Some recent developments in stereoelectronic theory. Reevaluations of ALPH and the reverse anomeric effect

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(received 01 Dec 04; accepted 24 Mar 05; published on the web 07 Apr 05)

Abstract

A critique of objections to the 'antiperiplanar lone pair hypothesis' (ALPH) and the 'reverse anomeric effect' (RAE) is presented. Whilst early fears that ALPH is incompatible with the Curtin-Hammett principle (CHP) were apparently unfounded, objections to ALPH based on the reactions of cyclic hemiorthoesters and amidinium salts are debatable. (The unreactivity of Kirby's bicyclic bridgehead acetal supports ALPH convincingly.) Objections to RAE were based on its apparent incompatibility with ALPH, studies on several models indicating (dubiously) the existence of a weak anomeric effect rather than RAE. However, this may well suggest that a normal anomeric effect is being offset by RAE. This apparently indicates different bases for the ground state and kinetic anomeric effects: the classical 'electrostatic *gauche* repulsive interaction' (EGRI) and the 'orbital interaction' (OI) respectively. The evidence against free oxocarbenium ions, but favouring the ion pair and the 'exploded transition state' (ETS) models apparently raises the question 'Whither ALPH?'. A rigorous application of the CHP to the stereochemistry of displacements at glycosyl anomeric centres, indicates that the α anomers react retentively *via* ion pairs, whereas the β anomers react with inversion *via* the ETS. (A substantial reassessment of the '*in situ* anomerisation technique' is also indicated.)

Keywords: ALPH, anomeric, Curtin-Hammett Principle, oxocarbenium, reverse-anomeric, stereoelectronic

Contents

Introduction

Stereoelectronic theory represents an important thrust area of modern organic chemistry, having provided a major boost to mechanistic research in recent decades. Much of the activity has centred around ALPH (the 'antiperiplanar lone pair hypothesis').[1,2] After several ups and downs, ALPH has apparently settled down as an important theory of chemical reactivity. The major impetus for the evolution of ALPH is the fact that it provides the mechanistic underpinning for glycosyl transfer – the key process in the burgeoning area of carbohydrate chemistry, which is set to play a prime role in chemical biology. It is apparently widely believed – although this by no means implies a consensus – that the present conceptual status of ALPH is highly satisfactory, and that the broad contours are well established: although ALPH will be fleshed out further, no

major surprises are expected. This review attempts a reassessment of this view, essentially based on a reinterpretation of some recent reports and developments.

Stereoelectronic theory, in fact, is a relatively young theory. Although stereoelectronic ideas were always considered the key to understanding stereospecificity – the Beckmann and the E_2 reactions coming readily to mind – modern stereoelectronic theory really surged with the advent of ALPH (1975).[1-2] Much of the fascination for ALPH derived from the belief that it offered a better and a sophisticated explanation for the anomeric effect – key to the structure and reactivity of the carbohydrates. (ALPH is more in tune with the highly successful molecular orbital theory, the earlier explanation for the anomeric effect having been based on charge repulsive effects.[1])

ALPH, however, introduced additional challenges in proposing that the spatial definition of electron lone pairs influenced reactivity. Although it is widely accepted that bonds between atoms are spatially well-defined – this indeed being the basis of the structural theory (!) – the theoretical basis for the spatial definition of electron lone pairs was contentious. Therefore, ALPH represented a special case of stereoelectronic theory – in fact, its most difficult formulation – and clearly attempted to kill two birds with one stone: the spatial definition of the lone pairs and their effects on reactivity.

Reaction to ALPH came swiftly. Many believed that ALPH possibly contravened the Curtin-Hammett principle.[3,4] (This is discussed in some detail further below.) It was also proposed that the principle of least nuclear motion (PLNM) was a better alternative to ALPH.[4] (One notes that PLNM predates transition state theory, but is not formally a part of it;[5] ALPH is essentially based on transition state theory.) Another proposal was that many of the reactions purported to be controlled by ALPH – particularly of certain iminium systems – were rather controlled by product stabilities.[6] (This is also discussed in some detail further below.)

In the view of many, however, ALPH seems to have prevailed. In fact, a relatively recent and interesting development may be mentioned, relating to the contentious 'reverse anomeric effect' (RAE). The RAE is, in a way, a derivative of the anomeric effect itself, and proposes that the anomeric effect is reversed under some conditions. The RAE, however, could never be satisfactorily explained on the basis of ALPH, and was thus the proverbial thorn in the side for the proponents of ALPH. Recently, however, reports have appeared that claim to have disproved the RAE,[7,8] thus apparently strengthening the case for ALPH (although one school disapproves of both ALPH and the RAE!).

Paradoxically, on the other hand, the view has gained ground that the free oxocarbenium ion – an 'old faithful' among the reactive intermediates – is practically a chimera![9] Instead, the heterolytic reactions of the acetals and the glycosides are believed to occur *via* rate-determining nucleophilic attack on an (oxocarbenium) ion pair. Although this development does not dethrone ALPH, it does raise fundamental questions about its role in structure and reactivity.

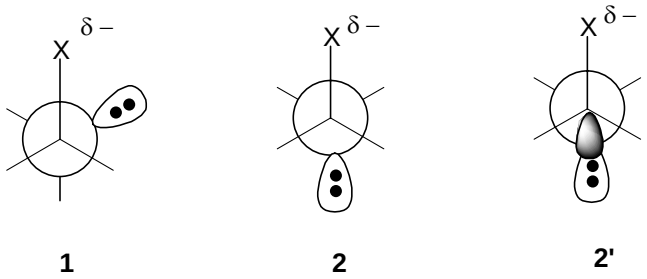
So where *does* ALPH stand today? This review attempts to answer this obviously difficult question, but in the hope that it is possible to search for the answer by disentangling the skein of claims and counter-claims that has grown over the recent decades. This paper thus charts a course away from both the proponents and the detractors of ALPH, in the belief that ALPH is

indeed supportable – but only after a dispassionate reevaluation. (That stereoelectronic theory and ALPH indeed remain in the forefront of chemical research, is indicated by the vigorous experimental and theoretical work that continues to be reported.[10])

2. Anomeric and kinetic anomeric effects: 'EGRI' and 'OI'

2.1 Anomeric effect[1,11]

The anomeric effect was originally believed to arise from the electrostatic *gauche* repulsive interaction (given the acronym 'EGRI' herein) between the heteroatom lone pair and the partial negative charge on the anomeric substituent, when these were mutually *gauche* or *synclinal* (**1,** Scheme 1). This was relieved if the substituent went into the antiperiplanar alignment **2.**



1 **2** **2'**

Scheme 1

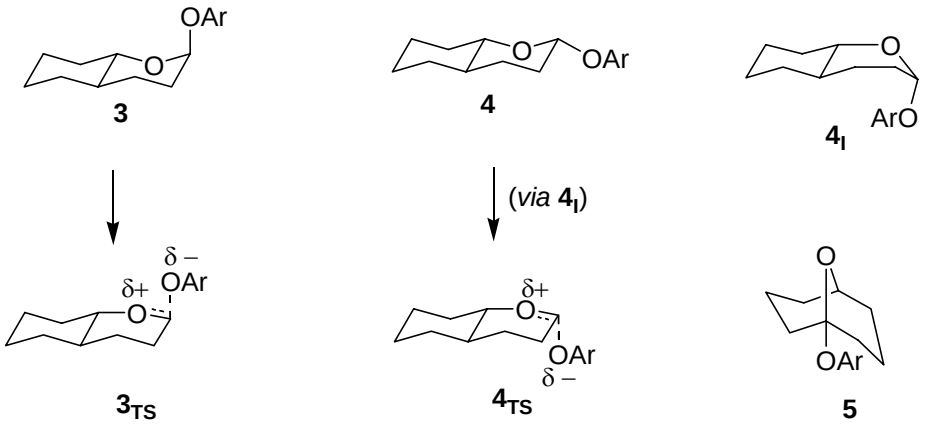
However, this explanation was gradually abandoned in favour of the more sophisticated ALPH, which proposed that **2** was stabilized by charge transfer from the heteroatom lone pair on to the antibonding orbital (σ*, shaded lobe in **2'**) of the bond between the anomeric centre and the substituent. This may be termed the orbital interaction (given the acronym 'OI' herein) model. Essentially, therefore, EGRI proposes that the *synclinal* conformer **1** is destabilized, whereas ALPH proposes that the antiperiplanar conformer **2** is stabilized (by OI). One notes – perhaps with hindsight (!) – that EGRI and OI need not be mutually exclusive, but can both operate independently. They need not be alternative formulations, and the overall anomeric effect could indeed contain both the EGRI and the OI components (however startling the dichotomy may be!).

