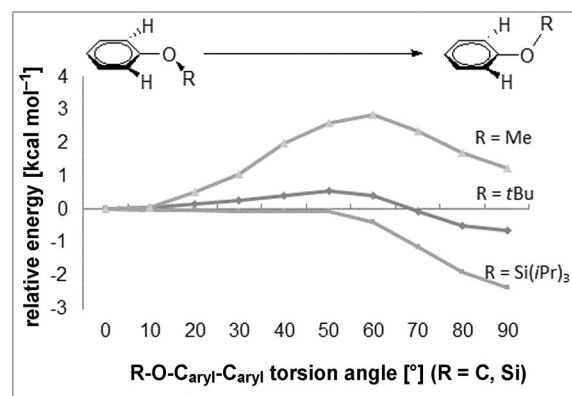


Figure 11. The relative energies of coplanar and perpendicular conformations of an OR substituent at the benzene ring can be controlled by the steric bulk of R (energies at wB97xd/6-31 + G(d,p) level, in kcal mol⁻¹).

favorable, the *p*-OMe substituent can provide dramatic [43 kcal mol⁻¹ (M06-2X(D3)/6-311 + G(d,p)) stabilization. The dominant role of the stereoelectronic factors is illustrated by near disappearance of the stabilizing effect for the phenyl cation [0.6 kcal mol⁻¹ (M06-2X(D3)/6-311 + G(d,p))], in which the σ -cationic center does not stereoelectronically communicate with the aromatic π -system (Figure 12).

The anionic species derived from *p*-OMe-substituted toluene and benzene (i.e., the benzyl and benzene anions) have clearly different stereoelectronic preferences in comparison to the cations, because both carbanions prefer perpendicular geometries, in which it is not the oxygen lone p-type lone pair but the $\sigma^*_{\text{O-C}}$ orbital that is aligned with the aromatic π -system (Figure 13).

Despite the above conformational preferences, the *p*-OMe group still remains destabilizing for the benzylic anion and, hence, does not fully justify the “chameleon” designation. In other words, the perpendicular conformation simply looks like “the lesser of the two evils”. However, the OMe group does become a stabilizing group for the aryl anion if a suitable geometry for the neutral reference point (i.e., the perpendicular

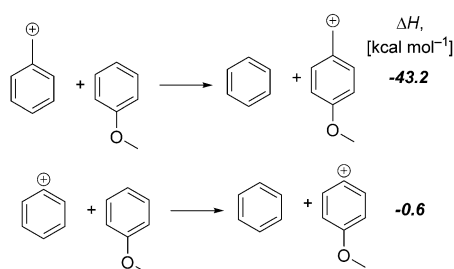


Figure 12. Calculated examples of cation stabilization by the MeO group at M06-2X(D3)/6-311 + +G(d,p) level.

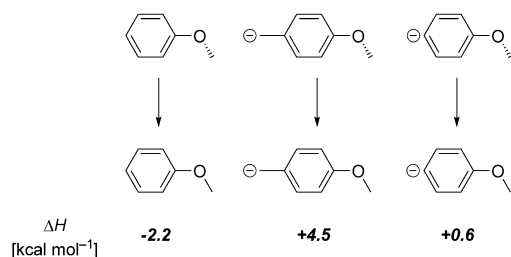


Figure 13. Calculated energy differences for the two orientations of the OMe group in anisole and related anionic species at M06-2X(D3)/6-311 + +G(d,p) level.

conformer) is taken to compensate for the destabilizing loss of conjugation between the oxygen p-lone pair and the aromatic system itself (Figure 14).

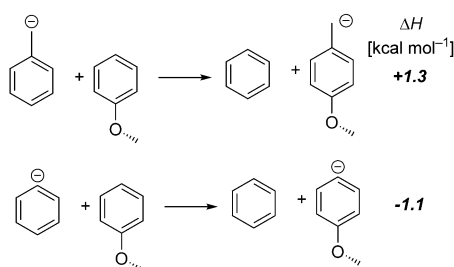


Figure 14. Calculated examples of stabilization of the cationic and the anionic centers by the MeO group at M06-2X(D3)/6-311 + +G(d,p) level.

One of the reasons for the often incomplete chameleonic behavior for ethers is that oxygen has two lone pairs; a high energy p-orbital and a lower energy sp^n hybrid (Figure 15).^[15] Misaligning both of them with the aromatic π -system is impossible and, although the hybridized lone pair is a less potent donor, it still can engage in an unfavorable communication with the anionic center. However, the same orbitals can make an efficient chameleonic system when their electronic populations are different (i.e., in carbenes, vide infra).

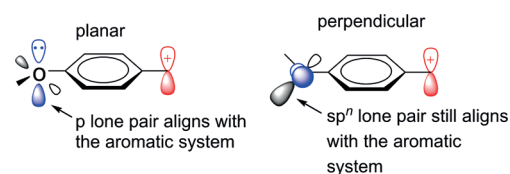


Figure 15. It is hard to make a perfect chameleon from a heteroatom with two lone pairs.

2.2 Amines as stereoelectronic chameleons

Unlike oxygen and other chalcogens, trivalent nitrogen and its pnictogen congeners have only one lone pair available. In enamines, this pair is engaged in the interaction with the π -system. When two bulky groups are attached to the nitrogen atom (i.e., in *Z*-substituted enamines), steric hindrance imposed by these groups is unavoidable and can strongly disfavor the coplanar conformation. In such systems, the nitrogen lone pair can assume a misaligned (even orthogonal) orientation, with the partial loss of the $n_N \rightarrow \pi^*_{C=C}$ interaction or, in the extreme case of (*Z*)-1-(dimethylamino)propene **12b** (Figure 16), with the replacement of the above interaction with $\pi_{C=C} \rightarrow \sigma^*_{C-N}$ hyperconjugation.^[16] The loss of the $n_N \rightarrow \pi^*_{C=C}$ interaction in orthogonal conformations of enamines is clearly reflected in their ^{13}C NMR spectra as well.

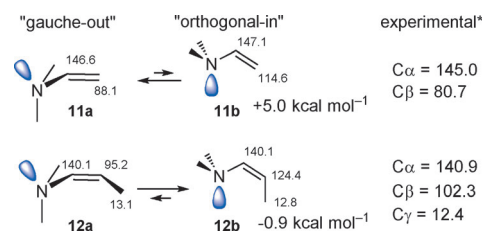


Figure 16. Preferred conformations and ^{13}C NMR shifts (theoretical and experimental) of dimethylaminoethene and (*Z*)-1-(dimethylamino)propene (^{13}C NMR shifts in C_6D_6) (MP2-full/6.31 + G(d)).^[16] Note that the tug of war between hybridization and resonance^[9,17] leads to the allocation of s-character to the nitrogen lone pair and complicates the stereoelectronic picture.

Reference ^{13}C NMR values for the $\text{N}-\text{C}(1)=\text{C}(2)$ fragment are 147 and 84 ppm, respectively. In general, C(1) is within 134–157 ppm and C(2) is 79–132 ppm. Figure 17 shows examples **14** and **16** in which structural constraints for sterics disturb the conjugation between lone pair and double bond.^[18] It is clear that the lesser is an n_N interaction with the π -system, the higher is the C(2) chemical shift.

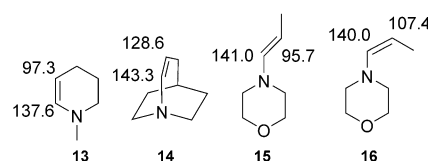


Figure 17. Differences in ^{13}C chemical shifts show the degree of $n_N \rightarrow \pi^*_{C=C}$ interaction.

A variety of organocatalytic transformations are based on reliable C–C bond formations in which enamines serve as regioselective nucleophilic reagents in reactions with carbon electrophiles. Addition of HBr proceeds through the formation of α -cation **17**⁺ stabilized by resonance. When the lone pair is constrained and the overlap with the cation is less efficient, the regioselectivity of addition changes and the cationic center **19**⁺ is formed further away from the nitrogen (Figure 18).^[19] The conformational constraint changes the apparent effect of nitrogen on the adjacent double bond from a donor to an acceptor.

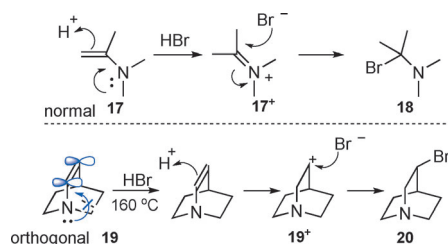


Figure 18. Switch from the selective β -attack in normal enamines to an α -attack in the “orthogonal” enamine in the reaction with HBr.

The disappearance of the lone pair/ π -bond interaction in the “orthogonal enamines” is illustrated by the position of their equilibrium with the respective allyl amines. Usually, this equilibrium favors the enamine by about 2–5 kcal mol^{−1}. However, in the 1-azabicyclo[3.2.2]non-2-ene, the difference in stability disappears (Figure 19) and the equilibration produces the mixture of enamine **23** and allyl amine **24**.^[20]

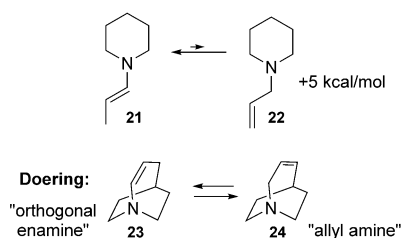


Figure 19. Deactivation of $n_N \rightarrow \pi^*$ resonance in “orthogonal enamines”.

