The Problem of Origins and Origins of the Problem: Influence of Language on Studies Concerning the Anomeric Effect
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In science, it is tempting to subordinate language to empirical data. Yet the words we use to describe our observations and conclusions have the capacity to bias the way we understand the world. This Essay provides two critical analyses of studies concerning the anomeric effect in order to illustrate how precision of language can influence the quality of our science. The first case study argues that the longstanding terminology that poorly differentiates cause and effect contributes to a high-profile controversy over the cause of spectroscopic shifts in a sugar–peptide complex (J. Am. Chem. Soc. 2011, 133, 13731 vs. Nature 2011, 469, 76). In the second case study, incomplete definitions encourage the rejection of a straightforward hypothesis for the conformational behavior of certain heterocyclic systems in favor of a dubious one: the reverse anomeric effect. It is desired that the insights gained by studying these cases will persuade scientists in all disciplines to take care not only in performing research but in communicating it.

1. Introduction

We know from undergraduate-level organic chemistry that equatorial conformers of substituted cyclohexanes are favored at equilibrium. This preference arises because steric interactions between a substituent and axial hydrogen atoms destabilize the axial conformer. The magnitude of these 1,3-diaxial interactions increases with the size of a substituent, or A value, which is quantified experimentally from differences in free energy [Figure 1, Eq. (1)–(3)] [1]. Substituents with larger A values favor the equatorial position to a greater degree than those with smaller A values. Methylcyclohexane ($A_{Me} = 1.7 \text{ kcal mol}^{-1}$), for example, shows a higher population of the equatorial conformer at equilibrium than methoxycyclohexane ($A_{OMe} = 0.8 \text{ kcal mol}^{-1}$), as a C–H bond is “larger” than a lone pair (LP) [Figure 1, Eq. (1) vs. (2)].

Carbocycles are not privileged. Many six-membered heterocycles show similar conformational preferences to cyclohexanes [2]. Like methylcyclohexane, 2-methyltetrahydropyran favors the equatorial conformer at equilibrium [Figure 1, Eq. (3)]. In fact, some 2-substituted heterocycles exhibit stronger equilibrium preferences for the equatorial isomer than analogous cyclohexanes, because shorter carbon–heteroatom bonds can intensify diaxial interactions [Figure 1, Eq. (1) vs. (3)]. This equatorial preference can be thought of as an increase in the effective size of a substituent in the heterocycle relative to cyclohexane.
1.1. Definition of the Anomeric Effect (AE)

Heterocycles with electronegative substituents at the 2-position often show a higher population of axial conformers at equilibrium than would be predicted based on a steric model of conformation [Figure 1, Eq. (4)–(6)].[4] When a physical observation demands explanation, an “effect” is born. The term “anomeric effect” (AE), which describes this surprising equilibrium preference, was introduced by Lemieux and Chu in response to the observation that many glucose derivatives exist predominantly as the α-anomer at equilibrium.[5,6] Indeed, predominance of the axial isomer of a 2-substituted heterocycle at equilibrium is the most obvious manifestation of the AE [Figure 1, Eq. (4) vs. (5)];[7] but it is not the only one.[8] The phenomenon that challenges our understanding is not an axial:equatorial ratio that necessarily exceeds 1:1 but an axial:equatorial ratio that exceeds what we can account for with the established steric model of conformation. Thus, a 2-substituted heterocycle that resides predominantly as the equatorial conformer, but to a smaller degree than a steric model predicts, also exhibits an AE [Figure 1, Eq. (4) vs. (6)].[9] For this reason, this Essay advocates an established[6,10] but often condensed[9] definition of the “anomeric effect:” an equilibrium preference for the axial isomer of a 2-substituted heterocycle that exceeds expectations based on a steric model of conformation.[10]

Mathematical and visual representations of the AE may help clarify why it is important to define the phenomenon in terms of steric expectations. The AE has a magnitude, and its magnitude can be separated into an observed free-energy component, \( \Delta G_{\text{obs}} \), and an invisible steric component, \( \Delta G_{\text{steric}} \), according to Equation (7) (Figure 2).[11] \( \Delta G_{\text{obs}} \) represents the degree of axial preference exhibited by a system of interest. It is the portion of the AE we see directly: for instance, \( \Delta G_{\text{obs}} \) can be calculated by comparing integration values of specific resonances of axial and equatorial conformers in equilibrating mixtures [Figure 2, Eq. (8)].[11b] But \( \Delta G_{\text{obs}} \) is not the whole story. To \( \Delta G_{\text{obs}} \) must be added the amount of energy required to overcome intrinsic steric bias toward the equatorial isomer. This steric energy is represented by the parameter \( \Delta G_{\text{steric}} \). In contrast to \( \Delta G_{\text{obs}} \), \( \Delta G_{\text{steric}} \) cannot be observed directly, but it can be approximated using a values of cyclohexane [Figure 2, Eq. (9)].[11] For a substituent larger than a hydrogen atom, \( \Delta G_{\text{steric}} > 0 \): the equatorial conformer is sterically favored, and the magnitude of the AE > \( \Delta G_{\text{obs}} \).

A visual representation recapitulates the dependence of the AE on both \( \Delta G_{\text{obs}} \) and \( \Delta G_{\text{steric}} \). Let the AE equal the actual height of a location above sea level (Figure 2). The portion of the AE we can see, \( \Delta G_{\text{obs}} \), corresponds to the height of the location relative to an observer (us). A positive \( \Delta G_{\text{obs}} \) represents an axial:equatorial ratio greater than 1:1 or a location at higher elevation than the observer. As Figure 2 illustrates, however, the apparent elevation of the indicated location is not equal to its actual elevation. To obtain the location’s actual elevation, it is necessary to take into account the fact that the observer himself is above sea level. The observer’s elevation is analogous to the steric component of the AE, \( \Delta G_{\text{steric}} \). Just as the observer can see only a portion of the total height of a location from his position, we can see only part of the AE exhibited by a system of interest. Yet we must remember the equally important steric contribution that is invisible to us.

1.1.1. Quantification of the AE in Specific Systems

Division of the AE into free-energy and steric components not only helps us understand the phenomenon qualitatively. Rather, the magnitude of the AE in specific systems can be quantified [Figure 3, Eq. (10)]. For example, 2-methoxytetrahydropyran (I) shows roughly 0.9 kcal mol\(^{-1}\) preference for the axial conformer at equilibrium [Figure 3, Eq. (14)].[12] This preference corresponds to \( \Delta G_{\text{obs}} \). Yet, the methoxy substituent is expected to favor the equatorial position of I by an amount of energy equal to \( \Delta G_{\text{steric}} \). \( \Delta G_{\text{steric}} \) is roughly equal to the A value of the methoxy group in cyclohexane \( [A_{\text{cy}}]^{1} = 0.8 \text{ kcal mol}^{-1} \), Figure 3, Eq. (15)]. A more accurate value for \( \Delta G_{\text{steric}} \) can be obtained if \( A_{\text{cy}} \) is multiplied by a heterocycle-specific correction value, \( f \), which accounts for shorter bond lengths in the heterocycle relative.
to cyclohexane [Figure 3, Eq. (13)]. For tetrahydropyran, \( f = 1.53 \), and \( A_{\text{THP}} = 1.53 \) kcal mol\(^{-1}\) = 1.2 kcal mol\(^{-1}\). Addition of \( \Delta G_{\text{obs}} \) to \( \Delta G_{\text{st}} \) according to Equation (10) gives the magnitude of the AE in 1: \( \Delta G = 0.9 \) kcal mol\(^{-1} \) + 1.2 kcal mol\(^{-1}\) = 2.1 kcal mol\(^{-1}\). This is more than double the amount of energy we observe in Equation (14)!