The anomeric effect may act on the ground state, as also at the transition state of a reaction ('kinetic anomeric effect'). The ground state anomeric effect is experimentally well established, particularly by NMR spectroscopic measurements of the *α/ß* ratios in tetrahydropyranyl (THP) systems, but also X-ray diffraction studies of crystal structures.[1] The anomeric effect in these systems has been estimated to be in the range 3-10 kJ/mol for most of the common substituents.

2.2 Kinetic anomeric effect

These have been the most controversial part of ALPH, essentially because transition states are not directly observable (in contrast to ground states).[1] Thus, the kinetic anomeric effect can only be substantiated by indirect kinetic evidence. However, the problem is that molecules undergo competitive conformational transitions during the course of the reactions at the anomeric centre: thus, it is not always clear whether the ground state stereoelectronic relationships have been maintained at the transition state.

Thus, early kinetic studies on the epimeric oxadecalin models **3** and **4** (Scheme 2) led to the intriguing finding that the equatorial anomer **4** is relatively more reactive in exocyclic C-O cleavage, although it is the axial anomer **3** that possessed an antiperiplanar lone pair in the ground state (to the exocyclic C-O).[12]



Scheme 2

The simplest explanation for this result was that the stereoelectronic advantage in **3** was lost at the transition state $\mathbf{3_{TS}}$**,** which is barely distinguishable from its equatorial congener $\mathbf{4_{TS}}$**,** because of their similar half-chair conformations**.** (This is essentially the result of a 'late' transition state, in which C-O cleavage is considerably advanced.) Thus, the two transition states $\mathbf{3_{TS}}$ and $\mathbf{3_{TS}}$ are not only nearly equal in energy, but also accessed equally easily (*i.e.* without any additional barriers). Therefore, reactivity is governed largely by the ground state energy difference, and **4** – lacking anomeric stabilisation – is then the more reactive. (However, the rate ratio of **4:3** is marginal at ~3, and is reversed under acid catalysis; this has been ascribed to an earlier transition state for the acid reaction, with correspondingly greater stereoelectronic control. Note also that the relatively greater reactivity of the equatorial anomer **4** is substantiated in carbohydrate systems.[4])

In fact, the above condition that $\mathbf{3_{TS}}$ and $\mathbf{4_{TS}}$ are both equally accessible is an important one, and indicates considerable residual conformational flexibility in the corresponding model compounds **3** and **4.** In the ingeniously designed bicyclic system **5,** however, all relevant conformational flexibility has been obliterated:[13] in the oxocarbenium ion resulting from

exocyclic C-O cleavage a lone pair on the bridging oxygen atom can only be orthogonal to the cationic *p* orbital at the bridgehead. Thus, ALPH predicts that **5** would be extremely unreactive, as it indeed is. The kinetic anomeric effect was thereby estimated to be of the order of 57 kJ/mol. (Note that ALPH assumes that the anomeric effect is generally greater at a transition state than at the corresponding ground state. This is because the OI effect would increase with increasing electron demand at the anomeric site, as discussed further in **6.1:** otherwise the kinetic anomeric effect would not be observed!) An interesting challenge to ALPH was apparently encountered in the mechanism of the acid hydrolysis of the 1,3-dioxolanes (reviewed in ref. 1a, pp. 91-94). It is believed that endocyclic *C-O* cleavage in these is assisted not by an antiperiplanar lone pair but by two anticlinal ones. In this reviewer's opinion, however, the evidence is equally consistent with ALPH on the basis of a full-fledged envelope conformation for the dioxolane ring, with an oxygen atom at the 'flap': the equatorial lone pair of this atom would be antiperiplanar to the *C-O* bond involving the other (protonated) oxygen atom.

The unreactivity of **5** is reasonably convincing evidence in support of ALPH – at the very least, it proves that the partial double bond in an oxocarbenium ion is geometrically very similar to a normal alkene double bond. However, it is also true that ALPH is not clearly manifest – if at all – in many conformationally mobile systems (*e.g.* **3** and **4** above). Apparently, this raises very fundamental questions about the general validity of ALPH, particularly as it was originally proposed in the case of the highly flexible acyclic tetrahedral intermediates. (Does an effect exist when it is not manifest?)

The problem appears to be that most of the reactions that are normally studied at the anomeric centre, are much slower than the conformational changes that reorient the oxygen lone pairs ('Curtin-Hammett systems'). This gave rise to the view that ALPH – in proposing that each conformer was faithfully 'transposed' to a corresponding transition state – violated the Curtin-Hammett principle,[3,4] and that many of ALPH's problems may be traced to this conflict. It would be appropriate at this juncture, therefore, to review briefly the position of ALPH *vis-à-vis* the Curtin-Hammett principle.

3. ALPH and the Curtin-Hammett Principle

3.1 General discussion on their compatibility

The Curtin-Hammett principle (CHP) was originally formulated in terms of product ratios,[14,15] which were correlated with the difference in the free energies of the precursor transition states (when the ground state conformers are interconverting relatively rapidly). In fact, there are two alternative (but equivalent) formulations of the CHP.[15] One of these effectively states that the relative rates of passage over two transition states solely depend on the difference in their standard free energies ($\Delta G_o^{\dagger}$; eqn. 1). However, for the purposes of ALPH the alternative formulation of the CHP is apparently more meaningful (eqn. 2): this effectively states that the relative rates of passage over two transition states are determined both by the relative populations

of the ground state conformers (*K*), as also their relative reactivities (k_1/k_2). {The CHP is depicted in Figure 1, in which 'A' and 'B' refer to two conformers and 'TS_A' and 'TS_B' to the corresponding transition states. Note that 'B' is the more stable conformer in the ground state, but either 'TS_A' [case (b)] or 'TS_B' [case (a)] may be the more stable transition state. The representation is general and not restricted to the ALPH case.

$$\exp(-\Delta G_o^{\dagger}/RT) = P_1/P_2 \qquad \text{eqn. 1}$$

$$K(k_1/k_2) = P_1/P_2 \qquad \text{eqn. 2}$$

$$\exp(-\Delta G_o^{\dagger}/RT) = K(k_1/k_2) \qquad \text{eqn. 3}$$

$$k = N_1k_1 + N_2k_2 \qquad \text{eqn. 4}$$

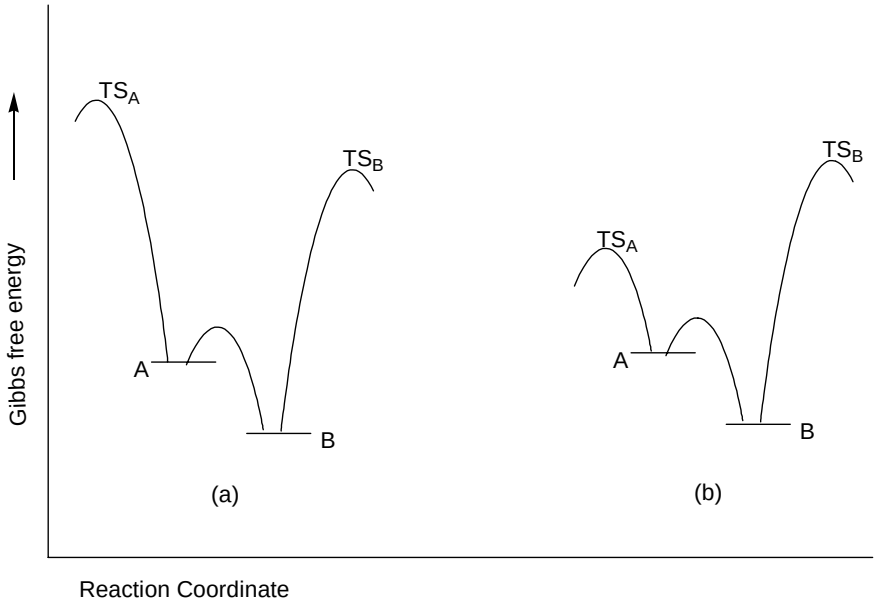
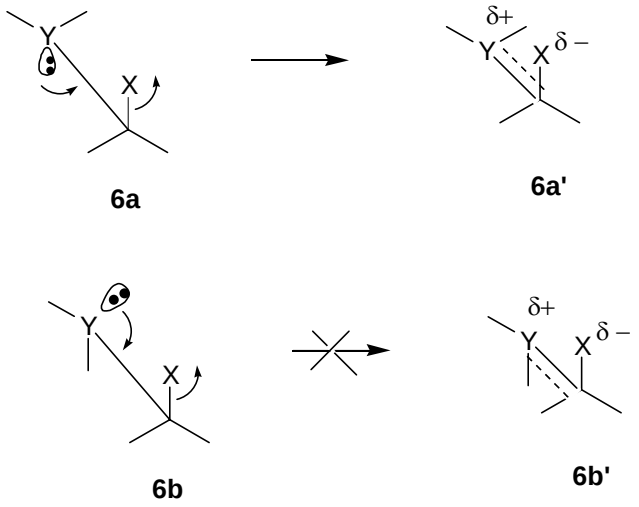