Cis-trans isomerization of the C=C bond in enamines is generally faster relative to that in alkenes without a heteroatom.^[21] This effect is consistent with the decreased double-bond character originating from the $n_N \rightarrow \pi^*$ resonance. When the $n \rightarrow \pi^*$ interaction is switched off by giving the lone pair of nitrogen a better alternative that consists of the strong acceptor anti-periplanar $\sigma^*_{C=O}$ orbitals (Figure 20), the alkene π -system reorients itself perpendicularly to the lone pair to decrease steric repulsion.^[22] This enamine is so unreactive that it cannot be isomerized into the *trans* double-bond isomer without fission of the heterocyclic ring.^[23] Interestingly, the ¹³C NMR shift of C _{β} at 111 ppm also confirms the lack of conjugation between n_N and the π -bond (compare to Figure 17).^[18]

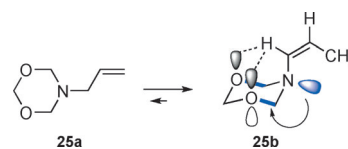


Figure 20. The electronic approach towards deactivation of $n_N \rightarrow \pi^*$ resonance in enamines.

2.3 Amides as stereoelectronic chameleons

Whereas the stabilization due to $n_N \rightarrow \pi^*_{C=C}$ donation is modest, the analogous $n_N \rightarrow \pi^*_{C=O}$ interaction (i.e., the amide resonance) is much stronger. The donor ability of nitrogen greatly deactivates the carbonyl moiety towards nucleophilic attack. In return, the acceptor ability of the carbonyl neutralizes basic properties of the nitrogen atoms. As a result, amides are distinctly different from vinyl amines in terms of reactivity.

Nevertheless, the situation can be changed when the latent chameleonic properties of the amino group are activated by torsion that misaligns the nitrogen lone pair and the carbonyl (Figure 21). For example, deactivation of the amide resonance in highly strained lactams leads to dramatic increase in the rate of solvolysis.^[24] Interestingly, such torsion has also been implicated in catalysis by polypeptide lyase, making it plausible that nature has been taking advantage of stereoelectronic chameleons for a long time.^[25]

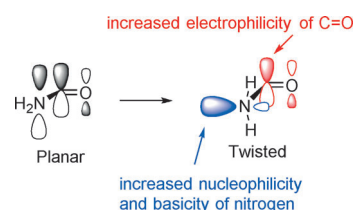


Figure 21. Disruption of amide resonance changes the reactivity of amides.

The inhibition of the amide $n \rightarrow \pi^*$ resonance has played an important role in the history of science.^[26] For a number of years after the discovery of the antibiotic activity of penicillin, the structure of this celebrated molecule lacked elucidation (Figure 22). An important part of the challenge was the discrepancy between spectroscopic hints and observed reactivity. Robinson pointed out that penicillin displayed an unusually high reactivity in hydrolysis reactions and, thus, it could not have been an amide because amides are generally stable to hydrolysis. Woodward suggested that the paradox could be re-

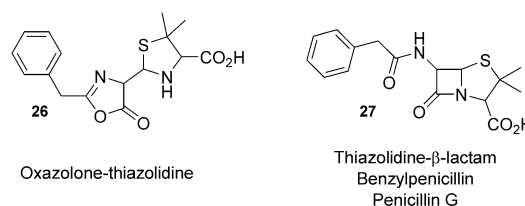


Figure 22. The two possible penicillin structures discussed in 1944.

solved by including the amide moiety in a four-membered cycle in which the cyclic constraints twist the lone pair out of conjugation with the carbonyl. Hence, the classic β -lactam structure **27** of the important antibiotic was born of stereo-electronic rationale. Deactivation of nitrogen donor ability leads to a marked increase in the electrophilicity of penicillin in comparison to a normal amide and explains the discrepancy with classic amide reactivity. The inefficiency of amide resonance in β -lactams has another historic consequence: their spring-loaded reactivity associated with the release of angle and electronic strain enabled the key step in the Holton's synthesis of Taxol **30** (Figure 23).^[27]

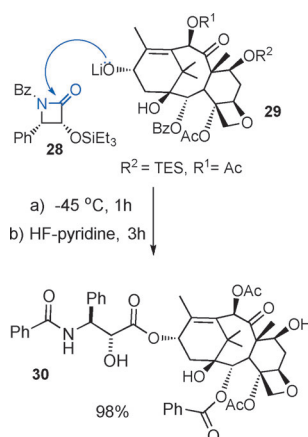


Figure 23. Holton's synthesis of Taxol was assisted by the weakened amide resonance in β -lactams (Bz = benzoyl, TES = triethylsilyl, Ac = acetyl).

Despite the above examples, the full deactivation of amide resonance is difficult to achieve—even sterically hindered amides still often have the ground-state structures that are geometrically analogous to “normal” amides **31**. However, exceptional reactivity can still be observed for such molecules.^[28] In particular, the barriers to N–C(O) rotation decreases as the nitrogen center in **33** becomes more crowded because steric decompression partially compensates for the loss of $n \rightarrow \pi^*$ resonance. Because the $\pi_{C=O}$ is aligned with a sigma acceptor (σ^*_{C-N}) instead of a lone pair, the carbonyl π -system provides better stabilization of the partial negative charge at the α -carbon accumulated in the TS. “Steric decompression” and charge neutralization lead to the elimination of amine and formation of the highly reactive ketene intermediate **36**, shifting the reaction from the common formation of a tetrahedral intermediate towards an alternative mechanism (Figure 24).

The “umpolung” of dominant stereoelectronic interactions between amine and carbonyl imposed by the sterically demanding substituents leads to experimental observations that differ dramatically from the usual trends observed in acyl substitutions. Usually, thioesters can serve as acylating agents for amines. However, the unusual amides **37** in Figure 25 display reactivity that is biased in the opposite direction. In these systems, PhSH readily displaces the amine in a nearly quantitative non-catalyzed reaction at room temperature. The reactivity of

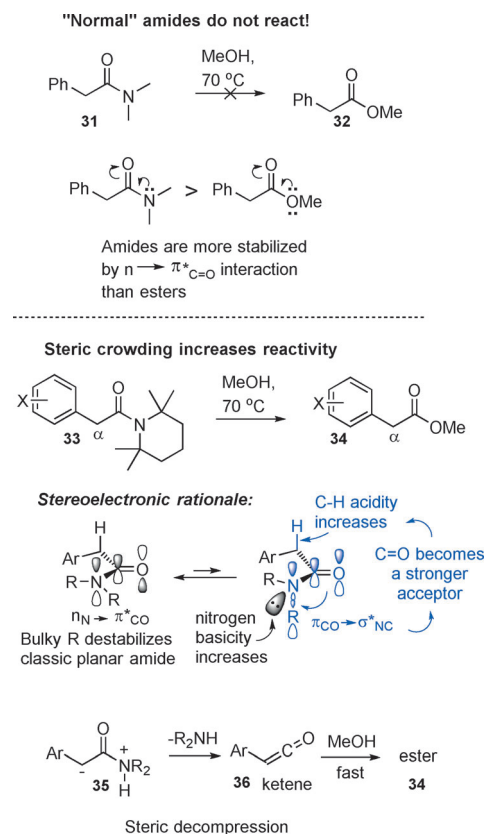


Figure 24. Effect of “steric decompression” on the reactivity of sterically hindered amides.

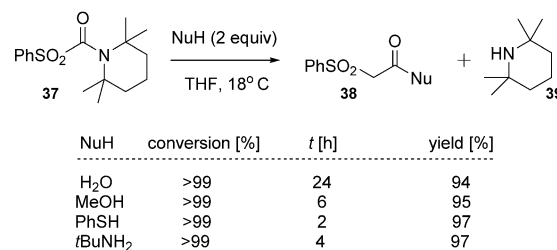


Figure 25. Sterically crowded amides are highly reactive.

such amides was suggested to resemble the reactivity of acyl chlorides.^[28]

In the presence of structural modifications that disrupt this resonance, the reactivity of amides toward Lewis acids drastically changes as well.^[24c] When the nitrogen lone pair is forced out of alignment with the carbonyl π -system of **40** (Figure 26),

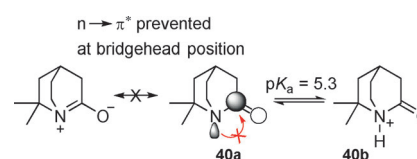


Figure 26. “Anti-Bredt’s” amides: nitrogen atoms at the bridgehead of bicyclic compounds cannot participate in negative conjugation, which is characteristic of amides.

the decreased basicity at the nitrogen, the hallmark property of amides, is not observed. The twisted amides attracted much experimental and theoretical attention recently due to their unprecedented structural and reactivity features.^[29]

Free of the deactivating effect of amide resonance, the N atoms of twisted amides **41** can react with C-electrophiles under mild conditions (Figure 27). This reaction leads to highly reactive amidinium ions **41**⁺, which undergo selective ring opening at the σ_{C-N} bond that is best aligned with the carbonyl π -system.^[30] Regioselectivity of reactions of twisted amides with electron deficient species is also different. For example, protonation on oxygen rather than on nitrogen is favored by 10–15 kcal mol^{−1} for unstrained amides and lactams but protonation on nitrogen is favored by about 20 kcal mol^{−1} for strained bridgehead bicyclic lactams (e.g., “2-quinuclidone”^[24b] and 1-azaadamantan-2-one^{[31], [32]}

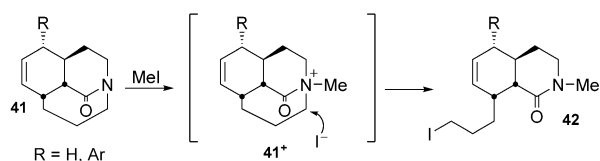


Figure 27. Quaternization of nitrogen in twisted amides can lead to selective C–N cleavage under mild conditions.