We see quantitatively, then, that \( \Delta G_{\text{st}} \) can contribute just as significantly to AE magnitude as \( \Delta G_{\text{obs}} \).

1.1.2. Electronic Origins of the AE

We’ve said that 2-methoxytetrahydropyran (1) exhibits an AE of 2.1 kcal mol\(^{-1}\). But what does that mean? It means that our steric model of conformation is off. And it is off by 2.1 kcal mol\(^{-1}\). Clearly, steric interactions are not the whole picture. And if steric interactions are not everything, then something else must be at play. The AE, then, testifies to the presence of a conformationally dependent electronic interaction or collection of interactions that selectively stabilizes the axial conformer in these systems.

Although myriad interactions have been invoked to explain the AE,\(^{[7]}\) two explanations predominate.\(^{[4]}\) Perhaps the most popular invokes stabilizing orbital overlap between a LP of an endocyclic heteroatom and a low-lying \( \pi^* \) orbital of the bond to the electronegative exocyclic substituent (Figure 4a, right). This interaction is maximized in the axial conformer, which experiences good orbital overlap, but is minimal in the equatorial conformer, which does not (Figure 4a, left).

An alternative model implicates electrostatic destabilization of the equatorial conformer to explain the AE (Figure 4b).\(^{[6]}\) Here, repulsion between the exocyclic C–Y substituent and the dipole created by both endocyclic C–X bonds and the LP of X destabilizes the equatorial conformer. Because repulsion is minimized in the axial conformer, it experiences greater stability than its equatorial counterpart.\(^{[4]}\)

Considered separately, hyperconjugation and electrostatic explanations for the origin of the AE are, of course, simplistic (Figure 5a).\(^{[8, 9]}\) Conformational or configurational equilibria of systems exhibiting the AE are influenced by a host of steric and electronic interactions, which vary in magnitude with the substrate and the conditions (Figure 5b). Some interactions, such as familiar LP–C–X \( \sigma^* \) donation, favor the axial conformer, while others, such as the indicated LP–C–H \( \sigma^* \) interaction, favor the equatorial isomer (Figure 5b).\(^{[21]}\)

2. Role of Language in Experiments Probing the Origin of Various “Anomeric Effects”

Simplified and real descriptions of the origins of the AE converge if a particular interaction, such as LP–C–O \( \sigma^* \) donation, dominates axial stabilization (\( E_{\text{ax}} \), Figure 5b). Our
For instance, people who speak languages that use absolute spatial terms (cardinal directions) navigate much better in new environments than people who speak languages that use relative spatial terms (left, right). Presumably, language can strengthen certain cognitive processes: a language built upon cardinal directions heightens a speaker’s propensity to see the world in terms of them.

If language can influence cognitive processes such as navigation, why can’t language influence cognitive processes used in science? The answer, presumably, is that it can. Physicist and philosopher David Bohm postulates that our language limits our ability to understand quantum physics and relativity. Specifically, he proposes that a subject-verb-object structure encourages us to see the world in terms of independent particles (subjects and objects) when reality may be wave-like and continuous. Bohm even goes so far as to create a mode of language that would be more suitable for discussion of a continuous universe. He calls this language the “rheomode”, and it privileges the flow of energy rather than discrete subjects and objects that possess it.

Most disciplines of science are far less abstract than quantum mechanics. Surely these more concrete fields are less susceptible to biases imposed by language? This author believes all fields of science, no matter how concrete, are susceptible to the influence of words. At heart, any scientific discipline is a process of seeing. When we run an experiment, we choose to see a certain collection of data. When we analyze that data, we choose to see certain patterns within it. So long as language directs our perception, it has the power to direct our experiments and our conclusions. The two case studies that follow are intended to highlight the intimate connection between our words and our science. In the first study, terminology that poorly differentiates the AE from interactions that underlie it may contribute to a recent controversy over the origin of spectroscopic shifts in a sugar–peptide complex. In the second study, language that accounts for the subtle and often forgotten role of steric interactions in the AE helps us rationalize unexpected shifts of conformational equilibria upon protonation. The AE, per se, may interest only a small audience. Yet the author hopes that these studies can persuade a broader community that science and language work together to obscure or clarify our understanding of the world.

2.1. Case Study 1: A Modern Controversy Surrounding Interactions Underlying the Anomeric Effect

To understand how language can complicate investigations into the origin of the AE, it is useful to consider what it would mean to elucidate a cause of the AE in the first place. Studies of the origin of the AE typically apply one of two strategies—laboratory experiments or computation. The experimental approach relies on the comparison of two systems that differ by some variables (substrate, solvent, charge). This variable is intended to perturb two electronic interactions—hyperconjugation or electrostatics, for example—in different directions. An increase in solvent polarity from system A to system B would be expected to amplify an AE derived from hyperconjugation, as polar solvents would stabilize the charge-separated resonance form of the axial conformer.
On the other hand, an increase in solvent polarity would diminish an AE derived from electrostatic interactions, as polar solvents would attenuate dipole repulsion in the equatorial isomer.[12,13a]

While experimental methods seek to indirectly discriminate between potential causes of the AE, computational methods do so explicitly. In this approach, magnitudes of all electronic interactions that are presumed to contribute significantly to the AE are calculated in both conformers (Figure 5b). Whichever interaction is found to provide the greatest increase in stabilization from equatorial to axial conformers is then deemed to be most responsible for the AE. Targeted interactions may be large, amalgamated terms such as “total orbital interaction energy” (hyperconjugation) or “total electrostatic energy”, or they may be small, defined parameters, such as a specific hyperconjugative interaction.[4,21] Although the energy contributions of an anomic system can be partitioned in a number of legitimate ways, it is crucial to remember that the analysis must involve comparison. To show that an interaction is responsible for the AE in a given system, it is not sufficient to show that the interaction exists or even to calculate its magnitude. Rather, one must show that it contributes more to axial stability than all other major candidates combined.