Figure 1

Thus, the relative rates of passage over the two transition states can be obtained either from the product ratios (P_1/P_2), or (alternatively) from a knowledge of the relative conformer populations (*K*) and the rate ratio (k_1/k_2). Either of these methods would enable ALPH to be tested, by leading to the key quantity $\Delta G_o^{\dagger}$ (*via* eqns. 1 and 3, the latter deriving from eqns. 1 and 2), the difference in free energy between the ALPH and anti-ALPH transition states.

The application of these principles to the case of ALPH is, therefore, of much interest. In fact, they clearly indicate that the anti-ALPH route would be (practically) forbidden, as both the ALPH-stabilized conformer **6a** and its corresponding transition state **6a'** would be preferred over the alternative forms **6b** and **6b'** (Scheme 3 and Figure 1a). Thus – in principle – there appears to be no conflict between the CHP and ALPH as originally stated.[2] (Note that these arguments assume the validity of ALPH, and only enquire whether there exists a possible conflict with the CHP.)



Scheme 3

It is also noteworthy that by the CHP, the major fraction of the overall reaction may indeed occur from the predominant conformer, particularly when this is the more reactive. Interestingly, even when this is not the more reactive, its relative preponderance may well overcome this limitation: thus, in eqn. 2, even if $k_1 < k_2$, $P_1 > P_2$ if $Kk_1 > k_2$.

In fact, the Winstein-Holness equation (eqn. 4, k is the overall rate constant and the N's are the mole fractions corresponding to k_1 and k_2),[15] offers a direct estimate of the path taken by the major fraction of the reaction. In a typical ALPH system, (say) $N_1 > N_2$ and $k_1 > k_2$. (One of the conformers would be stabilized both in the ground state and the corresponding transition state; by the CHP $K > 1$, $k_1 > k_2$ (say), so $P_1 >> P_2$.) Thus, the original formulation of the theory of stereoelectronic control is indeed in accord with the CHP.[2]

3.2 Practical limitations of CHP *vis-a-vis* ALPH

There is, however, an important practical problem that needs to be recognized. This arises from the fact that in most of the model systems for ALPH, the same final products arise from different conformers. In these cases, the relative rates of passage over the two transition states, can only be measured from a knowledge of the relative conformer populations and reactivities (K, k_1 and k_2). Thus, eqn. 2 but not eqn. 1, may be employed: note that this is generally more complicated than measuring the product ratio (P_1/P_2), as obtaining the rate constants would – in principle – depend on observing the disappearance of the conformers. However, as the equilibration of the conformers is relatively rapid, this is generally impossible. Generally, therefore, the application of the CHP to ALPH is not experimentally feasible: but most importantly, however, this does not at all mean that the two are incompatible!

These problems, in fact, can manifest both in acyclic and relatively rigid cyclic systems. In the latter, residual conformational freedom enables the systems to circumvent the stereoelectronic restrictions that were enforced in the ground state: the quintessential problem,

then, is that any conformer can 'sneak through' an alternative low energy transition state, *via* a fast (prior) conformational change in the ground state. This sometimes leads to a high energy conformer intermediate which cannot be observed, so eqns. 2 and 3 cannot be applied.

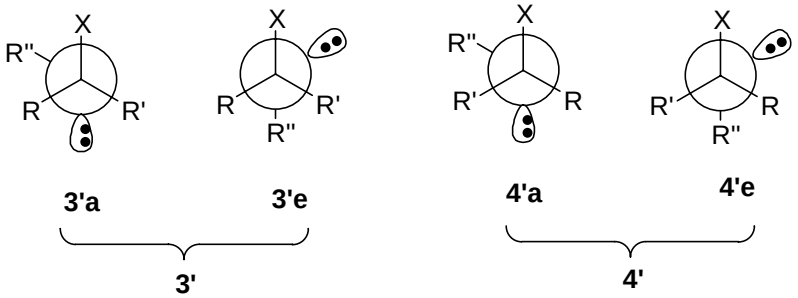
These arguments clearly apply to the oxadecalin acetals **3** and **4:** both disappear – apparently with nearly equal ease – under 'ALPH control', but with **4** after a preliminary – or concomitant – conformational change. [The preliminary conformational change implies a boat-like intermediate (**4$_I$,** Scheme 2),[12] but there is no reason why the requisite stereoelectronic changes cannot occur concomitantly with the approach to the transition state, a possibility that has been previously considered in other systems.[14]] These model systems, therefore, apparently define a grey area between a fully mobile acyclic system – to which the CHP may be applied *via* eqns. 2 and 3 – and a fully restricted system (*e.g.* **5** above[13]).

Possibly, the view that ALPH conflicts with the CHP may have arisen because of a general confusion with the CHP itself. The original formulation of the CHP had for long been misinterpreted to mean that the ground state conformational preferences are totally inconsequential, but this view was subsequently revised.[15] Thus, the key assumption of the theory of stereoelectronic control (based on ALPH)[2] – that the ground state orbital alignments are transposed to the transition state – does not (in principle) violate the CHP. (Although evidence for ALPH may be lost in many of the model systems, this does not invalidate ALPH, but only represents a limitation of the systems!)

3.3 Is ALPH generally valid and testable?

3.3.1 Configurational isomers as models of conformers: dangers of extrapolation

A possible source of confusion, however, that eventually leads to interesting semantic and didactic dilemmas, is noteworthy. This is the fact that **3** and **4** are configurational – rather than conformational – isomers. However, residual conformational mobility in **4** can circumvent the configurational barrier, to attain a similar – but not the same – *antiperiplanar* conformation as exists in **3.** Reference to the acyclic analogs **3'a, 3'e, 4'a** and **4'e** (Scheme 4, 'X´ being an electronegative group), is both interesting and instructive. Although the *synclinal* **4'e** can attain the *antiperiplanar* conformation **4'a,** this is not identical to **3'a** but a configurational isomer of it.



Scheme 4

Furthermore, let us assume that the order of ground state energies is (say) **4'a** > **4'e** > **3'e** > **3'a** (Figure 2). (Thus, the antiperiplanar conformation is the more stable isomer in the case of **3'** but the less stable isomer in the case of **4':** this is possible if the anomeric effect in **4'a** is offset by strain effects.) This then leads to the prediction (by ALPH) that **4'** would react faster than **3',** even though the *synclinal* **4'e** predominates over the *antiperiplanar* **4'a.** Note that by ALPH the (putative) transition states to which **3'e** and **4'e** are to be transformed, would be prohibitively high in energy (*cf.* Scheme 3, dotted lines). Reaction in both cases must occur *via* the *antiperiplanar* forms **3'a** and **4'a.** Furthermore, since both **4'a** and **4'e** are higher in energy than **3'a** – and assuming that the corresponding ALPH-allowed transition states are closely similar in energy (TS and TS' in Fig. 2) – **4'** would react faster than **3'.**