The carbonyl group of the twisted *anti*-Bredt amides is similar in reactivity to ketones. Such amides display enhanced sensitivity to hydrolysis and possess a number of interesting chemical peccadillos. For example, 1-aza-2-adamantanone **43** forms stable tetrahedral intermediates (Figure 28).^[31] Kirby and co-workers reported that this compound combines amine reactivity (it can be rapidly protonated to give **45**) with ketone reactivity (it undergoes Wittig olefination to give **44**).^[33] Structural parameters of twisted amides are close to those calculated for the TS of amide *cis*–*trans* isomerization.^[34] It was suggested that such twisted amides can serve as models for the understanding of structural and electronic effects that operate in the pre-organized binding site of rotamases, enzymes that play important roles in protein folding and signal transduction in immune cells.

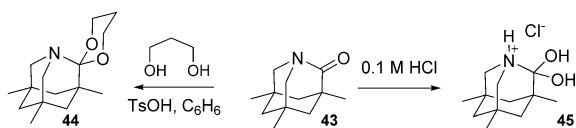


Figure 28. 1-Aza-2-adamantanone can be converted into stable tetrahedral intermediates (Ts = toluenesulfonyl).

The carbonyl group of amide **46** can be converted into amino carbene **48**^[35] (Figure 29a) or reduced under Wolff–Kishner conditions (Figure 29b).^[36] Reduction of such lactams with NaBH₄ (unreactive towards planar amides) proceeds without complications and can lead to stable hemiaminals **50** (Fig-

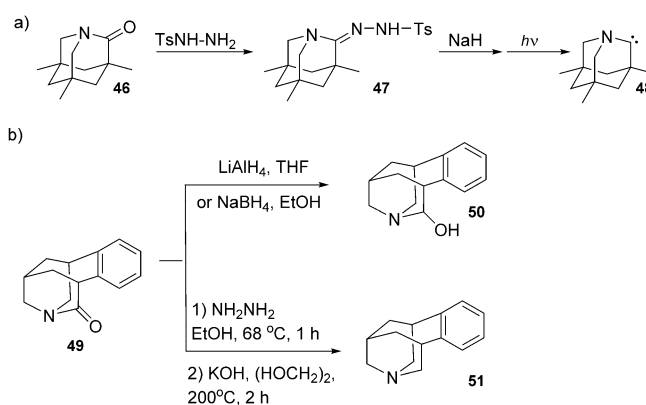


Figure 29. Reactivity of twisted amides in reductive reactions with hydrazines and hydride donors.

ure 29b).^[36] Aube and co-workers have illustrated that a variety of classic carbonyl reactions, such as addition of organometallic reagents, Petasis olefination,^[37] and Corey–Chaykovsky epoxidation^[38] are possible. Synthesis of twisted amides is challenging and requires creative approaches that can overcome the intrinsic instability of this functionality.^[39] For example, Tani and Stoltz succeeded in synthesizing 2-quinuclidone **53**, an elusive twisted amide, by using an intramolecular Schmidt ring expansion, in which dinitrogen (N₂) release served as a driving force. Remarkably for an amide, this molecule was isolated as tetrafluoroborate salt **53**, another indication of amine-like reactivity (Figure 30).^[24b]

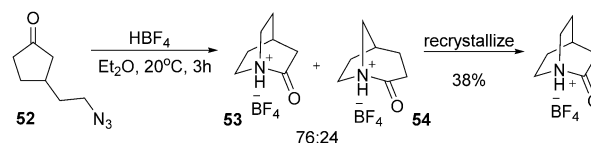


Figure 30. Synthesis of 2-quinuclidonium tetrafluoroborate by Tani and Stoltz.

The unique electronic structure of twisted amide **55** (Figure 31) leads to an extremely fast amide bond hydrolysis under mild conditions.^[40] Szostak and co-workers suggested that the amide bond activation by disrupting amide bond resonance can be applied as a general approach for involving this unreactive functionality in transition-metal-catalyzed reactions. The ability of a low-valent metal catalyst to insert into the inert amide N–C bond under mild conditions is compromised by

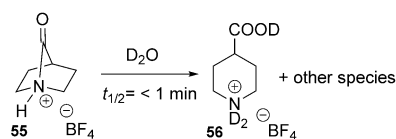


Figure 31. Enhanced reactivity of a bicyclic strained amide towards hydrolysis.

the loss of amide resonance with the concomitant energy penalty of about 15–20 kcal mol⁻¹. It was suggested that the non-planarity in such compounds can be complemented by the introduction of multiple carbonyl groups (such as changing from amides to imides) and, thus, decreasing the importance of amine conjugation with each of the individual C=O groups (Figure 32). By using this approach, it became possible to involve the N–C(O) bonds in transition-metal catalyzed C–H bond activation^[41] and cross-coupling reactions.^[42] Depending on the choice of catalyst, amides can react as either acyl or aryl donors.

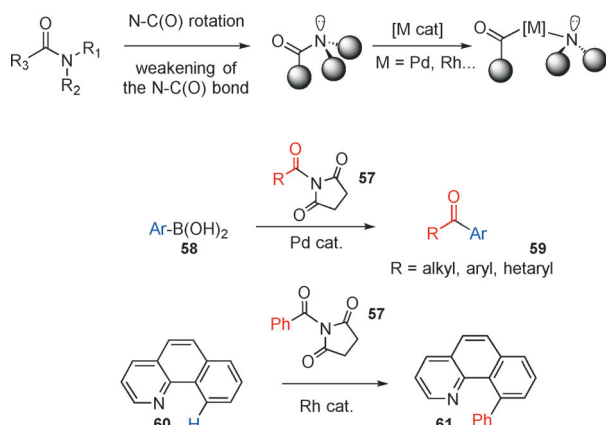


Figure 32. Transition-metal catalyzed C–H bond activation and cross-coupling reactions of imides.

Another illustrative example of reactivity change through deactivation of amide conjugation can be found in the chemistry of tertiary enamides.^[43] Unlike typical amides, the steric demands of the group adjacent to the carbonyl leads to the distortion of the carbonyl surroundings. This allows the nitrogen lone pair of **62** to display enamine-like reactivity and increase nucleophilicity at the β -carbon atom of the C=C double bond (Figure 33).

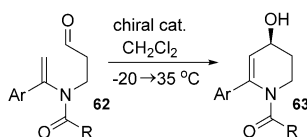


Figure 33. Effect of lowered conjugation on tertiary enamide reactivity.

The other way to diminish $n_N \rightarrow \pi^*_{C=O}$ conjugation is to increase the s-character of the n_N orbital. The change in hybridization decreases the donor properties of the lone pair and changes its orientation in space. An interesting example of such an approach is provided by aziridine amides. Yudin and co-workers exploited the high reactivity of such amides for the site-selective ring opening of cyclic peptides **64** (Figure 34).^[44]

The above examples concentrated on reactivity and stability features. However, the importance of stereoelectronic effects

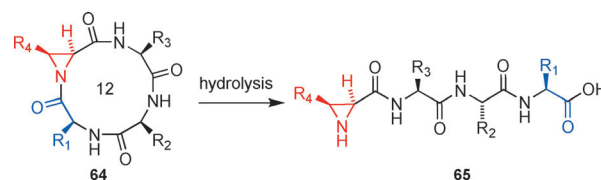


Figure 34. Site-selective ring opening using the unique amide reactivity of aziridine.

permeates the fabric of chemistry, manifesting itself in other fields as well. For example, the hidden “chameleonicity” of amines is used for an excited state design. Photophysical phenomena often provide a clear way to visualize electronic phenomena because photochemical excitation can amplify subtle differences and report potential energy variations by emission of photons of different energies. An illustrative example of this is provided by the properties of twisted (or twistable) *N,N*-dialkylamino aromatic chromophores. Aromatic amines with acceptor groups at the *para*-positions can display dual fluorescence emissions. In addition to the “normal” short-wavelength emission at about 330 nm, an anomalous emission can be observed at longer wavelengths (420–460 nm) in polar solvents. This emission is attributed to the formation of a twisted intramolecular charge transfer (TICT) state, in which a charge separation occurs in an orthogonal rotamer with respect to a C–N linkage between the acceptor (the aromatic system) and the donor (dimethylamino group) in the excited state (Figure 35).^[45] Compounds in which the nitrogen is constrained to alignment with the aromatic system, emit only short-wavelength fluorescence. In contrast, a twisted model compound displays only the anomalous longer wavelength emission.