In 2011, Davis and co-workers published a paper entitled “Sensing the Anomeric Effect in a Solvent-Free Environment.”[28] In it, they suggest that IR spectroscopy can detect subtle, configuration-dependent changes in orbital interactions relevant to the AE. The experiment works in the following way: the gas-phase IR spectrum of a free peptide “sensor” 2 is compared to spectra of the same peptide sensor, this time associated to either β or α anomers of sugar 3 (Figure 6a, α anomer shown). An interaction between sugar 3 and peptide 2 is evidenced by the fact that the IR spectrum of the peptide–sugar complexes differ from that of the free peptide. Moreover, the shift in IR spectra experienced by the peptide upon complexation depends on the configuration of the sugar. Because the N–H stretch of the peptide and the C_O–H stretch of the sugar change most dramatically from one anomer of the complex to the other, these shifts are displayed in Figure 6a (ΔN-H and ΔO-H, respectively). However, it is important to highlight that Davis’ analysis hinges on comparison of entire IR spectra of relevant species and not just indicated peaks.

Davis then compares experimental spectra to spectra calculated for relevant energy-minimized structures. The process is repeated iteratively to minimize energy and pinpoint structures that best converge with experiment. Finally, Davis et al. perform NBO calculations of relevant orbital interactions in optimized structures. Based on the results of these calculations, Davis argues that spectral changes associated with epimerization can be explained self-consistently in terms of hyperconjugative interactions. Specifically, it is found that endocyclic O_exocyclic C-O α* donation (green arrow, Figure 6a) intensifies from β→α anomers, and this intensification is concomitant with a decrease in calculated endocyclic O→peptide H-N α* interaction (dashed green line, Figure 6a). Different binding aptitudes of β and α anomers are rationalized, then, by invoking changes in electron density on the endocyclic oxygen atom from one anomer to the other: hyperconjugation (green arrow, Figure 6a) reduces Lewis basicity—and consequently binding aptitude—of the endocyclic oxygen atom in the α anomer relative to its β counterpart.

Soon after publication of Davis’ report, Mo and co-workers rebutted Davis’ claim that the described spectral changes could be explained in terms of orbital interactions (“Sensing or No Sensing: Can the Anomeric Effect be Probed by a Sensing Molecule?”).[29] Davis’ conclusion hinges on the assumption that the shift in N-H stretches from β-associated to α-associated peptide is caused by changes in electron density on the endocyclic oxygen from one anomer of 3 to the other. To challenge this assumption, Mo uses a procedure analogous to that of Davis et al. to predict IR frequencies of optimized structures corresponding to substrate 4, which lacks the endocyclic oxygen atom of 3 (Figure 6b). Mo claims that the N–H and O–H shifts from β to α complex 4 are similar in magnitude and direction to those observed in complex 3 (–67 vs. –40 and +53 vs. +80 cm⁻¹); thus, Davis’ observations cannot implicate a change in hyperconjugative stabilization from one sugar anomer to the other, as similar data is obtained when the relevant interaction is absent. Mo et al. reinforce their argument by calculating distances from the endocyclic oxygen of 3 to the amide N–H. As these distances are found to exceed that for typical hydrogen bonds, Mo et al. argue that the endocyclic oxygen atom of either anomer of 3 may not actually associate to the peptide at all (green dashed line, 3). Instead, Mo invokes an interaction between the
peptide and the CH$_2$OH group of the sugar to rationalize observed spectral shifts (red dashed line, 3 and 4).

Mo’s evidence does not unilaterally encourage rejection of an endocyclic O to N–H association: spectral changes calculated by Mo for a third substrate (5) are nearly identical to those of 3 (–41 vs. –40 and +87 vs. +80 cm$^{-1}$, Figure 6). Yet this particular spectral shift cannot be explained in terms of an N–H/CH$_2$OH association (red dashed line), as the CH$_2$OH residue is absent (Figure 6b).

Finally, using a computational method complementary to that of Davis (BLW-ED vs. NBO), Mo identifies deformation and charge transfer energy as predominant contributors to the different binding energies of anomeric complexes 3.

The debate between Mo and Davis is primarily one of interpretation—Davis explains the spectral shifts of anomeric complexes in terms of orbital interactions using the method of NBO; Mo denies the validity of this interpretation and uses a BLW approach to explain the observed shifts in terms of steric and dipolar interactions. But the debate takes a deeper form, too. At the end of their paper, Mo et al. levy a much more fundamental criticism of Davis’ study: it attempts (and fails) to shed light on the origin of the AE.

2.1.1. Role of Language

Though Mo’s criticism targets the core of Davis’ study, its blow may be a superficial one. Mo’s challenge is at least partially semantic. It has become established in the literature to use the term “anomeric effect” in reference not only to a ground-state, contrasteric preference for the axial conformer or configurational isomer of a 2-substituted heterocycle, as the Essay encourages, but also to specific hyperconjugative interactions. For example, donation of an endocyclic LP into the σ* orbital of a bond to an exocyclic substituent has been labeled an “endo AE” (Figure 7). Conversely, donation of an exocyclic LP to the σ* orbital of an endocyclic carbon–heteroatom bond is termed an “exo AE” (Figure 7).[4,30,31]

![Figure 7](image_url)

Figure 7. The AE has been misleadingly defined in terms of specific orbital interactions.

With multiple definitions of AE to choose from, established literature becomes chameleonic. One can read Davis’ paper as an argument in favor of a hyperconjugative origin of the AE. Davis introduces his study with the following statement: “Despite its importance in both chemistry and biology, a clear dissection of the anomeric effect in archetypal... molecules... has not been possible”. If we take AE to mean a contrasteric thermodynamic preference, then we might understand this statement as intent to partition the anomeric effect into possible causes (steric interactions vs. electrostatic interactions vs. hyperconjugation vs...). Through this lens, a sentence at the conclusion of Davis’ manuscript can appear to suggest that elucidation of the origin of the AE has been achieved: “the present strategy has allowed the peptide sensor to... reveal through experiment the physical mechanism underlying the AE.”[28]

If Davis’ paper aims to implicate a hyperconjugative origin of the AE, Mo’s criticism has validity. Even if shifts in N–H and O–H frequencies do reflect changes in hyperconjugative stabilization from one anomer to the other, as Davis argues, Davis’ experiment would still not constitute direct evidence in favor of a hyperconjugative origin of the AE. No chemist is likely to refute that there exists an n–σ* interaction of nonzero magnitude in sugar 3. Moreover, no chemist is likely to deny that this particular interaction is more stabilizing in the α anomer than in the β anomer. As Figure 5 shows, many electronic interactions besides hyperconjugation can preferentially stabilize the axial isomer.

Hyperconjugation (or any interaction, for that matter) can only be deemed responsible for the AE if it is shown to contribute more to selective axial stabilization than other electronic interactions combined.

Though Davis does not directly address the relative stability or the origin of stability of anomeric complexes, it is possible he never intended to. With the chimeric term “AE” at play, Davis’ text (and the text of many others) can be read in diverse ways. If, instead of a ground-state preference, we take AE to represent an orbital interaction, Davis’ agenda can appear quite humble. Davis et al. may merely aim to show that spectroscopic changes in a sugar–peptide complex can be interpreted in terms of orbital interactions in a self-consistent way. If so, combined experimental and computational data allow comparison of specific orbital interactions in both anomers. In other words, Davis and co-workers can “dissect”[28] a combined orbital term into interactions of differing contributions.