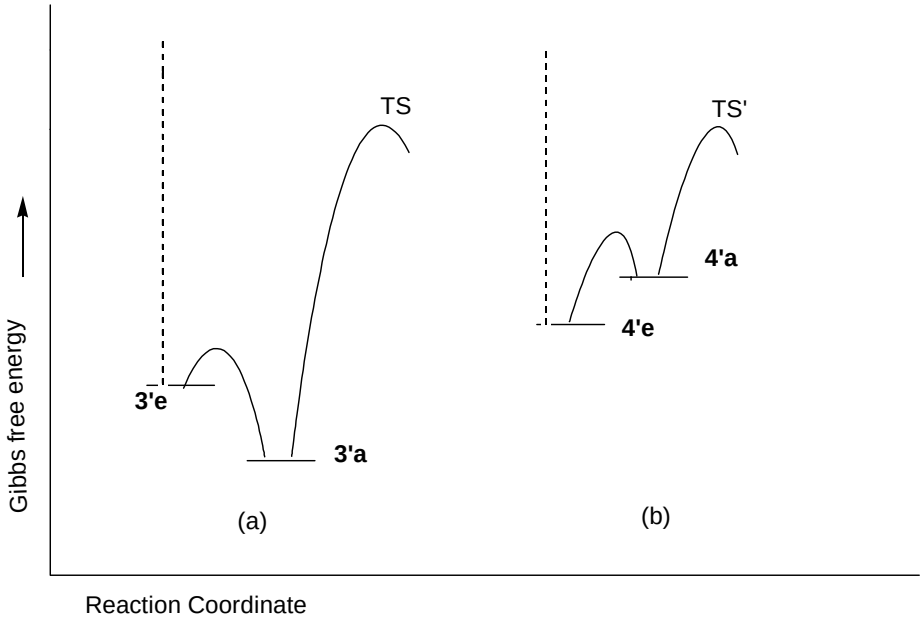


Figure 2

It is useful to compare this scheme of reactivity with that of the restricted models **3** and **4.** The conversion **4'e** → **4'a,** in fact, is analogous to the proposed[1,12] formation of a twist-boat intermediate in the case of **4.** (Scheme 2, *cf.* $\mathbf{4_I}$**.** This twist boat is a higher energy form – despite the presence of the anomeric effect – because of various types of strain, in contrast to the general acyclic case.) This demonstrates that the relatively high reactivity of the bicyclic **4** arises from a combination of its relatively high ground state energy and residual conformational flexibility, rather than representing a failure of ALPH. However, two comments on the above approach are noteworthy.

Firstly, the fact is that acyclic *synclinal* and *antiperiplanar* conformers have been modeled by the (bicyclic) configurational isomers **3** and **4** respectively. (The acyclic conformers would be of the type shown in Schemes 3 and 4; however, note that Scheme 4 shows both configurational and conformational isomerism.). The problem is that the effect of the ground state energy on the

reactivity in the case of the configurational isomers does not imply a similar effect in the case of the freely interconverting acyclic conformers: in the latter case, the relative reactivity would be governed by the CHP, with the ground state energy playing no role! This is because the ground state energy (*per se*) appears in none of the above relationships, eqns. 1-3! This is valid despite the fact that the equilibrium constant for the conformer interconversion (*K*) appears in eqn. 2. The roots of this apparent paradox lie in the fact that, in a conformationally mobile system, the higher energy conformer is also present at a correspondingly lower concentration, so that its energetic advantage is neatly cancelled out. This clearly demonstrates the dangers of extrapolating the results obtained from 'conformationally-restricted models' to the acyclic case. In fact, an interesting application of these arguments will be presented in a later section.

3.3.2 Defining ALPH: with or without a prior conformational change?

Now for the second of the above mentioned comments. A possible objection to the above explanation of the relatively higher reactivity of **4,** could be that therein the sanctity of ALPH is *presumed.* (Thus, the reactivity of **4** is explained by proposing that it can attain an ALPH-allowed transition state.) Although this may seem like sophistry, it does raise an important question about the general validity and testability of ALPH. In this reviewer's opinion, the answer to this seems to lie in the manner in which ALPH is phrased: if ALPH allows for the possibility of a prior conformational change, the above arguments would be valid and ALPH remains testable. If, however, ALPH does not allow for a prior conformational change, it would considerably circumscribe its validity and testability.

Thus, to state that the *synclinal* forms **3'e** and **4'e** should convert to the respective *antiperiplanar* forms **3'a** and **4'a** prior to reacting, leaves open the possibility that such a conversion could be thwarted in a restricted model compound, as a *de facto* test of ALPH. (This was thus achieved in the case of **5.**) However, merely to state that the *synclinal* forms **3'e** and **4'e** would not react at all – ignoring the possibility of any conformational change – would mean that ALPH is practically invalid, as the conformational change is unavoidable. (Thus, even the bicyclic **4** does react although its ground state is a *synclinal* form.)

3.3.3 What is the proper formulation of the CHP? Path-independent modes

In fact, some of these dilemmas may well originate in the manner in which the CHP is interpreted. Originally, only the thermodynamic formulation (eqn. 1) was believed to represent the CHP. It was accordingly widely believed that the ground state conformer composition was totally inconsequential. Allied to this was the (supposed) basic premise of transition state theory that the route between the reactants and the transition state was 'undefined'. Both these ideas are not *per se* incorrect, of course, but they can be misinterpreted. In the context of ALPH, apparently, the basis of the critique was that the prior conformational conversion of a *synclinal* form to the *antiperiplanar* form should not be invoked, as it was not required by the CHP.

This view apparently implies that any conformer may directly access any transition state, in the general case of a rapidly interconverting mixture of reactant conformers. (This represents a

'criss-crossing' of the potential energy surface.) Interestingly, this would not violate the conventional formulations of the CHP – eqns. 1 and 2 would still result – although the theoretical basis for this 'concomitant mechanism' is unclear.[14] (In fact, the possibility of concomitant conformational and bond changes has been discussed by Hammett, in a qualitative way.[14a]) However, in the context of ALPH the 'conventional' view, which assumes a step-wise process of conformational change (to a reactive conformer) followed by reaction, appears more reasonable.

This may be illustrated by reference to the reaction of the oxadecalin **4,** which was proposed to undergo a prior conformational change to a twist-boat form. This change brings it into a stereoelectronically-favourable position for reaction, as the (donating) oxygen lone pair is pre-aligned, and may thus assist the departure of the nucleofuge in a continuous and sustained manner. It is noteworthy that this would prevent any precipitous rise in the potential energy of the system, which may occur if the bond-breaking and the assistance are not concerted. (Strictly speaking, such paths – presumably with 'abnormal' barriers – are avoided by the concerted process.)

In the alternative 'concomitant' process, however, the conformational change effecting the requisite stereoelectronic alignment and the nucleofugic process, need to be precisely coordinated, in order to avoid the above-mentioned 'abnormal' barriers. As it stands, in fact, the CHP does not distinguish the two alternative modes. Apparently, however, the 'concomitant' mode – which is apparently a path-independent mode – makes a mockery of ALPH, as the ground state stereoelectronic alignments are not transposed to the corresponding transition states. Note also that the path-independent mode precludes the possibility of testing ALPH with the help of conformationally restricted models (*e.g.* **3**-**5**). This is because an acyclic *synclinal* form, *e.g.* **3'e** or **4'e,** may (directly, in principle) attain the ALPH-favoured transition state, whereas this is not possible in the restricted case. (Thus, the unreactivity of **5** does not prove that an acyclic *synclinal* form is also unreactive.)

3.3.4 Can ALPH be defined only at the transition state?

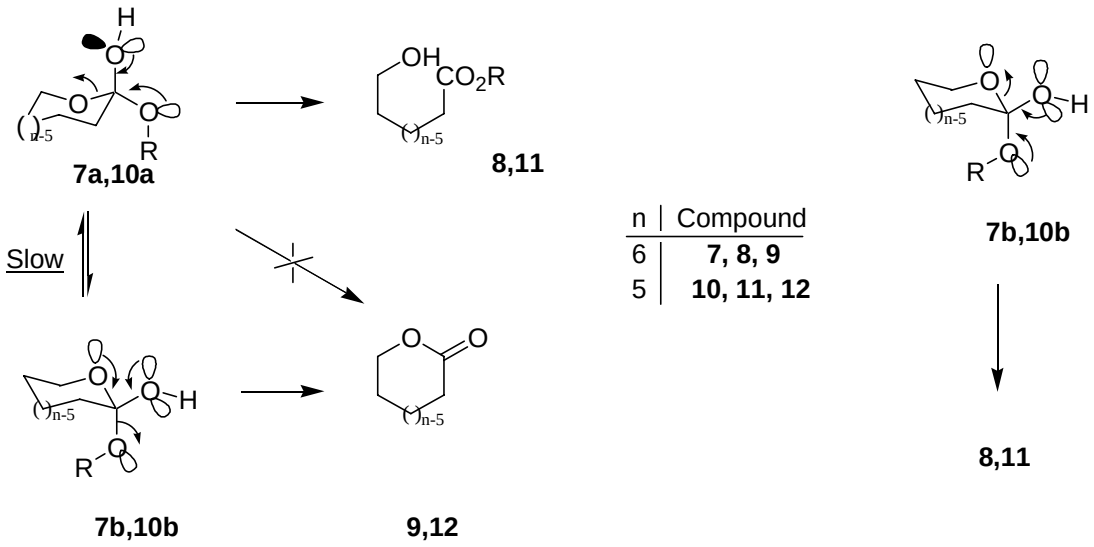
In other words, the unreactivity of restricted models such as **5** would not constitute proof of ALPH[4] – but only if ALPH is defined without the caveat of a prior conformational change. It must be noted, however, that the path-independent formulation of the CHP thus renders ALPH practically untestable, a position, it would appear – at least to the proponents of ALPH – of scientific nihilism!