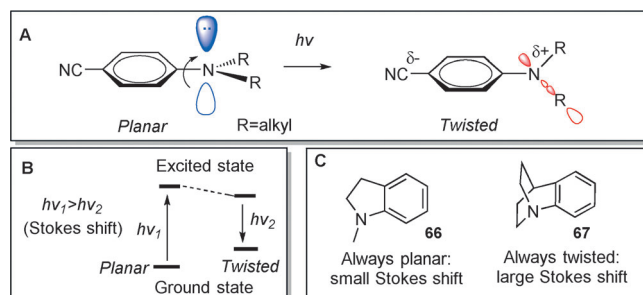


Figure 35. A) Photochemical excitation can promote chameleonic behavior of aromatic amines. B) Perturbation of the chameleonic energy differences by photochemical excitation. C) Model compounds in which chameleonic behavior is restricted by conformational constraints.

The TICT phenomenon is responsible for the useful properties of many fluorescent molecular rotors that are sensitive to their environment.^[46] When the balance between the two chameleonic states is perturbed by excitation, the energy difference between the two structures is different in the ground and excited states. This effect is important from a practical point of view because such differences lead to large Stokes shifts in the emission spectra and minimize the problems with

self-absorption in the design of fluorescent solid state materials. Remarkably, even relatively simple twistable amines can achieve Stokes shifts that are comparable to those in much more complex and carefully engineered systems.

2.4 Imines and nitroso compounds as chameleons

The nitroso group belongs to the strong electron-withdrawing substituents (Hammett's *sigma-para* constant = 0.91; compare to $\text{NO}_2 = 0.78$). Furthermore, the dipole moment of Ph-N=O (3.14 D) is comparable to the dipole moment of PhNO_2 (3.97 D). However, the nitroso group is an *ortho/para*-directing substituent.^[47,48] A nitroso group can only donate electron density to the phenyl ring efficiently in the orthogonal conformation when the n_{N} lone pair, rather than the N=O bond, is aligned with the aromatic π -system. Thus, it is possible that the nitroso group may behave, under the right circumstances, as a conformational chameleon, like the OMe group.

The imine group possesses a combination of an acceptor π -bond and a lone pair that is similar to the nitroso group. It also displays an interesting directional dichotomy; whereas Hammett's *sigma-para* constant for the $-\text{CH=N-Ph}$ fragment of Ph-CH=N-Ph is 0.42, the value for the $-\text{N=CH-Ph}$ part is -0.55 . This means the imino group possesses the ability to donate electron density to the phenyl ring only when it is connected to the π -system through nitrogen. Again, such donation should be more efficient in the orthogonal conformation when the lone pair of nitrogen is aligned with the aromatic system.

2.5 Carbenes: carbon-centered chameleons

Chameleonic behavior at carbon is harder to detect because stable functionalities do not generally bear a lone pair at carbon (with a few notable exceptions like CO and isonitriles). Furthermore, when such a lone pair is present, it comes with a negative charge (i.e., in carbanions), so the donor properties of carbon are dominant. Still, the chameleonic properties of carbon come into play in the neutral reactive intermediates, such as radicals, ylides, and carbenes (Figure 36). Alkynes also have chameleonic potential that stems from the presence of orthogonal π -systems.^[49]

Selected carbon-centered functionalities with donor and acceptor orbitals at a carbon:

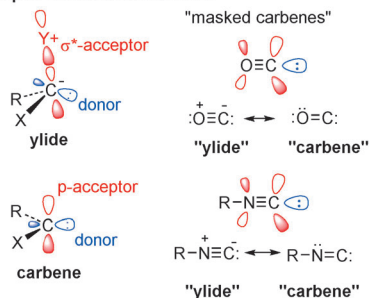


Figure 36. Selected carbon functionalities and molecules with pronounced chameleonic character.

To provide a connection with the earlier discussion, it is instructive to compare carbenes with ethers (Figure 37). As was illustrated in Figure 15, the presence of two lone pairs at oxygen makes it difficult to switch off oxygen donor properties in ethers. Even though ethers and carbenes have essentially

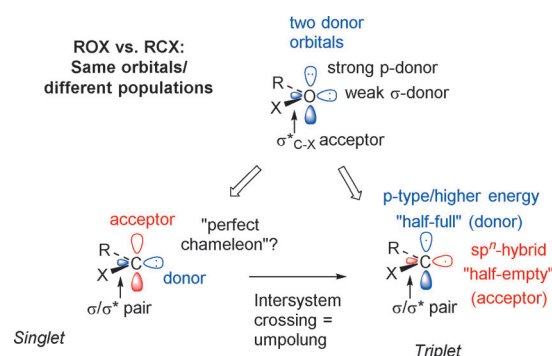


Figure 37. Singlet carbenes are perfect chameleons with mutually orthogonal non-bonding orbitals of opposite donor/acceptor properties. The half-filled non-bonding orbitals in the triplet carbene have different electronic properties as well, but the difference is smaller. Note that donor and acceptor orbitals of singlet and triplet carbenes have opposite spatial arrangements.

identical MOs, it is easier to make chameleons from carbenes due to the difference in electron count for the two functionalities. The HOMO of ethers corresponds to the LUMO of singlet carbenes. As the result, singlet carbenes are perfect chameleons, even without the involvement of σ^* -orbitals, because they possess mutually orthogonal non-bonding orbitals of drastically different properties; the in-plane orbital is populated with two electrons whereas the out-of-plane orbital is empty. This electronic duality means that carbenes, like Dr. Jekyll and Mr. Hyde, can change their nature and serve as either electrophiles or nucleophiles, depending on the reaction partners and stereochemistry of interactions. Recently, Moss and co-workers analyzed in detail changes in carbenic electrophilicity and nucleophilicity as a function of substituents in "iconic" carbenes.^[50] The reactivity of the carbenic carbon as well as the adjacent positions could be varied widely and controlled by the proper choice of the substituents.

The purely conformational aspects of carbene reactivity remain scarcely studied. However, it is obvious that unlocking chameleonic behavior of carbenes can result in interesting behavior. For example, conformational changes in carbenes can control their spin states. McMahon, Bally, and co-workers found such a switch between the singlet and the triplet states in 2-naphthyl(carbomethoxy)carbene. In the triplet state, the acceptor π -system of the ester group is aligned with the p-type radical center (the σ -radical in a hybrid orbital is lower in energy, and, thus, is a relatively poor donor). In the singlet state, the relative ability of σ - and p-type non-bonding orbitals switches because the p-orbital is now empty, so the carbonyl group reorients itself to overlap better with the σ -donor (Figure 38).^[51] The singlet state of other carbonyl carbenes is also non-planar,^[52,53] so such conformational switching is likely

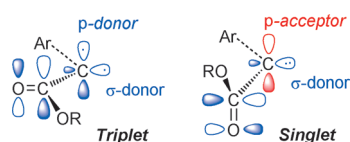


Figure 38. Spin-state chameleons. Left: in the triplet 2-naphthyl(carbomethoxy)carbene, the carboxyl π -system is aligned with a better donor, the p-type radical center. Right: in the singlet carbene, the p-orbital is empty and the carbonyl π -system aligns with the σ -lone pair.

to be general. Although chameleonic properties of carbene functionality in intramolecular settings are underexplored, we will show in Section 3 of this review that the donor/acceptor duality of carbenes plays a key role in their intermolecular reactivity and in the applications of carbenes as ligands for stabilization and electronic fine-tuning of unusual main group and organometallic species.

3. Chameleons by Translocation

An interesting stereoelectronic feature of a number of substituents is a switch from donor to acceptor character observed upon moving the substituents one extra bond away (i.e., translocation) from the same reference functionality.

3.1 Contrasts between α - and β -substituent effects in cations

The same functional group can impose very different effects at the α - and β -positions relative to a cationic center. Substituent effects on the stability of a carbocation can be estimated from the isodesmic reactions in Figure 39 (performed at HF/6-31G** level).^[54] Substituent effects on stability are complex and involve a number of factors including electrostatic effects.⁵⁵ However, these stabilization energies have a clearly manifested stereoelectronic component as illustrated by differences in stabilization energies imposed by substituents in the eclipsed and perpendicular conformations.

The stereoelectronic considerations readily explain the chameleonic behavior of substituents that can switch from being a donor to being an acceptor depending on their position and orientation relative to the cationic center. For example, an α -F substituent stabilizes the cationic center by approximately 15 kcal mol⁻¹ (HF/6-31G**), whereas β -F in the eclipsed geometry exerts a destabilizing effect of 29.2 kcal mol⁻¹ (HF/6-31G** level). In the first case, the fluorine lone pair is aligned with the vicinal cationic p-orbital and behaves as a p-donor. In the second case, the empty p-orbital at the cationic center is aligned with the vicinal C–F bond and fluorine behaves as a σ -acceptor.