Data in Davis’ paper may support this latter interpretation. For instance, energies of discrete orbital interactions rather than total anomer energies are reported. Moreover, Davis et al. conclude their study not with a discussion of the origin of the AE, but with an analysis of the relative contributions of exo and endo interactions; specifically, the exo n–σ* interaction is found to be more stabilizing in both anomers than its famed endo counterpart.

In reality, Davis (and Mo) use the term AE in multiple ways, and some interpretive confusion is inevitable. Yet this Essay doesn’t chastise Davis or Mo for use of imprecise language, as the language is not theirs alone. Rather, to the extent that the Mo–Davis debate is exacerbated by ambiguous use of the term “AE”, it serves as a high-profile and contemporary microcosm of a bigger linguistic snafu:[29] language endorsed by the scientific community does not always adequately demarcate cause from effect. The AE belongs to the family of stereoelectronic effects, which are often confused with the stereoelectronic interactions that give rise to them (Figure 8).[15] Stereoelectronic interactions are electronic interactions whose magnitude is modulated by

[28] Note from the editorial office: snafu = situation normal, all fouled up.
spatial orientation: stereoelectronic effects, on the other hand, are what we observe—they are reactivity and selectivity consequences that result from stabilization by stereoelectronic interactions in ground or transition states. Stereoelectronic interactions cause stereoelectronic effects. For instance, inversion of configuration in an $S_{N}2$ reaction is a stereoelectronic effect, whereas stabilizing orbital overlap between a nucleophile lone pair and an $\sigma^*$ orbital of the carbon−leaving group bond is the interaction believed to be responsible for inversion. Similarly, contrastropic preference for the axial conformer (or configurational isomer) of a 2-substituted heterocycle (the AE) is a stereoelectronic effect. Electrostastics or $\pi\rightarrow\sigma^*$ hyperconjugation are examples of stereoelectronic interactions presumed to underlie it.

The AE is only one of a host of stereoelectronic effects in the chemical literature. Others include the Perlin effect,[32] the reverse Perlin effect,[33] the homooanomeric effect,[34] the Bredt’s rule,[35] the Thorpe Ingold effect,[36] the Burgi–Dunitz angle,[37] Baldwin’s Rules for ring closure,[38] the Cieplak effect,[39] and the list goes on. Regardless how one defines these experimental curiosities, each can be partitioned into an observable (the effect) and its presumed cause. Take Bredt’s rule.[40] Generally interpreted as a prescription against bridgehead alkenes of a certain size, the “rule” emerged in response to discrete experimental observations, for instance, that dehydrobromination of a bridgehead anhydride fails, whereas analogous dehydrobromination of the ring-opened acid succeeds.[41] Reluctant reactivity of bridgehead systems stems from the fact that geometry compromises the overlap of bridgehead $\pi$ bonds, and the barrier to their formation is thus prohibitively high. In this case, difficult synthesis or abnormal reactivity of bridgehead systems is an effect, and constrained orbital overlap is a cause. Or consider the Cieplak effect.[42] Nucleophilic addition to isosteric faces of carbonyl moieties can proceed selectively under the influence of remote directing groups. Facial selectivity is what is observed, and it is explained by invoking configuration-dependent hyperconjugative interactions between the developing $\sigma^*$ orbital and antiperiplanar $\sigma$ bonds within the substrate.

Though this Essay differentiates stereoelectronic interactions from stereoelectronic effects, established scientific terminology does not always honor this distinction. We saw, for example, that “AE” can describe an observed, contrastropic equilibrium preference or a specific orbital interaction presumed to give rise to it. “Cieplak effect” has been used with similar promiscuity. In fact, it most often designates not observed patterns of facial selectivity as the word “effect” implies, but a specific orbital model that rationalizes these selectivity patterns.[43] Pierre Deslongchamps, a father of stereoelectronic effects, used the term in reference to interactions: “stereoelectronic effects”, he says in the opening of his classic text, “have long been known to influence the configuration and the conformation of acetals”.[15a]

Though he uses “effect” to designate both effects and interactions, Deslongchamps preserves a conceptual distinction between the two: “it is possible and probably very likely”, he continues “that [many] types of electronic effects are occurring in the acetal function”.[15b] In this case, linguistic union of effect and cause is relatively harmless: we are left with the correct understanding that acetals display certain observed conformational preferences, and these preferences arise from a complex interplay of electronic interactions that cannot always be easily differentiated through experiment.

A blurred semantic boundary between cause and effect can become problematic, however, if it encourages us to irreversibly bias one explanation for an observed phenomenon above others. Consider the AE. Use of the terms “endo AE” and “exo AE” to describe orbital interactions is not innocent; it reinforces a very strong community bias toward the hyperconjugation model for the origin of the AE. Indeed, some organic textbooks present hyperconjugation as the one and only explanation.[41] Nor does the bias stop with the AE itself. A variety of related phenomena, such as the kinetic anomeric effect, which describes relative rates of formation or cleavage of acetal derivatives,[35,43] the homooanomeric effect, which describes accelerated solvolysis of equatorial leaving groups in a position $\beta$ to $\pi$ donor atoms in cyclohexanes,[34] and the Perlin effect, which describes configuration-dependent $C\rightarrow H$ coupling constants at the 2-position of heterocycles,[33] are conventionally explained in terms of orbital interactions, despite the fact that other explanations are tenable.[43,44]

Here, then, lies the danger. Every stereoelectronic interaction is one of many possible hypotheses invoked to rationalize an effect. Some hypotheses are better than others.
No chemist is likely to reject poor π overlap as the origin of Bredt’s rule. Other models, however, are quite tenuous. Experimental and conceptual grounds to question the Cieplak orbital model for addition reactions to carbonyl moieties are somewhere in the middle; they are neither improbable nor indisputable. Hyperconjugation may very well contribute most significantly to the AE effect in some systems. But in other systems it may not. The point is this: effects are concrete—we see them. Stereoelectronic interactions are not and can thus not be observed. Our language should reflect this distinction. It makes sense to speak of an effect in concrete language, since it can be checked against reality. But we should not use the same language to describe a presumed stereoelectronic cause, because it is at best still conjecture! No stereoelectronic explanation, no matter how firm, can be absolutely, positively confirmed. Indeed, Deslongchamps reminds us to respect the intangible nature of stereoelectronic interactions with an opening quote by Claude Bernard: “When we propound a general theory in our sciences, we are sure only that, literally speaking, all such theories are false. They are only partial and provisional truths which….must change with the growth of science.”

If we are to allow this growth, we must keep an open mind. Language that closes it does us no favors.

2.2. Case Study 2: Should We Believe in the Reverse Anomeric Effect?

The previous case study illustrates the danger of using identical terminology to describe a stereoelectronic effect and the stereoelectronic interactions that underlie it. But semantic separation of cause and effect is not sufficient. Even if we correctly separate an effect from its cause, we must still define the effect itself with sufficient precision. Case study 2 shows what can happen if we don’t. In the example that follows, a condensed definition of the AE encourages us to overlook an obvious explanation for a surprising observation—that the conformational (or configurational) equilibria of some 2-substituted heterocycles shift toward the equatorial conformer (or epimer) in acidic solution—in favor of a much more insidious one.