It is also noteworthy, in fact, that ALPH may be reinterpreted to enable the application of the path-independent CHP (*i.e.* the concomitant reaction mode). In this case, ALPH (*i.e.* the kinetic anomeric effect) may be defined in terms of the stereoelectronic requirements of the transition state, thus abandoning the idea that the ground state alignments are transposed to the transition state. In practice, however, the problem now becomes one of designing models in which ALPH may be observed in the transition state, although the ground state is conformationally free – an apparently Herculean task!

4. Other objections to the kinetic anomeric effect

4.1 Cyclic orthoester substrates

Originally ALPH was the basis of the theory of stereoelectronic control in the breakdown of tetrahedral intermediates.[2] Evidence essentially centred around the decomposition of cyclic hemiorthoesters, themselves derived from the ozonolysis of the corresponding cyclic acetals. Thus, the six-membered orthoester **7a** produces the hydroxyester **8,** but not the corresponding lactone **9** (Scheme 5): according to ALPH, this is because the formation of **8** is stereoelectronically assisted by two neighbouring lone pairs (open lobes), whereas the formation of **9** is assisted only by one lone pair (shaded lobe). The supporting assumption here is that the conformational change of **7a** to **7b** is relatively slow (in **7b** both the above cleavages are assisted by two lone pairs, and hence are equally feasible, as shown).



Scheme 5

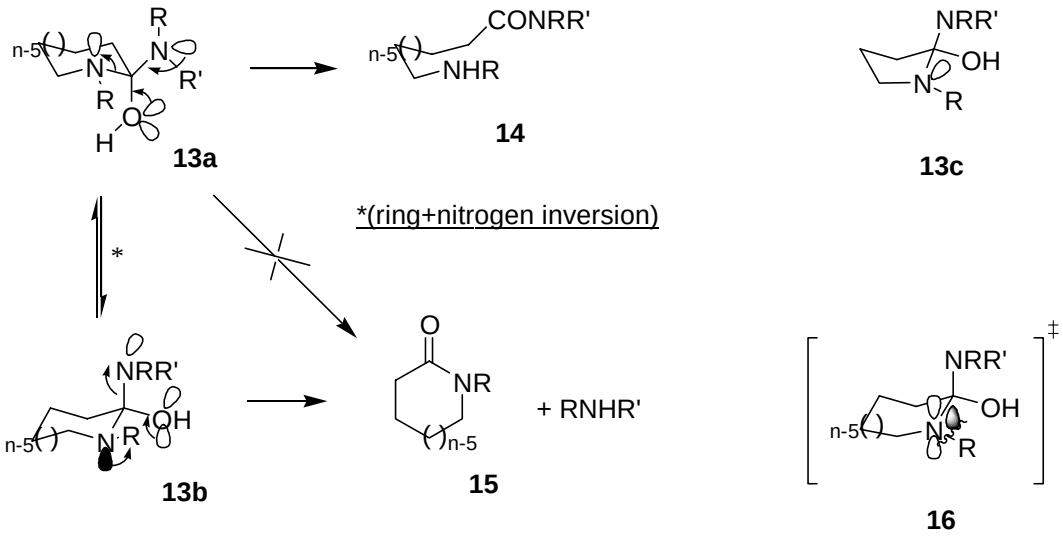
An interesting objection that has been raised to the above arguments is that, in the five-membered case (**10a**) also, only the corresponding hydroxyester **11** is produced, although the ring inversion to **10b** should be a relatively fast pseudo-rotation.[16] It was, therefore, concluded that the decompositions are controlled by product stability rather than ALPH, as the hydroxyesters **8** and **11** would be more stable than the corresponding lactones. (Apparently, this is not generally valid – δ-lactones, for instance, forming extremely readily – but is likely in the case of **11** and **12** because of strain.)

This objection to ALPH, however, is strictly not valid, for the following reasons. In the five-membered conformers **10a** and the putative **10b,** both the modes of cleavage – endocyclic in both **10a** and **10b** and (additionally) exocyclic in **10b** – are stereoelectronically equally favoured. However – and even assuming that both **10a** and **10b** are indeed present – the fact that only the

endocyclic mode occurs does not invalidate ALPH at all, as it only means that the endocyclic mode is (possibly) being additionally stabilized in some way. In fact, this additional stabilization is most likely relief of strain in the five-membered ring: the strain in a five-membered ring is worth 25 kJ/mol,[17] and the release of even half of this at the transition state would ensure the above favoured endocyclic decomposition of **10a,** in a kinetically-controlled process that would also displace the equilibrium between **10a** and **10b.** (Thus, the cleavage of **7a** may be determined by stereoelectronic considerations alone; but these are similar in **10a** and **10b,** which may indeed both cleave in the absence of an additional effect; this, however, is present in the form of strain relief upon the cleavage of **10a** to **11.**)

4.2 Cyclic amidinium substrates

The above purported invalidation of ALPH led the above workers to seek other model systems, and they report interesting results from various ingeniously-designed nitrogenous systems.[6] These generate intermediates in which alternative modes of cleavage are possible, one of which is assisted by only one (neighbouring) lone pair, and the other by two lone pairs (ALPH preferred). Thus, the basic hydrolysis of the cyclic amidinium ions **13a** (Scheme 6) was believed to offer evidence for the breakdown of ALPH, as the ALPH-predicted (**14**) and anti-ALPH (**15**) products were both produced, depending on the ring size and the conditions employed. Apparently, however, the arguments proposed are finely balanced, and depend crucially on several assumptions.

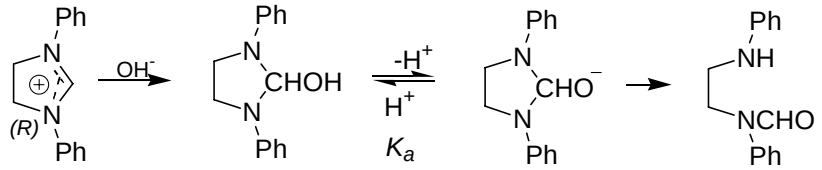


Scheme 6

The most important of these is that nitrogen inversion is relatively slow, and that the alternative form **13b** is inaccessible; (**13b** can form *via* ring inversion of **13a** followed by nitrogen inversion, and lead to the lactam **15** by ALPH). In fact, it is not inconceivable that nitrogen inversion in these systems is itself accelerated by the anomeric effect, *via* overlap of the

inverting lone pair and the antibonding σ^* orbital (shaded lobe) of the exocyclic C-N bond at the anomeric centre, as in the inversion transition state representation **16.** Also, the nitrogen inversion rates were estimated by an involved procedure,[16] and the evidence seems at best circumstantial.

In fact, the relative importance of nitrogen inversion was estimated not in the actual system studied (**13**), but from data reported for the base hydrolysis of the diphenylimidazolinium ion **17** (Scheme 7).[16] A value of 2.4×10^8 s^{-1} for the rate constant for the final breakdown of the conjugate base **19** was estimated, and this was taken to be faster than the reported rate of nitrogen inversion. However, this possibly ignores the fact that nitrogen inversion can occur also in **18** (and, by implication, the corresponding stage in the reaction of **13**). Although it is apparently assumed that the deprotonation of **18** to **19** is relatively fast, the (estimated) pK_a of 13.9 for **18** implies a substantial energy barrier for this deprotonation.



17 **18** **19**

Scheme 7

In fact, a free energy difference of ~ 95 kJ/mol between **18** and **19** – which would represent the minimum kinetic barrier – is implied: by the Eyring equation this means a maximal value of ~ 10^{-3} s^{-1} for the rate of deprotonation. This is lower than the estimated rate of cleavage of **19** by a factor of ~ 10^{11}. This may well allow for nitrogen inversion in **18** and – by implication – in **13a.** These arguments apply particularly under neutral conditions, although (admittedly) the barrier would be reduced for the base-induced deprotonation.