The donor ability of fluorine lone pairs presents itself in many situations but is still underappreciated. For example, fluorine is a *para*-activating group in electrophilic aromatic substitution (EAS), which is opposite to what is found in many undergraduate textbooks! The following quote from Rosenthal and Schuster describes the situation well: “Most striking, however, is the fact that reactions at the *para*-position of PhF are

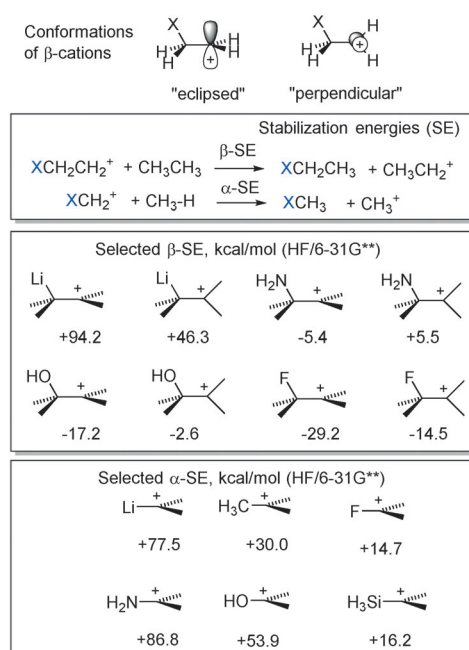


Figure 39. Stereoelectronic aspects of substituent stabilization in β -substituted ethyl cations and selected α -substituent effects in methyl cations.^[54] For clarity, H-atoms at the end of C–H bonds in the substituted ethyl and methyl cations are not shown.

typically faster than the corresponding reactions at a single position of benzene. Furthermore, EAS on PhF results in 90% of the *para*-substituted product, while the other halobenzenes give ratios of *ortho*- and *para*-substituted products that are closer to the simple statistical distribution. These striking observations are not discussed or, for that matter, even reported in introductory or advanced textbooks of organic chemistry and are clearly not compatible with the typically superficial textbook discussions of this subject.”^[56]

Another example that illustrates the value of stereoelectronic thinking is the straightforward rationalization of the differences in α -stabilizing effects of NH₂ and Li substituents on cation stability. The relative stabilizing power of these two substituents [NH₂ (87 kcal mol⁻¹) > Li (78 kcal mol⁻¹)] (HF/6-31G**) is opposite to that expected from the much greater electronegativity of nitrogen. However, it is fully consistent with the stabilization provided by the nitrogen lone pair (something that Li lacks) of the cationic center by direct orbital overlap with the cationic p-orbital (Figure 39).

Laub and Mayr elegantly demonstrated the interplay of such effects with the stereoelectronic stabilization of transition states by comparing rates of reactions of electrophiles with vinyl and allyl silanes.^[57] The two reactions form analogously stabilized β -silyl substituted carbenium ions. However, the hyperconjugative β -silyl stabilization is only effective in the transition state for the addition to allyl silanes. In vinyl silanes, the C–Si remains orthogonal to the σ -bond and the developing cationic center at the early reaction stages with electrophiles (Figure 40).

Interestingly, different placements of Si-groups lead to large differences in the nucleophilicity of alkenes. The allylic tri-

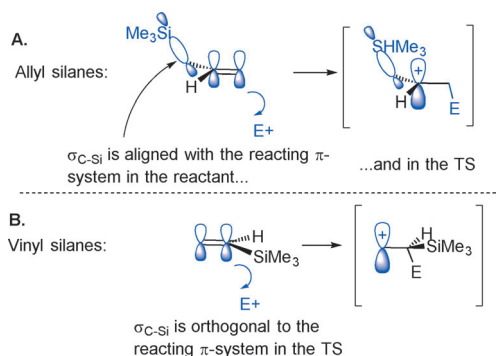


Figure 40. Stereoelectronic effects on TS stabilization in reactions of electrophiles with A) allylsilanes and B) vinylsilanes.

thylsilyl (TMS) group of **68** is activating such that it increases reactivity about 1000-fold in comparison to a hydrogen or a Me group. In contrast, the β -vinyl TMS group of **69** accelerates electrophilic attack by a factor of 10 in comparison to hydrogen but slows the reaction 100-fold in comparison to Me. Furthermore, at the α -vinyl position of **70**, the TMS substitution slows the reaction relative to both H and Me (Figure 41).

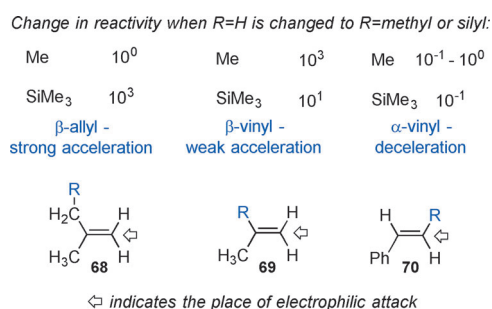


Figure 41. Nucleophilicity changes as a function of alkene substituents.

Radicals are chameleons of their own, non-stereoelectronic kind. The odd-electron orbital is half-filled and half-empty at the same time. Not surprisingly, radical reactivity can change widely depending on the substitution, ranging from highly nucleophilic to highly electrophilic.^[58] The response of radicals to the presence of an α -F or an α -CF₃ group can be evaluated from the C–H bond dissociation energies (BDEs) in respective substituted methanes (Figure 42). The effects are very different; whereas an α -F atom in **71** or **74** decreases the C–H BDE, an α -CF₃ group of **73** or **76** has the opposite effect. It is also instructive to compare how these substituent effects respond to the introduction of additional methyl groups at the carbon atom of the breaking C–H bond. The α -F effect in **77** is greatly diminished (ca. 24-fold) by these additional donor substituents, but the α -CF₃ effect in **79** changes only slightly (1.4-fold).

The difference in the effects of α - and β -substituents is not limited to the short-lived reactive intermediates. An example of functional group transposition for the control of reactivity is provided by the unusual properties of a family of bis-peroxides that are remarkably stable and can melt without decomposition at temperatures as high as 142 °C.^[59] An increase in stabi-

ΔH_{298K} [kcal mol ⁻¹]		ΔH_{298K} [kcal mol ⁻¹]	
F-CH ₂ - \dot{C} H	101.0	F-CH(CH ₃)- \dot{C} H	99.3
71	↑ -3.0	74	↑ -1.5
H-CH ₂ - \dot{C} H	104.0	H-CH(CH ₃)- \dot{C} H	100.8
72	↓ +1.9	75	↓ +1.4
F ₃ C-CH ₂ - \dot{C} H	105.9	F ₃ C-CH(CH ₃)- \dot{C} H	102.2
73		76	
		ΔH_{298K} [kcal mol ⁻¹]	
F-C(CH ₃) ₂ - \dot{C} H	98.4	F-C(CH ₃) ₂ - \dot{C} H	98.4
77	↑ -0.1	77	↑ -0.1
H-C(CH ₃) ₂ - \dot{C} H	98.5	H-C(CH ₃) ₂ - \dot{C} H	98.5
78	↓ +1.4	78	↓ +1.4
F ₃ C-C(CH ₃) ₂ - \dot{C} H	99.9	F ₃ C-C(CH ₃) ₂ - \dot{C} H	99.9
79		79	

Figure 42. Contrasting effects of α - and β -fluorine substitution at the homolytic C–H bond dissociation energies (BDEs), at the G3(MP2)-RAD level of theory in kcal mol⁻¹.

ty is observed when an α -oxygen substituent of **80** is moved from a central oxygen atom to a β -position in **81** (i.e., a peroxide is changed into an acetal) or when a β -oxygen atom is introduced relative to one or both oxygens of the peroxide moiety. This allows the lone pairs of the peroxide oxygen (or both oxygens in the cyclic structure **82** shown in Figure 43) to participate in the anomeric $n_O \rightarrow \sigma^*_{C-O}$ interaction.^[60] Similarly, the strong p-donating properties of an α -F substituent stabilize epoxides **83** and dioxiranes **87**.^[61] Indeed, difluorodioxirane is stable at 22 °C for more than 12 h.^[62] In contrast, an α -CF₃ group has a destabilizing effect on the same two functionalities (Figure 44).

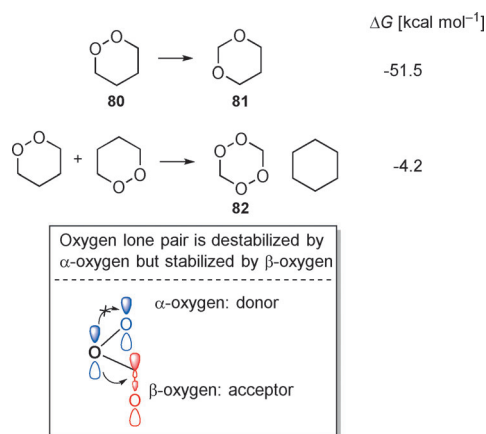


Figure 43. Contrasting stabilities of peroxides and acetals are accentuated by the opposite effects of α - and β -oxygen substituents. Calculations performed at the M06-2X/6-311 + G^{*}(d,p) level of theory.^[60]

3.2 Carbonyl as a chameleon: Ketenes versus ketones/aldehydes

Chemical chameleons often come from “orthogonal” functional groups, that is, functionalities with two sets of orbitals con-

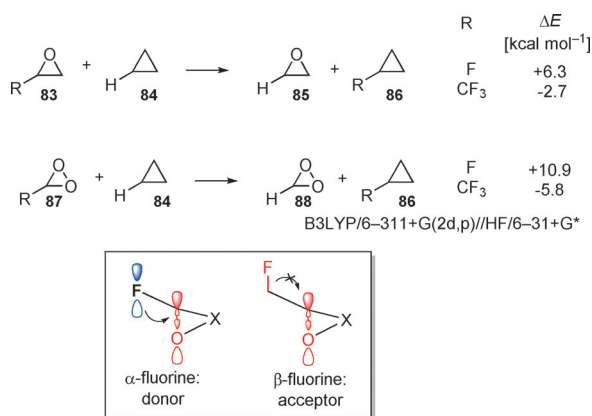


Figure 44. The opposite effects of α -F and α -CF₃ groups on the stability of oxiranes and dioxiranes.

strained to orthogonality. The carbonyl family is one such chameleon. The carbonyl group is commonly considered an acceptor but its oxygen lone pair can also act as a donor towards groups positioned directly at the carbonyl carbon. For example, acylium cations are quite stable and find numerous applications in synthesis due to the stabilizing interaction between the oxygen lone pair and the cationic center. To illustrate the contrasting effects of the carbonyl group at different positions, let us switch from the reactivity to spectroscopy and show how chameleonic properties of this functionality are reflected in the NMR spectroscopy of carbonyl compounds.