It is perhaps easiest to start with an example. Consider the conformational equilibrium of 2-imidazolyltetrahydropyran (Figure 9a). We might imagine that a small AE operates in this system, which, for the purpose of illustration, we will say leads to a small preference for the axial isomer at equilibrium. Now consider a related conformational equilibrium in which the imidazolyl substituent is protonated. Given our understanding of the steric and electronic interactions presumed to give rise to the AE, we should be able predict how the cationic equilibrium will shift relative to its neutral progenitor. As protonation takes place on the nitrogen atom distal to the tetrahydropyran ring, we might approximate that the size of the substituent will remain roughly constant upon protonation (\(A_N \approx A_{N^+}\)). In this case, the change in magnitude of the AE will govern the shift in equilibrium position across systems. Electronegativity of the imidazolyl substituent should increase upon N protonation. In the orbital model, this increase in electronegativity will lower the energy of the C–N \(\sigma^*\) orbital and intensify hyperconjugative stabilization in the axial conformer. We predict that the cationic equilibrium will favor the axial conformer to a greater degree than the neutral one.

While our understanding of the AE makes us anticipate that equilibrium (16) will shift toward the axial conformer upon protonation [Figure 9a, Eq. (16)–(17)], nature has other outcomes in store. The equilibria of many heterocyclic systems bearing basic substituents at the 2 position actually show an increase in population of the equatorial conformer upon protonation [Figure 9a, Eq. (16)–(18)]. Because it defies predictions based on our model of the AE, the shift in equilibrium preference of these systems toward the equatorial conformer upon protonation of a basic exocyclic substituent has come to be known as the reverse anomeric effect.

\[\Delta G_{\text{obsd}} = \Delta G_{\text{obsd}, N^+} - \Delta G_{\text{obsd}, N} \] (19)

if \(A_N = A_{N^+}\) predict observe
\(\Delta G_{\text{obsd}} > 0\) \(\Delta G_{\text{obsd}} < 0\)
(\(\text{Axial} N\)) (\(\text{Axial} N^+\))

why? \(\uparrow\) AE reverse AE?

<table>
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<th>N</th>
<th>N*</th>
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![Figure 9. Predicted and observed shifts of heterocyclic equilibria upon protonation.](a.png)

vs. LP

\(\uparrow\) axial stabilization from N to N* → \(\uparrow\) axial population from N to N*

\(\uparrow\) AE
perhaps the most obvious manifestation of the “RAE” is an axial preference in a neutral equilibrium that flips to an equatorial preference in a protonated one. It is this scenario that is described in Figure 9.

Invocation of a RAE, then, responds to an unexpected shift, or change, in equilibrium position of some 2-substituted heterocycles upon protonation. Rigorously, this change in equilibrium position is described by the parameter $\Delta \Delta G_{\text{obs}}$ where $\Delta \Delta G_{\text{obs}} = \Delta G_{\text{obs}} - \Delta G_{\text{obsN}}$ [Figure 9a, Eq. (19)]\(^{[50]}\) Because the equilibria in Figure 9a are defined in the direction of the equatorial conformer, a positive $\Delta \Delta G_{\text{obs}}$ corresponds to an increase in population of the axial conformer upon protonation [Eq. (16)–(17)], whereas a negative $\Delta \Delta G_{\text{obs}}$ corresponds to an increase in equatorial conformer upon protonation [Eq. (16)–(18)].

As we said before, $\Delta \Delta G_{\text{obs}}$ depends on a change in both substituent size and AE magnitude from neutral to cationic systems. We will describe the change in size, or $A$ value, of a substituent as $\Delta \Delta G_{\text{steric}}$, where a positive $\Delta \Delta G_{\text{steric}}$ represents an increase in substituent size upon protonation. In a similar fashion, we can define the parameter $\Delta AE$ as the change in magnitude of the AE across systems. Putting these parameters together, we craft the relationship $\Delta \Delta G_{\text{obs}} = \Delta AE - \Delta \Delta G_{\text{steric}}$ [Figure 10, Eq. (20)].\(^{[51]}\)

### 2.2.1 Steric vs. RAE Model for Protonation Induced Equilibrium Shifts

Separation of $\Delta \Delta G_{\text{obs}}$ into $\Delta AE$ and $\Delta \Delta G_{\text{steric}}$ according to Equation (20) is useful, since we have an intuitive handle on the direction and magnitude of these steric and electronic components (Figure 10). Fundamentally, the RAE is created to explain a negative $\Delta \Delta G_{\text{obs}}$, which is unexpected, given one critical assumption: that protonation does not significantly change the size of an exocyclic substituent. If this assumption is true, then $\Delta \Delta G_{\text{steric}} = 0$, and Equation (20) reduces to $\Delta \Delta G_{\text{obs}} = \Delta AE$. We predict that $\Delta \Delta G_{\text{obs}} > 0$, as $\Delta AE > 0$ according to reasoning described in Figure 10b.\(^{[52]}\) Observation that $\Delta \Delta G_{\text{obs}} < 0$ in many systems motivates the introduction of a correction factor that opposes the presumed increase in AE across systems. We call this correction factor the RAE (Figure 10c.1). It represents an interaction that selectively stabilizes the equatorial conformer of a protonated 2-substituted heterocycle.

Although introduction of the RAE enables us to account for an empirical, negative $\Delta \Delta G_{\text{obs}}$ from neutral to cationic systems, another explanation exists. As stated, treatments invoking a RAE make the critical assumption that $\Delta \Delta G_{\text{steric}} = 0$, or that protonation of a substituent does not significantly change its bulk. If we instead allow $\Delta \Delta G_{\text{steric}}$ to float, we can easily account for a negative $\Delta \Delta G_{\text{obs}}$ without invoking the RAE. Given an empirical $\Delta \Delta G_{\text{obs}}$ and an estimated $\Delta AE$, we simply allow $\Delta \Delta G_{\text{steric}}$ to adopt whatever positive value makes Equation (20) true (Figure 10c.2). A steric model for equilibrium shifts is simpler than the RAE model, as it does not require introduction of a correction factor. Yet the chemical community has been quick to embrace the RAE.

### 2.2.2 A Case for a Steric Model

A challenger of the RAE, Charles Perrin, has undertaken a series of investigations to evaluate whether steric interactions alone can account for the changes in equilibrium positions of 2-substituted heterocycles upon protonation.\(^{[49,53]}\) Recall that what is troublesome about a steric model is that we cannot easily explain why a cationic substituent should be significantly larger than its neutral counterpart. In the case of 2-imidazolyltetrahydropyran (Figure 9), for instance, protonation occurs remote from steric congestion of the ring and should not change the hybridization of the exocyclic imidazolyl nitrogen atom. Perrin hypothesized that the environment may play a role in modulating the size of basic substituents. Specifically, he postulated that solvation of a cationic group might increase its effective size, or $A$ value,
relative to that of a neutral substituent [Figure 11, Eq. (23) vs. (22)]. If this hypothesis is true, then perhaps the equatorial shift observed in the described heterocyclic systems upon protonation can simply be attributed to the fact that it is much harder to put a large, solvated group in the axial position.