Most importantly, it is unclear why ALPH (apparently) breaks down only in the five- and seven-membered cases, but not in the six-membered.[6] It is, in fact, possible that stereoelectronic relationships are well-defined only in the six-membered rings. In the five-membered rings, relatively rapid pseudorotation would lead to the eclipsed conformations **13c** (Scheme 6). In these, because of electrostatic repulsion between the lone pairs on the ring and exocyclic nitrogen centres – which are mutually *syn* – the nitrogen inversion may well be accelerated.

The mechanistic analyses are generally complicated by the presence of far too many competing effects, *e.g.* conformational and lone pair inversions, basicities of leaving groups, product stabilities, position of the transition state and ring size! The authors, at one stage, propose that neighbouring *syn* lone pairs could be driving the cleavages,[6] in analogy to the case of certain acid-catalysed acetal hydrolyses.[18] There are two problems with this proposal: firstly, the relevant lone pairs in the intermediates of the above amidine reactions (*e.g.* in the putative cleavage **13a** → **15**), would be *gauche* but not *syn* to the cleaving C-N bond; and secondly, the

syn lone pair effect in acetals is believed to be a ground state one,[18] and thus cannot apply to the reactivity of intermediates. (In fact, a *gauche* (*synclinal*) lone pair offers the least assistance in the acetal case.[18]) The overall conclusions, therefore, are tinged by elements of ambiguity at various stages.

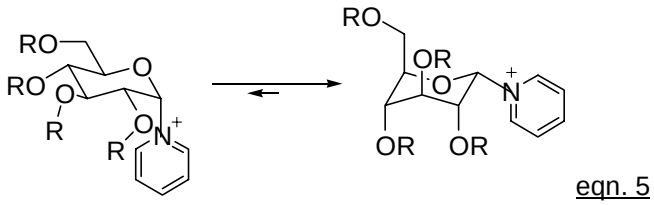
Thus, although the above investigators clearly launched an impressive mechanistic *tour de force* to settle the status of ALPH, a clear-cut conclusion was apparently elusive.[6] The extensive studies indeed generated a wealth of interesting results, but the arguments are apparently involved and – importantly – too crucially predicated on the possibility of a relatively slow nitrogen inversion. (The evidence for this is not conclusive, but the validity of ALPH is clearly supported[13] by the unreactivity of Kirby's bicyclic acetal **5.**) Thus, ALPH was seriously challenged, but not finally invalidated: Deslongchamps' notional and intuitively-reasonable proposal,[2] apparently, must remain for the present!

5. Reverse anomeric effect

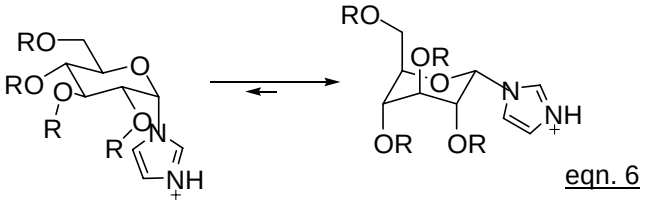
5.1 Background and general discussion

The anomeric effect places an electronegative substituent at the anomeric centre preferentially in the axial position (in THP and related systems), although this is sterically less favourable. The so-called reverse anomeric effect (RAE) is supposed to reverse this trend when the partial negative charge on the anomeric substituent is neutralized in some way.[7,8] It was first observed in the case of pyridinium (and later imidazolium) anomeric substituents in glycosyl systems.[19] The RAE can only be justified on the basis of EGRI.: it is, in fact, incomprehensible *vis-à-vis* ALPH, because OI should be enhanced in the above conjugate acid forms, *via* a lowering of the energy of the σ* orbital (LUMO) involved. [With a positively charged substituent (X^+) at the anomeric centre in a glycoside or a THP derivative, the LUMO of the C-X^+ bond would be considerably lowered by the electron withdrawal by the X^+, thus enhancing the charge transfer from the oxygen lone pair to the LUMO (the OI effect, *cf.* **2',** Scheme 1).]

As already mentioned, the RAE was originally adumbrated in certain glycosylpyridinium systems.[19] In several of these, NMR coupling constants indicated that the conformational equilibrium between the two chair forms, was decidedly weighted in favour of that form which placed the anomeric pyridinium moiety in the equatorial position (eq. 5, Scheme 8; note that all axial/equatorial positions are interconverted in this conformational equilibrium). This was confirmed in several gluco-, xylo- and arabino-pyranosyl systems,[20] and extended to glycosylimidazolium systems (eq. 6, Scheme 8).[21] However, although the experimental results were beyond doubt, a nagging problem was that the RAE could not be accommodated within the framework of ALPH.



eqn. 5



eqn. 6

Scheme 8

The RAE, however, can be justified on the basis of the older EGRI model of the anomeric effect (as mentioned above): the charge repulsion between a (partially) negatively-charged substituent (X^-) and a neighbouring *synclinal* lone pair, can be relieved if they become mutually antiperiplanar. Conversely, if the negatively-charged substituent is replaced by a positively-charged one (X^+) the above *gauche* repulsion disappears, as should the resultant antiperiplanar preference. In glycosyl and THP systems at the anomeric centre, this means a preference for the axial position for X^-, but for the equatorial position for X^+. In fact, the RAE would also relieve X^+ of the greater steric congestion it would suffer at the axial position. Thus, by the EGRI model, both electronic and steric effects would place a positively-charged anomeric substituent in the equatorial position, in glycosyl and THP systems.

Intriguingly, in fact, the strongly biased equilibria in eqns. 5 and 6 place a number of fairly bulky groups in the axial position. The resulting steric strain would be considerable, amounting to ~ 16 kJ/mol, based on reported *A* values for OAc and CH_2O substituents.[11b] This is presumably being offset by the RAE. Indeed, this does raise the possibility that the RAE is being driven by a stabilization – possibly electrostatic – of the positively charged group by a *synclinal* lone pair. This has apparently not been seriously considered. (In fact, X ray crystal structures reveal the existence of boat forms,[7] which indicates a strong drive toward the above *synclinal* disposition between the anomeric substituent and the lone pair.)

With the eclipsing of EGRI by ALPH in recent decades, however, there has been a corresponding reluctance to accept the RAE, which has been viewed with suspicion as a curious anomaly. Apparently, therefore, a vigorous experimental investigation was launched by several groups to decide the status of the RAE phenomenon. A wealth of experimental results was thus gathered, and the conclusion was reached that the RAE generally does not exist.[7,8] The experimental results leading to this conclusion are briefly reviewed now.

5.2 Recent tests of the reverse anomeric effect

The vast majority of experimental results in the carbohydrate systems, mostly based on NMR coupling constant data, indicate the existence of the RAE. There are indeed exceptions, but the overall evidence is strongly in favour of the RAE – this conclusion itself is widely accepted.[7,19-21] The few exceptions refer mostly to the case of the non-acetylated sugars in aqueous media, but these may be explained on the basis of solvation effects. Other apparent exceptions involve sulphur and phosphorus derivatives,[7] but these again possess altered steric preferences – essentially because of the relatively long C-S and C-P bonds – so their relevance is unclear. (The longer bonds would thwart both the OI and EGRI effects, so the anomeric effect itself would be weak, and the RAE difficult to define.)

Ever since the inception of the controversial RAE idea, the needle of suspicion had pointed to the possibility that steric effects – greater at the axial sites – were the basis (for the observed equatorial preferences). It was believed that a positively-charged group possessed a greater steric demand, because of the enhanced solvation (presumed) necessary to stabilize the charge.[7] It was for this reason that the glycosylimidazolium system was preferred to the glycosylpyridinium, as the imidazole is protonated – and solvated – at a remote site. Consequently, it was believed that the imidazolium moiety would possess a relatively low steric demand and thus highlight purely electronic effects. Interestingly, however, the imidazolium systems also strongly indicated the existence of the RAE.[7,21] All the same, further confirmation in other systems was deemed necessary, and several interesting studies have since been reported, although the conclusions are debatable.