Geminal NMR coupling constants: Spin–spin interactions between magnetic nuclei in the NMR spectra are broadly used in structure determination and conformational analysis. Although NMR reports on the spins of nuclei, the nuclear spin–spin interactions are mediated by bonding electrons. As stated by Pople and co-workers, “the existence of ... coupling constants, therefore, is an indication of intrinsic delocalization of the bonding orbitals.”^[63] In particular, the two-bond (geminal) H–H couplings can adopt a remarkably large range from about +42 to –25 Hz as a function of a complicated interplay of effects that modify both the magnitude and sign of the coupling constant. The electronic effects of substituents can be approximated by the perturbation molecular orbital (PMO) analysis of Pople and Bothner-By.^[64] In a simplified form, the spin constant [Eq. (1)] is proportional to $\pi_{h,h'}$, which is the “mutual polarizability coefficient” for the hydrogen 1s orbitals h and h' .^[65]

$$J_{HH'} \propto \pi_{h,h'} = -4 \sum_i^{\text{occ}} \sum_j^{\text{unocc}} (\epsilon_j - \epsilon_i)^{-1} c_{ih} c_{jh'} c_{jh} c_{ih'} \quad (1)$$

This analysis concentrates on the interaction between filled and empty CH₂ group orbitals, giving the largest role to the HOMO–LUMO ($\psi_2 \rightarrow \psi_3$) transition (transition with the largest $1/\Delta E$ term). Symmetry restrictions dictate π -donors and acceptors to have the largest effects on ψ_2 and ψ_4 of a methylene group, with the major effect on coupling constants being the change in energy of ψ_2 . Donors (lone pairs or electron rich π -bonds) will raise the energy of ψ_2 , decreasing the HOMO–

LUMO gap and increasing the $1/\Delta E$ term, giving an increased (+) contribution to the coupling constant. Acceptors have the opposite effect, lowering the energy of ψ_2 , increasing the HOMO–LUMO gap and decreasing the $1/\Delta E$ term, having a negative effect on the coupling constant, Figure 45.

The effects of π -donors and acceptors on the $^2J_{HH}$ are compared in Figure 46. Relative to ethylene, $^2J_{HH}$ values for 1,1-difluoroethylene and ketene are more negative, whereas the donor α -lone pairs of the directly connected carbonyl (i.e., formaldehyde) give positive values. The same substituent, a C=O group, has the opposite effect at the two positions relative to the “reporter” nuclei.

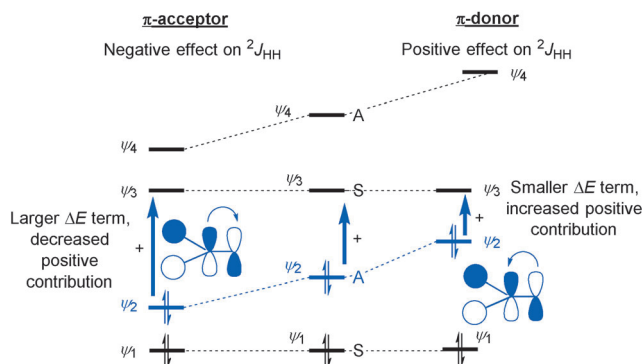


Figure 45. Effect of π -donors (right) and π -acceptors (left) on the relative energies of methylene MOs and effects on $^2J_{HH}$.

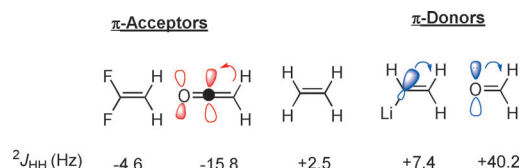


Figure 46. Effects of π -donors and acceptors on $^2J_{HH}$ in which acceptors have a negative contribution and donors have a positive contribution.

4. Utility of Chameleons: Versatile Partners for Unusual Reactive Species

4.1 Interaction of chameleonic functionalities

The two orbital arrays of opposite polarity present in chameleonic functionalities discussed in the earlier parts of this manuscript are well suited for stabilizing other bipolar species. For example, substituents that combine a p - (or π -) donor with σ -acceptor character can strongly stabilize carbenes by providing a suitable delocalization partner for both the donor and the acceptor orbitals of the carbene moiety (Figure 47A). Similarly, the chameleonic nature of carbenes is useful for stabilization of exotic reactive species derived from both main group elements and transition metals. There is strong evidence that even such seemingly “unidirectional” ligands as phosphines display a combination of donor and acceptor properties in their interactions with metals. In addition to the classic σ -dona-

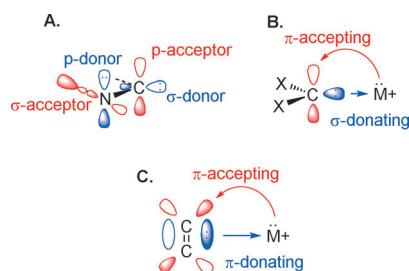


Figure 47. A) Chameleonic amine functionality is a perfect stabilizing substituent for a carbene because it can engage in the two complementary sets of donor–acceptor interactions, both of the σ - and the π -type. B) The donor/acceptor duality of carbenes leads to two stabilizing ways for its interaction with a metal center through the two sets of orbitals. C) Unlike carbenes, the donor and acceptor orbitals are not clearly separated in space for an alkene.

tion from the lone pair of P to the metal, these ligands also engage in back-bonding using the σ^*_{P-C} orbitals.^[66]

However, the duality of donor and acceptor properties is particularly well-displayed for complexes of metals with carbenes. It is interesting to compare carbene binding with the Dewar–Chatt–Duncanson (DCD) model for alkene/metal complexes (Figure 47B and C). The DCD model also considers each of the two partners, the alkene and the metal, to be donors and acceptors in the pair of complementary interactions ($\pi \rightarrow$ metal and metal $\rightarrow \pi^*$). Note that both donor and acceptor orbitals of the ligand (alkene) are in the same plane. The distinct difference and a potential advantage for carbenes is that the donor and acceptor orbitals are orthogonal to each other and, thus, can be controlled with a greater degree of independence.

Not surprisingly, common metal ligands such as carbon monoxide that are well-known to have similar duality of σ -bonding and π -backbonding interactions of different polarity can be, from the electronic point of view, considered as “over-stabilized” carbenes. “Recoloring” of chameleonic carbene ligands accomplished by variations in the nature of substituents allows for fine tuning and optimization of their interaction with a variety of metals in a number of oxidation states. In complexes with electron-poor transition metals with π -acceptor ligands (Fischer carbenes), carbenes display electrophilic properties and often behave similarly to a carbonyl compound (Figure 48, top). Such carbenes also often have p-donor substituents, such as -OR or -NR₂, on the carbenic carbon to moderate electron deficiency and provide stabilization. In contrast, carbene complexes with electron-rich transition metals (Schrock carbenes) are nucleophilic.^[67] The electron-withdrawing property of the metal in the Schrock carbenes is moderated by donor ligands (Figure 48, bottom). The strongly electrophilic Fischer-type carbene complexes are readily attacked by nucleophiles,^[68] whereas Schrock-type carbenes show Wittig’s ylide-type reactivity.^[69]

Computational analysis has revealed the interplay between the donor/acceptor duality of carbenes and the variable electronic nature of the metal.^[70,71] The reactivity at the carbenic carbon is controlled by an interplay of σ -donation by the carbene lone pair and π -backdonation from the metal d-orbital of

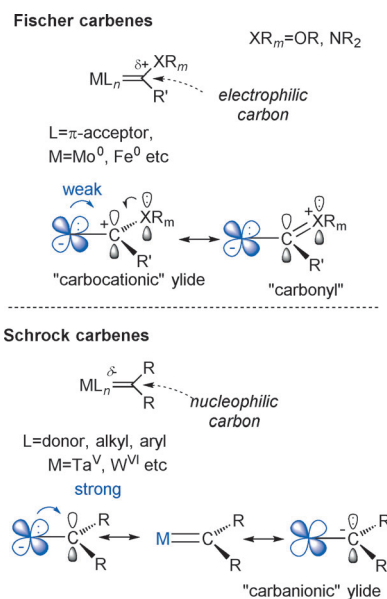


Figure 48. Revealing the chameleonic nature of a carbene moiety with substitution.

a suitable symmetry to the empty carbene p-orbital. In Fischer carbenes, the back donation is weak, giving the complex ylidic character with significant cationic nature of the carbenic carbon. Additional p-donor groups at carbon ($R = OR'$, NR'_2) are needed to stabilize such species. In Schrock carbenes, the π -backdonation is stronger leading to the double bond character of the carbene–metal moiety. Because both of the two bonds are polarized towards carbon, carbon is nucleophilic. Note that ylidic resonance structures are important for the description of the two carbenes but the polarity of the two ylidic structures is opposite.