To test the hypothesis that solvation can differentially increase the size of cationic groups relative to neutral ones, Perrin and Kuperman compared the equilibrium response of glucosyl- and cyclohexylanilines to protonation (Figure 12a vs. b). Glucosylamines (6) and cyclohexylanilines (8) serve as a steric control (Figure 12b). A shift toward the equatorial epimer in the cyclohexyl equilibrium upon protonation signifies that a protonated aniline is a larger substituent than a neutral one. If the cyclohexyl equilibrium shifts toward the equatorial epimer to the same degree as the heterocyclic equilibrium upon protonation; there is no need to invoke a RAE.

Moreover, if the magnitude of the equatorial shift in the cyclohexyl equilibrium exceeds that observed in the glucosyl equilibrium, then the normal AE in anomic system (a) increases upon protonation, as our electronic models predict. As expressed before, the shift in the population at equilibrium of the heterocyclic system upon protonation is given mathematically by parameter $\Delta G_{\text{obs}}$, which is equal to the difference in positions of cationic and neutral equilibria [Figure 12, Eq. (32)]. On the other hand, the difference in equilibrium positions of cationic and neutral equilibria in the cyclohexyl system approximates parameter $\Delta G_{\text{steric}}$, which is a measure of the change in size of the anilinic substituent upon protonation [Figure 12, Eq. (33)]. In this case, a positive $\Delta G_{\text{steric}}$ and negative $\Delta G_{\text{obs}}$ corresponds to an increase in equatorial epimer upon protonation. $\Delta G_{\text{steric}} > \Delta G_{\text{obs}}$, then, is the condition for which the magnitude of the normal AE in system (a) increases in response to protonation.

Although the logic of Perrin’s experiment is straightforward, its simplicity belies its sophistication. Given that they describe relative rather than absolute equilibrium positions, $\Delta G_{\text{obs}}$ and $\Delta G_{\text{steric}}$ have small magnitudes, and they must therefore be measured with great precision. Conventional methods for the determination of these parameters rely on measurement and subsequent subtraction of $\Delta G$ values for neutral and cationic equilibria separately, according to the relationship $\Delta G = \Delta G^+ - \Delta G$ [Figure 12, Eqs. (24) and (25)]. $\Delta G^+$ and $\Delta G$ are traditionally obtained by $^1$H NMR spectroscopy of relevant equilibria [AG: Eq. (24) or (26); $\Delta G^+$: Eq. (25) or (27)], either by integration of isomer-specific resonances or by calculations using time-averaged coupling constants.

Determination of $\Delta G$ values by subtraction of $\Delta G$ values is problematic, as the large errors associated with this method can approach the magnitude of the desired $\Delta G$ values themselves. Perrin had the beautiful insight that $\Delta G_{\text{obs}}$ and $\Delta G_{\text{steric}}$ could be obtained with very high precision without relying on calculation of $\Delta G$ values. Perrin’s analysis hinges on recognition that equations (24) and (25) constitute a thermodynamic cycle if two protonation steps are invoked, one from the axial anomer [Eq. (28)] and one from the equatorial anomer [Eq. (29)]. Given that equilibria (24) and (25) are mathematically coupled to equilibria (28) and (29), the equilibrium constants $K_{\text{ax}}$ and $K_{\text{eq}}$ follow:

$$\Delta G_{\text{obs}} = \Delta G^+ - \Delta G = RT \ln \frac{K_{\text{ax}}}{K_{\text{eq}}}$$

$$\Delta G_{\text{steric}} = \Delta G^+ - \Delta G = RT \ln \frac{K_{\text{ax}}}{K_{\text{eq}}}$$

Acidity constants, $K_{\text{ax}}$ and $K_{\text{eq}}$, are obtained with high precision by $^1$H NMR titration of eqs. (28)–(31). If $\Delta G_{\text{steric}} > \Delta G_{\text{obs}}$, then AE increases from N $\rightarrow$ N$^+$ (eq. (24) to eq. (25)).

In fact, this is true for NR$_2$ is NH$^+!$

**Figure 11.** Perrin’s hypothesis: solvation selectively increases the bulk of cationic groups. **Figure 12.** Perrin and Kuperman’s experiment showed that a steric model accounts for acid-induced equatorial shifts of glucosylanilines. Their conclusion: taken together, steric interactions and a normal anomic effect adequately describe the observed equatorial shifts (negative $\Delta G_{\text{obs}}$ values) from neutral to cationic equilibria in the systems that were studied. It is not necessary to invoke a reverse anomic effect.
(29), \( \Delta G_{\text{obs}} \) can be expressed in terms of acidity constants \( K_{a,ax} \) and \( K_{a,eq} \) instead of \( \Delta G \) values [Eq. (32)]. In fact, axial and equatorial isomers of substrates 6–9 do not interconvert in the experiment—equilibria (24)–(25) [and (26)–(27)] are probed only indirectly. Perrin et al. calculate acidity constants, \( K_{a,ax} \) and \( K_{a,eq} \) by \( ^1H \) NMR titration of equilibria (28) and (29), respectively.\(^{[3b,60]}\)

Analogous logic applies to cyclohexyl system (b). In this case, \( \Delta G_{\text{obs}} \) is related to the ratio of acidity constants for equilibria (30) and (31) according to Equation (33). Expression of \( \Delta G_{\text{obs}} \) and \( \Delta G_{\text{steric}} \) in terms of acidity constants [for Eqs. (28)–(31)] rather than \( \Delta G \) values [for Eqs. (24)–(27)] is beneficial, as acidity constants can be determined with far greater precision than \( \Delta G \) values. This precision is a consequence of the fact that acidity constants are measured from NMR signal frequencies rather than integration values or time-averaged coupling constants.

Using this NMR titration method to isolate electronic and steric responses to protonation, Perrin and Kuperman found that the magnitude of \( \Delta G_{\text{obs}} \) significantly exceeds that of \( \Delta G_{\text{steric}} \) for a series of electronically diverse anilines. In other words, cyclohexylanilines 8 undergo an equatorial shift of greater magnitude than the corresponding glucosylanilines 6 upon protonation. The observed equatorial shift of the heterocyclic system upon protonation, then, can be simply attributed to the increased bulk of the anilinium substituent relative to the neutral one. Steric interactions can alone account for protonation-induced equatorial shifts of glucosyl system (a); there is no need to invoke a RAE. On the contrary, Perrin’s experiment indicates that a normal AE in glucosylanilines increases upon N-protonation exactly as theory predicts.\(^{[61]}\)

If a steric model can explain the equilibrium behavior of glucosylanilines 6, perhaps it can also explain the behavior of other systems deemed to exhibit a RAE. There are a number of reasons why the adoption of a steric model over a RAE model is desirable. First and foremost, the steric model agrees with established theory, while the RAE model does so only with provisions. Occam’s Razor, or the principle of parsimony, states that when deciding between multiple hypotheses, we should favor the one with the fewest assumptions.\(^{[62]}\) If a RAE is used to explain unexpected equatorial shifts in cationic equilibria, then we must invoke an additional interaction or interactions in these systems that cause it.\(^{[49]}\)

Such an interaction would selectively stabilize the equatorial conformer of the protonated system. Yet theory provides no basis for such an interaction.\(^{[49]}\) Because it makes assumptions the steric model does not, the RAE fails to satisfy Occam’s Razor.