Thus, an NMR study has been reported of the anomeric epimerization of glucopyranosylamines in the presence of acid.[7,22] The problem with this approach, however, is that the amine group has no anomeric effect at all,[1] so the RAE cannot be defined either. In other words, the axial/equatorial preferences in the glucopyranosylamines would reflect merely the relative steric situation, which should be similar to the cyclohexane case. It is then hardly surprising that the conclusion was reached that 'the preference for equatorial NH_2 or NHR in glucosylamines is largely due to steric bulk'! Unsurprisingly, again, the protonation of the amine resulted only in marginal changes. (In fact, a low anomeric effect was indicated for NH_2 if a corrected *A* value for a THP was employed; and interestingly, a correspondingly low RAE was also indicated upon protonation, the fraction of the axial α form decreasing perceptibly from 10% to 3.5%.)

In another NMR approach, the change in the *A* value of the imidazole moiety upon protonation, was determined in a 4-methylcyclohexyl derivative.[7,23] It was concluded that ΔA = 0.089, indicating only a marginal (albeit detectable) relative increase in the size of the imidazolium moiety. Although this (again) clearly ruled out the alternative steric explanation for the RAE observed in earlier studies, further confirmation was sought with alternative experimental methods.

Thus, a reinvestigation *via* an NMR titration method of the RAE in glucopyranosylimidazoles,[7,24] led to the conclusion that there was a small, but perceptible

anomeric effect (rather than a RAE) upon protonation. The observed enhanced axial preference of imidazolium (relative to imidazole) in these systems, corresponded to a free energy difference of 0.8-1.6 kJ/mol, depending on the solvent (D_2O, CD_3OD and DMSO-d_6). However, these findings were compared with an earlier study that had reported a significant RAE for the same system in $CDCl_3$.[21] The arguments below are noteworthy.

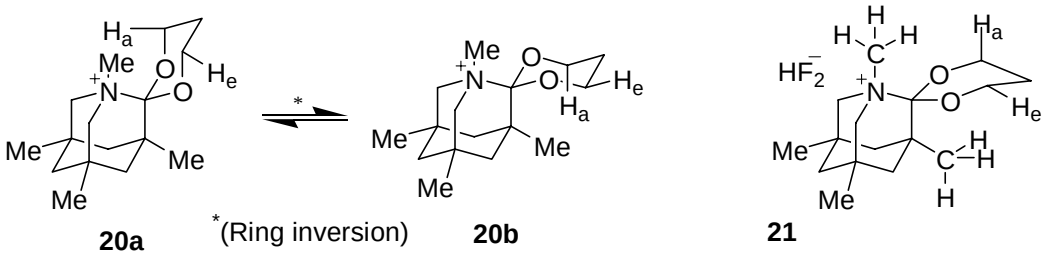
5.3 Why is the (purported) anomeric effect so weak?

Firstly, it is well known that the anomeric effect is strongly solvent dependent,[1] being often favoured in relatively non-polar media. (The anomeric equilibrium strongly favours the equatorial ß hydroxyl group in the case of glucose in water.) Therefore, cross-comparison between widely-differing solvent conditions (as above) is not meaningful. Secondly – and even more importantly – the problem, in fact, is explaining why the anomeric effect in the case of the glucosylimidazolium ion is so weak!

This conclusion may be reached by a comparison of the pK_a of imidazolium (7.03)[25a] and that of (say) phenol (9.89):[25b] the anomeric effect of the OPh group is worth 5.0 kJ/mol,[1] so that for an imidazolium ion should be at least that! This is because the anomeric effect is (roughly) inversely related to the pK_a of the anomeric substituent: although this relationship is indeed approximate, there are few instances of the anomeric effect's being substantially lower for a substituent with a lower pK_a.[1] Yet, the reported anomeric effect for imidazolium is worth ~ 1.5 kJ/mol – barely a third of that of OPh! (The above pK_a correlation is far more accurate for the kinetic anomeric effect,[1] the anomaly for the ground state anomeric effect being indeed interesting, and discussed again below.)

5.4 An interesting tricyclic model system

Relatively recently, in fact, a test of the RAE has been reported, based on the ingeniously designed rigid tricyclic system **20** (Scheme 9).[8] In this, the trialkylammonium moiety can occupy either an axial or an equatorial position in the 1,3-dioxane ring, *via* a simple conformational change between the two chair forms **20a** and **20b.** (The bulky substituents presumably slow down this change, enabling the two diastereomeric forms to be observed.) If there is a clear preference of the trialkylammonium moiety for the equatorial position (**20b**), it would be a confirmation of the RAE. (Note that steric effects in both **20a** and **20b** have been maintained reasonably constant.)



20a *(Ring inversion) **20b** **21**

Scheme 9

The X ray crystal structure of **20,** however, indicated that the dioxane moiety exists in a nearly half-chair conformation (**21**), so the expected axial-equatorial distinction at the anomeric centre is practically absent. The dioxane conformations were almost similar regardless of the counterion (I^- or HF_2^-), although the orientation of the 'flap' portion was perceptibly inverted in the two cases. Interestingly, the anomeric C-N bond was considerably lengthened (more so in the I^- case): this, and the half-chair conformation of the dioxane system, indicate the onset of C-N cleavage assisted by the oxygen lone pairs, in the classic manner so well established earlier in THP systems (by the same group).[1,26]

In $CDCl_3$ solution the proton NMR spectrum of **20,** however, apparently indicated that conformation **20a** was preferred. This conclusion was based on a nuclear Overhauser effect (NOE) study, which showed the expected signal enhancements, to indicate the proximity of the axial *OCH*$_a$ proton to the trialkylammonium methyl. (The equatorial *OCH*$_e$ proton interacted relatively weakly with a neighbouring bridgehead methyl group.) These results apparently confirmed that the trialkylammonium moiety preferred the axial position, thus ruling out the existence of a RAE. Possibly, however, similar (NOE) results may be expected assuming the half-chair conformation (**21**) also, in which the proximities of the relevant hydrogen atoms (H_a and H_e) would be similar as in **20a.** (This possibility is apparently indicated in the crystal structure also.)

It was concluded that the results could be explained on the basis of a small anomeric effect (rather than a RAE),[8] which is reminiscent of the glycosylimidazolium systems mentioned earlier.[7,24] But once again, the question that arises is the same as was raised above: why should the anomeric effect for trialkylammonium be so weak, despite its substantial acidity? (The pK_a ~ 10.5 for trialkylammonium,[27] so an anomeric effect marginally smaller relative to OPh but still substantial, is to be expected.)

6. Reassessment of the anomeric effect and the role of ALPH

6.1 Do the ground state and kinetic anomeric effects have different bases?

It would be reasonable to state that all experimental tests so far, have not succeeded in convincingly disproving the existence of the RAE. (Perhaps more ambiguity attaches to the claims of disproof than to the claims of proof!) Accordingly, it is worth assessing the consequences of accepting (or assuming) the existence of the RAE.

An intriguing explanation for the weak anomeric effect of imidazolium mentioned above, is that the expected anomeric effect (on the basis of the pK_a) is possibly offset by a RAE! This would indeed be possible if the anomeric effect were to consist of both the EGRI and OI components. In other words, only the OI component of the anomeric effect would be influenced by the electron-withdrawing power of a substituent, which in turn is related to its pK_a. The EGRI component, on the other hand, is relatively unlikely to be affected by the electron-withdrawing ability of the substituent. However, EGRI would contribute towards a RAE when this is feasible

(RAE coming into play when EGRI is removed *via* protonation, etc.): and it is indeed feasible in the case of a positively-charged substituent, *e.g.* imidazolium.

It is interesting to speculate about the relative contributions of EGRI and OI to the overall anomeric effect. Although the available data do not allow a quantitative estimate of this, it is noteworthy that early work,[11a] including theoretical studies,[28] had considered the possibility in a qualitative way. However, it is interesting to consider that EGRI, being an electrostatic phenomenon, would be relatively more sensitive to solvent effects.[28] And the fact that the anomeric effect is largely diminished in relatively polar media apparently indicates that EGRI could be the major contributor to the ground state anomeric effect.

On the other hand OI would be expected to contribute significantly when the σ* (LUMO) of the anomeric C-X bond is sufficiently lowered (*cf.* Scheme 1), as this would enhance the charge transfer from the neighbouring heteroatom lone pair. (This is based on the general premise of frontier orbital theory that the interaction of orbitals that are energetically similar is favoured.[1]) Thus, the OI would increase with increasing heterolytic cleavage of the C-X bond, reaching a maximum at the transition state. On this basis, apparently, the ground state anomeric effect would be largely determined by EGRI, whereas the kinetic anomeric effect would be largely determined by OI.