Amplification of carbene acceptor ability by a suitable acceptor metal in Fischer carbenes can render them “super acceptor” π -ligands that, for example, can increase the Diels–Alder reactivity of alkenes **89** about 10000-fold in comparison to the carbonyl group of acrylates (Figure 49).^[72]

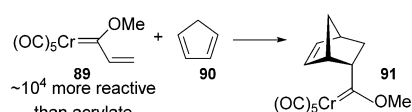


Figure 49. Fischer carbenes as super acceptor π -ligands

Changing the balance between donating and accepting properties of carbenes opens new opportunities in ligand and catalyst design. N-heterocyclic carbenes (NHCs) are known to stabilize cationic metal centers mostly through their strong σ -donation. On the other hand, cyclic alkyl(amino) carbenes (cAACs) were found to be much more effective in stabilizing electron rich species.^[73,74] In cAACs, replacement of one of the π -donating nitrogen atoms of NHC by a quaternary carbon atom leads to a lower lying LUMO. This change renders the π -

backdonation from the atom bound to the carbene carbon of cAAC energetically more favorable. It has been shown that the strong σ -donating and efficient π -accepting cyclic alkyl(amino) carbenes can be utilized as excellent ligands for the stabilization of transition metals in lower oxidation states with lower coordination numbers (**93**, Figure 50).^[75] In practice, a variety of ambipolar carbenes fill the continuum between the Fischer and Schrock extremes.

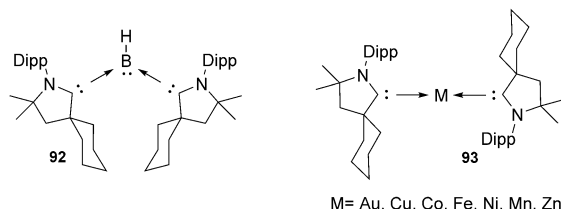


Figure 50. Unusual coordinatively unsaturated species stabilized by carbene ligands. Donation from the carbene lone pair forms dative bonds shown with arrows. At the same time, the lone pair at boron is delocalized in the empty carbene orbitals.

Thus, the π -acceptor ability of the carbenic carbon atom is defined by the substituent and increases in the following way: $N-C-N > N-C-C > \text{Fischer} > \text{Schrock}$. The most pronounced effect on the π -acceptor ability of a singlet carbenic carbon atom is found in a neutral trifluoromethyl group and a positively charged trimethylammonium substituent.^[76] In contrast, a negatively charged trimethylboron group stabilizes the triplet state. In general, according to their reaction ability, the singlet carbenes could be divided into three classes: (i) electrophilic, (ii) ambiphilic, and (iii) nucleophilic. All of these properties are controlled by the acceptor or donor nature of the substituents attached to the carbene carbon atom.^[77]

4.2 Design of superelectrophilic carbenes

The opposite effect of fluorine substituents ("translational chameleons") at a carbene center defines dramatic differences in the electronic properties of F-substituted vinylidenes and carbenes. Difluorocarbene is a relatively stabilized species and less reactive than many other carbenes;^[78] the electron affinity (EA) of the CF_2 is -0.18 eV (for the F atom itself -3.10 eV). In contrast, difluorovinylidene is extremely unstable and highly electrophilic; its EA is -2.26 eV.^[79] In general, a decrease in electron affinities upon introduction of fluorine atoms is observed in carbenes, whereas the opposite is true for vinylidenes.

The reverse influence of fluorine substitution in vinylidenes compared to carbenes reflects the difference in its relative position with respect to the vacant p-orbital.^[79] An empty p-orbital is an even better acceptor than a carbonyl π^* and its alignment with the C–F bonds is highly unfavorable. Consequently, terminal fluorines lead to even more extreme destabilization in vinylidenes (vinyl carbenes) than in fluoroketenes (Figure 51). Sander and co-workers referred to fluorovinylidenes as super-electrophilic carbenes, pointing out that these extremely reac-

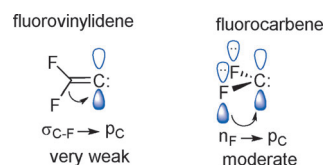


Figure 51. Chameleonic nature of fluorine leads to dramatic differences in the electronic structure of difluoro vinylidene and difluoro carbene.

tive species are markedly different in their reactivity from the stable nucleophilic singlet carbene analogues.^[80] This observation contrasts sharply with the parent CF_2 -carbene, in which F can be considered as a stabilizing group due to the interaction of empty carbon orbitals with lone pairs of fluorines. Fluorine in these two situations can be considered as a stereoelectronic chameleon (n-donor in carbenes and σ -acceptor in vinylidenes).

5. Supramolecular Stereoelectronic Chameleons

5.1 General considerations

The donor/acceptor dichotomy of chameleonic functionalities is also displayed clearly in supramolecular interactions in which the interacting groups are free of intramolecular constraints. Of course, any functionality capable of intramolecular chameleonic behavior can easily be a chameleon in intermolecular interactions. Thus, supramolecular donor/acceptor duality is a continuation of molecular donor/acceptor duality. Such well-known effects are responsible for the stereoelectronic preferences of many organic reactions. For example, reactions of carbonyls with electrophiles and nucleophiles proceed through different trajectories: nucleophilic attack from above the molecular plane (Burgi–Dunitz) and electrophilic attack within the molecular plane. The same is true for nitriles, isonitriles, and related functionalities.

It is less well appreciated that such common groups as ethers, sulfides, amines, phosphines, and even halides can also be considered stereoelectronic chameleons. The chameleonic nature of these groups manifests itself in supramolecular interactions, such as pnictogen, chalcogen, and halogen bonding (Figure 52).^[81] For example, the regions of high electron density correspond to the location of lone pairs that can serve as targets for electrophiles or H-bonding partners. On the other hand, the region of lower electron density at the extension of the σ^*_{Y-X} bond can function as an electron acceptor site capable of coordination with nucleophiles or halogen bond-forming partners.

Typical examples of donor–acceptor attractive supramolecular interactions are " σ -hole" and " π -hole" bonds,^[82] such as halogen bonds (XB) (Figure 53).^[83] Charge-transfer, electrostatic, dispersion, and polarization interactions are used to explain the nature of the halogen bond. In addition to the above, halogens participating in XB maximize their donor–acceptor orbital interactions by behaving as stereoelectronic chameleons.^[84] In Type II halogen bonds, the chameleonic nature of the halo-

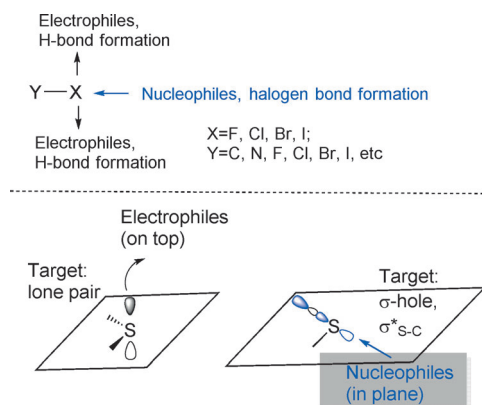


Figure 52. The stereoelectronic difference between hydrogen- and halogen-bond formation at a heteroatom with a lone pair stems from separation of donor and acceptor regions of YX in space.

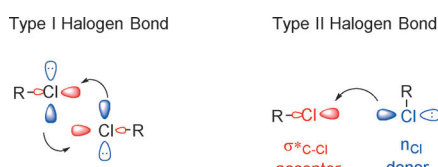


Figure 53. Two types of halogen bonds that take the chameleonic nature of the C–Cl moiety. Donor orbitals/atoms are shown in blue, acceptors are shown in red.

gen group is exhibited in clear form; one molecule behaves as a donor, and the other one as an acceptor. In the Type I halogen bond, both molecules serve as donors and as acceptors at the same time.

The chameleonic properties of carbenes have been creatively used by Sander in a variety of supramolecular approaches to spin-control. For example, both H-bonding^[85] and halogen-bonding^[86] can be used to selectively stabilize the singlet state. In species in which the singlet–triplet gap is sufficiently small (e.g., diphenyl carbene), such selective stabilization can invert the relative stabilities of the two spin states (Figure 54).

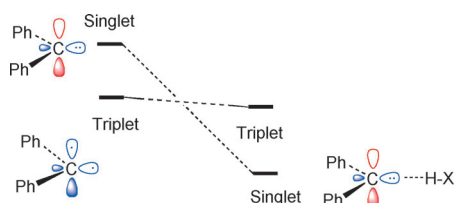


Figure 54. Supramolecular control of the preferred spin state of diphenyl carbene. The singlet state is selectively stabilized by H-bonding.

5.2 From supramolecular interactions to transition states

Chameleonic reactivity in cycloadditions: The supramolecular chameleonic behavior manifests itself in interesting ways in intermolecular reactions in which supramolecular interactions evolve into bond-forming events. In these systems, orbital in-

teractions play an important role in stabilization of developing negative and positive charges. In concerted reactions, charge accumulation needs to be minimized. This is a perfect task for chameleons! We will provide two such examples below.