The principle of parsimony is often misinterpreted in terms of probability: “the theory with the fewest assumptions is most likely to be correct”. Yet there is no necessary correspondence between economy and accuracy. What can accompany simplicity, on the other hand, is testability.\(^{[63]}\) Take Popper’s example: upon seeing the sun rise day after day, one could surmise that a) the sun will rise every morning, or that b) the sun will rise every morning until a certain day, at which point it will stop. While the simpler hypothesis (a) can conceivably be falsified (if the sun fails to rise), (b) cannot: we can always evade disproval by claiming that the fateful day hasn’t come yet. In a similar way, the RAE model is impervious to rebuttal: if we don’t find evidence for the RAE, then maybe we’ve just got the wrong system. We should favor Perrin’s steric hypothesis over the RAE not necessarily because it is a better fit to reality, but because it is more easily checked against it.

Acceptance of the RAE is not only problematic because it represents allegiance to a slippery hypothesis; it diverts subsequent scientific research toward the study of the novel phenomenon. Indeed, the scientific community has already undertaken investigations aimed at answering the following questions: what electronic interactions are responsible for the RAE?\(^{[64]}\) Is the RAE operative in other systems?\(^{[65]}\) Does the RAE behave as a synthetic control element?\(^{[66]}\) If the RAE model is a good one, then these questions are meaningful, and dedication of mental and physical resources to their elucidation is productive. But in the more parsimonious scenario in which no RAE exists, these inquiries are distracting. Indeed, experimental evidence in complementary systems challenges the operation of a RAE.\(^{[67]}\)

2.2.3. Role of Language

Looking back, Perrin’s steric model constitutes the null hypothesis for protonation-induced equilibrium shifts, as it fits within an established theoretical framework. (Indeed, recent work has appropriately favored the steric model).\(^{[68]}\) So why did many members of the scientific community accept the RAE model, which does not? This author believes that definitions play a role in our bias. The AE was previously defined as “a tendency for electronegative substituents to adopt the axial position of anomeric or conformational equilibria” to a greater degree than a steric model of conformation predicts”. Yet, a common condensation of this definition—“a tendency for electronegative substituents to adopt the axial position of anomeric equilibria”—neglects the steric contribution.\(^{[69]}\) This author believes that truncation to exclude the steric component predisposes us to forget about the role of steric interactions in the AE and related phenomena. In this case, the popular definition of the AE may make us less inclined to use a steric model to explain overly surprising equilibrium shifts even if we must grasp for a much more quixotic explanation: the RAE.

To this point, arguments favoring Perrin’s model for protonation-induced equilibrium shifts target weaknesses of the RAE model rather than strengths of the steric one. In fact, the most important advantage of Perrin’s model is productive: it can help us make sense of observations outside the system it was intended to explain. Here is one example. Early literature probed solvent effects to elucidate the origin of the AE.\(^{[12,13a,30]}\) Solvent polarity was found to vary inversely with the population of the axial conformer in a number of systems, and this was cited as evidence in favor of an electrostatic origin of the AE by reasoning discussed before.\(^{[12,13a,30]}\) Still, some results remained puzzling. Dielectric constant appeared to be a poor predictor of equilibrium population for solvents capable of hydrogen bonding; though deuteriochloroform has a much smaller dielectric constant than acetone (4.8 vs. 21,
respectively), the equilibrium population of equatorial 2-
methoxytetrahydropyran in both solvents is identical (29% vs.
28%, respectively).[2]

In light of Perrin’s work, we might explain the observed
inverse relationship between axial population and solvent
polarity using a steric model rather than an electrostatic one.
In the steric model, the AE remains roughly constant across
solvents, but the effective size of the exocyclic substituent
increases with solvation: a greater percentage of equatorial
conformer is observed in polar solvents.[30] Importantly, this
explanation is able to account for the unusually high axial
populations observed in solvents such as chloroform which,
despite their relatively low polarity, can solvate an electro-
negative substituent through hydrogen bonding.

While the solvation model successfully describes the
conformational behavior of several heterocyclic systems,
there is no reason to believe its predictive power stops there.
Indeed, the biggest selling point of Perrin’s work is that it may
have applications in other fields of chemistry. Consider
catalysis. Recall that the magnitude of the AE is on the order
of 1–3 kcal mol⁻¹. At the ground state, this is a tiny amount
of energy. But at the transition state, it’s everything. 1.8 kcal
mol⁻¹ is the difference between 0 and 90% ee! In the context
of synthetic chemistry, then, Perrin’s model may not only
provide understanding but control. Insight that solvation can
change the size of a substituent by 1–3 kcal mol⁻¹ may enable
rationale design to optimize reaction yield or selectivity.

3. Summary and Outlook

In this Essay, I have urged the scientific community to
adopt one definition of “anomeric effect”—“a contrasteric
thermodynamic preference for the axial isomer in certain 2-
substituted heterocycles”—rather than either “an absolute
thermodynamic preference...” (case study 2) or “a specific
n→σ* interaction” (case study 1). More generally, I have
advocated a clear semantic distinction between cause and
effect.

But what ground do I have to stand on? After all, IUPAC
defines AE in terms of absolute axial preferences,[40]
Lemieux used “anomeric effect” to describe hyperconjugation,[28]
and Deslongchamps references both effects and
interactions with the term “stereoelectronic effect”.[54] Witt-
genstein, a philosopher whose concept of language has
influenced many descriptions of scientific progress, appears
to defend IUPAC, Lemieux, Deslongchamps, and others: “a
meaning of a word” says Wittgenstein, “is its use in the
language”.[71] Our scientific discourse involves far more than
objects we can point to; we also talk about concepts—
electrons, orbitals, dipoles—that cannot be observed directly.
And if we can’t experience these concepts directly, then how
can we check to see if we, or others, are using the right words
to describe them? We can’t! Definitions are decided ulti-
mately by convention. And what greater authorities are there
to arbitrate than the IUPAC Gold Standard, the originator of
the AE, or the king of stereoelectronic effects? So in response
to another question—is use of the term “AE” to describe
absolute axial preferences or “stereoelectronic effect” to
describe a stereoelectronic interaction justified?—then my
answer is an unequivocal yes. But my rebuttal is this: what do
we gain by doing so?

Just because we are entitled to whatever definition we
please does not mean we should choose an arbitrary one.
Wittgenstein draws an analogy between games and language
to suggest that there is more to language than correctness;
language also serves a purpose: “The game, one would like to
say, has not only rules but a point.”[72] Perhaps the better
question is not whether our definitions are justified but
whether they are useful. Science demands a lot of us. We must
ask good questions, we must formulate multiple hypotheses,
we must design experiments to distinguish between them, and
when differentiating between tenable explanations, we must
honor values such as simplicity, testability, and scope. This
Essay illustrates how imprecise definitions can snare us: as
a filter through which we experience the world, they can bias
us to such a degree that we forget the distinction between
cause and effect, and we embrace complex explanations over
simple ones. This sounds cynical. Yet the driving force behind
this Essay is optimism. If language has the power to confuse, it
also has the power to clarify. We are not victims! Indeed,
sociologist Derek Phillips encourages us to view subjectivity
not so much as an impediment to science but as an
opportunity to control its destiny: “No longer do many of us
believe that science can provide the certainties which men
and women everywhere seem to seek and require. To
recognize this is not to be thrown into despair, but rather to
realize fully the freedom to choose and the responsibility of
choice”.[73] Here then, is the hope. As scientists, we already
value precision: we weigh catalysts to three significant figures,
calculate response factors for analytical yields, determine
enantioselectivities to fractions of percents. Why not choose
our language with equal sensitivity?

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[3] Ref. [1], p. 120.
[4] For selected reviews on the anomeric effect, see: a) E. Juaristi,
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M. Mikolajczyk in Topics in Stereochemistry, Vol. 21 (Eds.: E. L.
Eliel, S. H. Wilen), Wiley, New York, 1994, pp. 159–349; c) E.
Juaristi, Y. Bandala in Advances in Heterocyclic Chemistry,
This Essay focuses on enthalpic contributions to the AE, which can be parsed (though not always perfectly) into steric or electronic interactions. However, entropic factors have also been invoked to rationalize the effect: a) H. Booth, T. B. Grindley, K. A. Khedhair, J. Chem. Soc. Chem. Commun. 1982, 1047–1048; b) Ref. [4a], and references therein.


The AE in terms of configurational or conformational equilibria. Conformers are interconverted by bond rotation. Configurational isomers are interconverted by cleavage and reformation of one or more bonds. Epimers are a subset of configurational isomers that differ in configuration at one and only one stereogenic center. Anomers are a subset of epimers that differ in configuration at the hemiacetal or hemiketal carbon atom (anomeric carbon atom) of a cyclic saccharide. The terms conformer, configurational isomer, epimer, and anomer are all used in this Essay. Unless otherwise specified, configurational rather than configurational equilibria are used to illustrate concepts. For simplicity, the terms “axial” and “equatorial” are used to designate isomers of multisubstituted heterocycles such as carbohydrates. In this case, axial and equatorial always designate the position of the substituent at the 2-position of the heterocycle or anomeric carbon atom of the carbohydrate.

The AE in terms of configurational or conformational preferences about an endocyclic or exocyclic carbon atom of the carbohydrate. This omission is problematic for reasons that will be examined in the second case study.

A more general formulation of the AE describes the tendency for acyclic RYCX units to adopt a gauche conformation about the C–Y bond to a greater extent than a steric model predicts: R. U. Lemieux, Pure Appl. Chem. 1971, 25, 527–548. This Essay will use the term AE to describe heterocycle conformation or configuration only.

Many (if not most) formulations of the definition of AE neglect to include an explicit reference to steric expectations (see Ref. [69]). This omission is problematic for reasons that will be examined in the second case study.

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a) Ref. [15]; b) Ref. [22c]; c) Ref. [22e]; d) Ref. [35e]; e) Ref. [35j].

For references that challenge the significance of n→α* interactions as major sterocontrol elements in the formation or cleavage of acetal derivatives, see: a) Ref. [35d]; b) Ref. [35g]; c) Ref. [35j]; d) Ref. [35k]; e) Ref. [35n], and references therein.

For an explanation for the Perlin effect that does not invoke n→α* interactions, see: Ref. [32d].

Some bias is inevitable even in the identification or description of an effect. Yet discrimination of effects and interactions based on a criterion of objectivity can still be useful, as manifestations of effects are typically observable.

The argument does not require that Equation (16) exhibit a net axial preference. However, the logic is more easily followed if we let Equation (16) favor the axial conformer.


The author chose to assign the sign of the parameters to best match intuition; an increase in axial isomer (positive ΔGΔ) will relate positively to an increase in AE magnitude and negatively with an increase in substituent size.

To be more correct, the AE vector in Figure 10 does not correspond to the AE itself. Rather, it represents the magnitude of the sum total of electronic interactions presumed to selectively stabilize the axial isomer of a conformational or configurational equilibrium. The prediction that ΔAE > 0, then, more correctly means that we expect the relative stabilization of the axial isomer by either hyperconjugation or electrostatics to increase upon N protonation.


Perrin is not alone to invoke steric interactions to explain equatorial shifts of heterocyclic equilibria upon protonation. Yet, his experiments represent perhaps the most precise and convincing demonstration that substituent size is modulated by protonation, either through solvation (see below) or counterion association. For examples of other work that acknowledges the possible role of steric interactions in protonation-induced equilibrium shifts, see: a) Ref [47b]; b) K. D. Randell, B. D. Johnston, D. F. Green, B. M. Pinto, J. Org. Chem. 2000, 65, 220–226; c) A. R. Vaino, W. A. Szarek, J. Org. Chem. 2001, 66, 1097–1102.


Though this is not the only study that Perrin and co-workers performed to probe the role of steric interactions in protonation-induced equilibrium shifts (see Ref. [53a–d] for other examples), it is the most illustrative.

The glucosylanilines used in Perrin's study are simplified to substituted heterocyclic aniline 6 in Figure 12 for sake of illustration.

As shorter bond lengths in heterocyclic system (a) should exacerbate steric interactions between an anilinium substituent
and axial hydrogen atoms in relative to those in cyclohexane, cyclohexane system (b) should, if anything, serve as a conservative control. In other words, $\Delta G_{\text{calc}}$ calculated from Equation (33) (see below) is expected to underestimate the increase in size of the aniline substituent upon protonation.

For a discussion of the limitations of $\Delta G$ calculations based on coupling constants, see: Ref. [53d].

Of the systems examined by Perrin and co-workers (Ref. [53c]), glucosylanilines (Ref. [53c]) show a particularly large steric response to protonation. The change in $A$ value of substituents such as amines (Ref. [50]) and imidazoles (Ref. [53b–d]) upon protonation was found to be more subtle. Yet steric interactions and a normal anomeric effect still adequately describe equilibrium shifts in these systems.


Lemieux and co-workers postulated that hydrogen bonding might contribute to solvent-dependent equilibrium shifts, but this contribution was not rigorously established at the time: Ref. [12].


Ref. [71], Part I, SEC 564.


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