Carbenes: This discussion will highlight the ability of carbenes to behave as either a nucleophile or an electrophile depending on their orientation relative to the target. When both of these properties are important (i.e., the target has both donor and acceptor properties), a carbene finds the best compromise between the two possible frontier molecular orbital (FMO) interactions as illustrated by the non-direct approach of carbenes to alkenes (Figure 55).

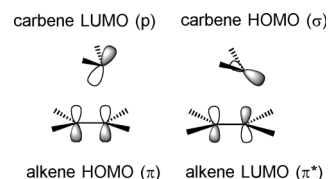


Figure 55. Two sets of orbital interactions involved in the reaction of carbenes and alkenes.

An example of such transformations is provided by a complicated molecular dance along the internal reaction coordinate (IRC) path in the cyclopropanation of alkenes with singlet carbenes. As a four-electron process, this reaction is forbidden according to the Woodward–Hoffmann rules unless it has an antarafacial component. However, such cyclopropanations are known to occur under rather mild conditions with a high degree of stereoselectivity. Quasiclassical trajectory calculations using quantum mechanical energies revealed that the initial approach of carbene to the target directs the empty carbene orbital towards the π -system.^[87] Only when formation of the first bond is sufficiently advanced does the second bond start to form in an asynchronous process that is accompanied by rotation of the CCl_2 moiety relative to its target (Figure 56).

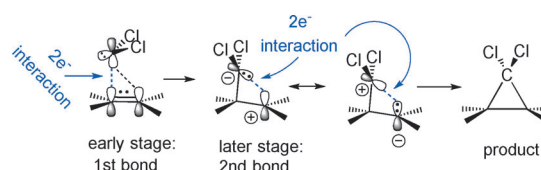


Figure 56. Changes in relative orientation at the different stages of approach of dichlorocarbene to an alkene.

These stereoelectronic peculiarities of carbenes make seemingly simple reactions sufficiently complex. For example, cyclopropanations are classified as reactions with hidden intermediates and hidden transition states.^[88] Multiple steps involved in sequential bond formation with ylides can be condensed into a single step in carbene cycloadditions.

Complementary chameleonic interactions in Diels–Alder reactions: We will finish this review with one more example of two chameleonic moieties meeting in a cycloaddition transition

state. Boger and co-workers reported that the Diels–Alder reaction of N-sulfonyl-1-aza-1,3-butadienes with vinyl ethers provided a single diastereomeric cycloadduct arising from an *endo* approach at the transition state.^[89] At this geometry, the lone electron pair on nitrogen **94** and the σ^*_{C-O} orbital of the dienophile **95** lie antiperiplanar to each other (Figure 57). The absence of a similar stabilizing $n \rightarrow \sigma^*$ interaction in the *exo* [4 + 2] transition state helps to explain the unusually large >20:1 *endo* diastereoselectivity of this reaction.

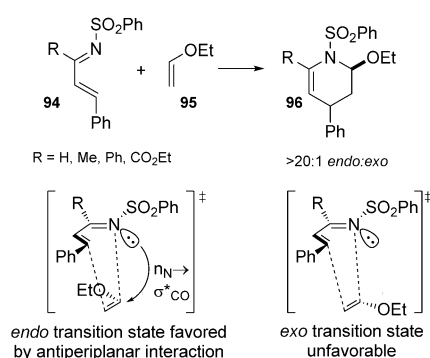


Figure 57. Two complementary „supramolecular chameleons“ use orthogonal sets of stereoelectronic interactions for the control of reactivity and regioselectivity.

The two layers of donor–acceptor interactions in this reaction play distinctly different roles. The formation of new σ -bonds in the cycle and the observed regioselectivity of cycloaddition are controlled by the $\pi_{alkene} \rightarrow \pi^*_{diene}$ interactions, in which the diene is an acceptor. On the other hand, the stereoselectivity of the reaction is controlled by the $n_N \rightarrow \sigma^*_{C-O}$ interaction, in which the alkene is an acceptor. Although the oxygen- and nitrogen-bearing functionalities participate in both interactions, they switch their donor–acceptor character, that is, the N-containing component is the acceptor and the O-containing component is the donor in the π -interaction but the N-containing component is the donor and the O-containing component is the acceptor in the σ -interaction.

6. Conclusion

An “unusual” behavior from common functionalities is not surprising. The stereoelectronic nature of chemical interactions imparts a variety of reactivity patterns, sometimes strikingly different, to most of the chemical groups. New reactivity patterns arise from spatial anisotropy that can be modulated by conformational flexibility.

The donor/acceptor duality is an intrinsic property of any chemical bond that corresponds to a pair of bonding and antibonding orbitals (i.e., the σ/σ^* or π/π^* pairs for organic molecules). As a result, any covalent C–X bond can be both a donor (by σ_{C-X}) and acceptor (by σ^*_{C-X}) in two-electron hyperconjugative interactions. This is, in fact, a typical pattern for neutral hyperconjugation.^[6] Of course, for any specific bond,

the balance of donor versus acceptor ability can be shifted to either end of the spectrum. Non-bonding orbitals, on the other hand, display the donor/acceptor duality only when they are partially filled (radicals). Filled non-bonding orbitals (lone pairs) are unidirectional donors. Empty non-bonding orbitals (e.g., the empty p-orbital of a carbenium ion) are unidirectional acceptors.

The situation with the lone pair donor and a σ^*_{C-X} acceptor is particularly common because it applies to N and O functionalities. Furthermore, even though carbon does not have non-bonding orbitals in most stable organic compounds, this structural feature is present in many reactive intermediates, being typical for singlet carbenes. It is applicable to halogens but with the caveat that a monovalent halogen atom cannot be a “rotating chameleon”. Chameleonic properties of halogens are revealed by moving the halogen atom one extra bond away (Figure 2B) or by approaching a carbon–halogen bond from different directions (Figure 2C).

In this review, we made an effort to highlight the more unusual behavior when a relatively strong donor and a strong acceptor coexist in the same functionality, giving the latter chameleonic nature, that is, the ability to “change its color” depending on molecular orientation, conformation, or connectivity.

Stereoelectronic chameleons can reveal their duality in several ways. In carbenes and in a wide variety of organic molecules with a heteroatom (e.g., with -F, -Cl, -C=O, -CN groups), the donor and acceptor centers can be located on the same atom but projected into different areas of space. Such chameleons change their electronic properties by changing their orientation relative to the other molecules (intermolecular reactivity) or relative to the other parts of the same molecule (intramolecular reactivity). Intramolecular patterns can be divided into two types:

- 1) *Conformational*: Changes in the dominant electronic interaction of a group of atoms with the rest of the molecule that occur upon a simple rotation reveal conformational chameleons. These groups involve common organic functionalities such as ethers, amines, amides, imines, nitroso compounds etc.
- 2) *Translocational*: Chameleonic behavior of the atom/group revealed by increased separation from its partner defines translocational chameleons and explains dramatically different properties and behavior of seemingly analogous functionalities (carbene vs. vinylidene or ketone vs. ketene).

The chemical duality of chameleonic groups in intermolecular interactions creates supramolecular chameleons. These functionalities can provide flexibility in the formation of non-covalent complexes and offer new ways to control the energies and other properties of transition states. Some of the most useful stabilization patterns result from constructive (i.e., mutually reinforcing) interaction between two chameleonic personalities. Such interactions bring more than one layer of donor–acceptor delocalizing interactions without significant net charge separation.

Because donor and acceptor properties are often engraved into our thinking about functional groups by the current educational paradigms, such a stereoelectronic “umpolung” can unlock useful ways of thinking about chemical reactivity and open new doors for reaction design. We are looking forward to new examples of stereoelectronic chameleons in control of structure and reactivity.

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Keywords: acceptors • donors • functional groups • reactive intermediates • stereoelectronic effects

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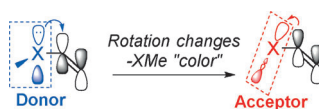
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Stereoelectronics

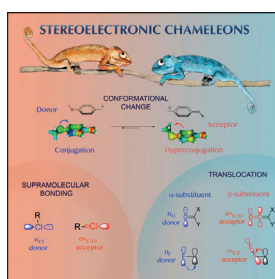
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G. d. P. Gomes, I. V. Alabugin*

■■ – ■■

**Stereoelectronic Chameleons: The
Donor–Acceptor Dichotomy of
Functional Groups**

CHEMeleon: Stereoelectronic factors account for the apparent reversal of donor–acceptor properties of a variety of functional groups by a simple change of their orientation in space. The new reactivity patterns that arise from spatial anisotropy are associated with chameleonic behavior of common organic functionalities.

Chameleonic Behavior



The traditional view of common functional groups as either donors or acceptors is challenged by stereoelectronic thinking. In the Review on page ■■ ff., S. Z. Vatsadze, I. V. Alabugin et al. discuss situations in which the donor–acceptor properties of substituents and, hence, chemical reactivity can be inverted as a function of their orientation in space with respect to the rest of a molecule. They discuss conformational, translocational and supramolecular “stereoelectronic chameleons” with focus on the situations in which the stereoelectronic “umpolung” unlocks useful ways of thinking about chemical reactivity and opens new doors for reaction design.