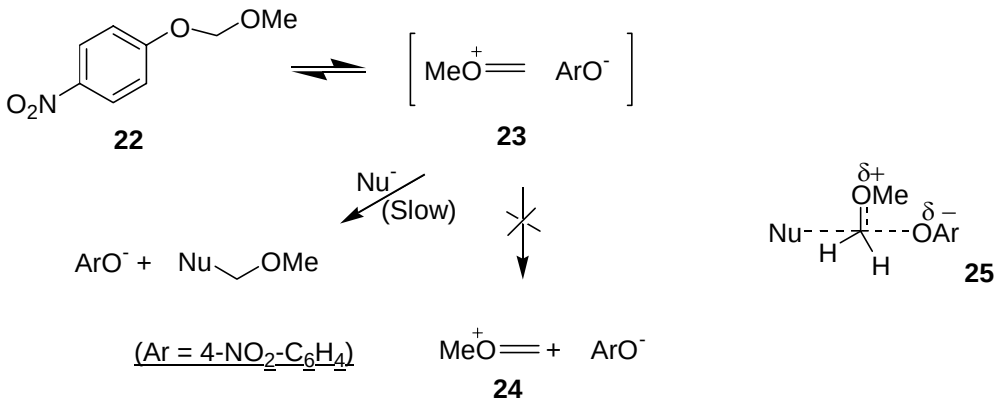
Intriguingly, there appears to be some evidence in favour of this scheme. Thus, the correlation between the anomeric effect and the pK_a of the anomeric substituent is far more accurate in the case of the kinetic anomeric effect,[1,26] as already mentioned above. This accords neatly with the proposal that OI essentially operates at the transition states of reactions, since OI correlates with the electron-withdrawal, and the pK_a is a measure of this. (Note that EGRI would be largely diminished at the transition state by the lengthening of the C-X bond, electrostatic effects falling exponentially with increasing distance.)

The above proposals, in fact, entail a fundamental revision of the current view of the anomeric effect and the role of ALPH. Essentially, the proposal is that the bases of the ground state and kinetic anomeric effects are different, the former being largely electrostatic in origin and the latter a manifestation of ALPH. (In fact, there is considerable evidence to indicate that ALPH is never fully manifested in the form of an oxocarbenium ion – in itself a fascinating development of great mechanistic significance, now briefly reviewed below.)

6.2 Intermediacy of ion pairs in glycosyl transfer – Whither ALPH?

Pioneering studies by Kirby and coworkers unearthed an intriguing phenomenon in the late 1970's.[29] This was the observation that the reaction of 1-methoxymethoxy-4-nitrobenzene (a mixed acetal of formaldehyde; **22,** Scheme 10) with nucleophiles was first order in both reactants. This clearly ruled out the intermediacy of oxocarbenium ions, which would have to be formed by a slow first-order process. This observation, in fact, is of far-reaching significance, and raises the following intriguing question: if a full-fledged oxocarbenium ion is not stable, is there a role for ALPH at all? (Note that the electron demand – and the consequent role for ALPH

– would be far less at the immediately preceding transition state than in the putative oxocarbenium ion.)



Scheme 10

The above reaction of **22** is most likely to occur *via* a (tight) ion pair intermediate (**23**), rather than by a S_N2 mechanism (either of which is compatible with the second order kinetics observed). This is because acetal cleavages are much faster than other substitutions – *e.g.* ether cleavage – and this enhanced reactivity is likely to involve the lone pair of the remaining oxygen atom in some way; on the other hand, there is apparently no reason why a simple S_N2 process should be enhanced at an acetal centre. A reasonable compromise would be the formation of a (tight) oxocarbenium ion pair intermediate in a fast pre-equilibrium, which is captured by the attacking nucleophile in an ensuing slow step.

The answer to the above question about the role of ALPH may now be attempted. It would appear that the absence of an oxocarbenium ion (**24**) in the reaction profile of **22** is due not to the ion's inherent thermodynamic instability, but to the fact that the nucleophilic capture of the ion pair (**23**) is relatively fast. In other words, the transition state for the formation of the ion from the ion pair (**23** $\rightarrow$ **24**) is much higher in energy than that for the nucleophilic capture. This itself would most likely derive from the relatively low nucleophilicity of the solvent, which would need to assist the further decomposition of the ion pair to the full-fledged ion. (This possibly would occur *via* the solvent-separated ion pair; the relatively rapid and preemptive nucleophilic capture of a tight ion pair has been considered in the generalized ion pair mechanistic scheme.[30])

6.3 Glycosidic cases and the exploded mechanism

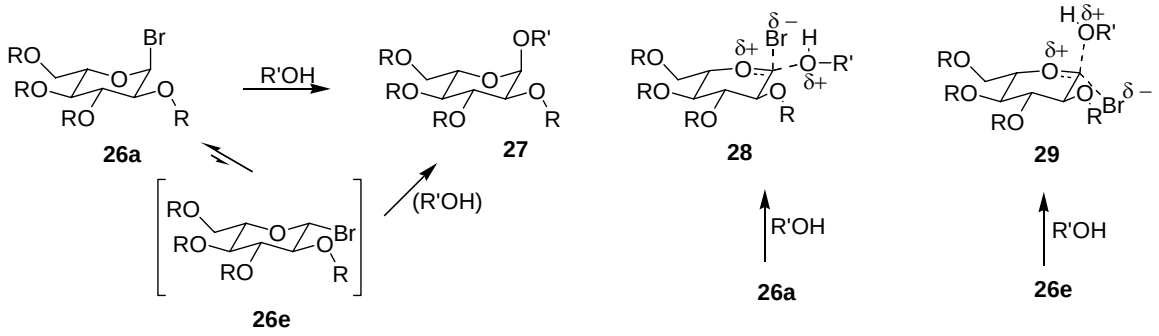
An interesting and important extension of the above observations to the glycosidic case is noteworthy.[31] It is known that glycosyl systems are far less reactive than **22** with nucleophiles: this seems to indicate that the intermediacy of oxocarbenium ions is even less likely in the glycosidic cases. Strictly, however, the relative ease of acetal cleavage should be a consequence of the relatively low free energy content of the rate-determining transition state: this is the nucleophilic attack step, which would be influenced by various effects (*e.g.* steric), apart from

the stability of the preceding ion pair. In the case of glycosyl systems, in fact, the oxocarbenium ion pair would be relatively destabilized by the presence of the electronegative oxygen substituents on the pyranose framework.[9,32] (This is evidenced by the fact that the esterification of the hydroxyl groups by an electron-withdrawing acyl group, decreases the reactivity further.[9,33])

In fact, there is some controversy as to whether an ion pair intermediate occurs at all.[31] An interesting and alternative explanation for the observed results invokes the formation of an open or 'exploded' transition state (**25**), which is somewhat like a S_N2 transition state but with substantial oxocarbenium ion character at the reaction centre. (The oxocarbenium centre in **25** is electrostatically stabilized simultaneously by both the nucleophile and the nucleofuge.) The major objection to the oxocarbenium ion pair mechanism is that it cannot apply to the case of neutral leaving groups (*e.g.* trialkylammonium): in these an ion-dipole pair may form in principle, but this would be expected readily to lead to oxocarbenium ion (not observed as discussed above), rather than recollapse to the substrate. It appears, however, that either the ion pair (**23**) or the exploded transition state (**25**) mechanism may operate, depending on the substrate and reaction conditions, as the following discussion shows. (In fact, the 'exploded mechanism' and the bimolecular nucleophilic reactions of glycosides, had been presaged in an elegant 1965 study by Lemieux and Hayami.[34])

6.4.1 Stereochemical consequences: a comprehensive mechanistic reappraisal

Interestingly – and apparently in accord with the oxocarbenium ion pair mechanism for acetal cleavages in general – it is believed that the configuration at the anomeric centre in glycosyl transfers is inverted.[9] Thus, the accepted mechanism for glycosidic transfers is essentially based on the high α selectivity observed in some typical reactions at the anomeric center, *e.g.* the alcoholysis of the bromides (Scheme 11). This has been explained as arising from the preferential reaction of the less stable – hence (apparently) more reactive – β anomer with inversion of configuration. (In the so-called *in situ* anomerisation procedure,[9,34,35] the anomeric equilibration is accelerated by added tetralkylammonium halide).



Scheme 11

However, whilst the above explanation would be valid in the case of restricted configurational isomers (*e.g.* **3** and **4**),[12] it cannot be valid in the case of freely interconverting conformers: in these, by the CHP, the less stable conformer would not necessarily be the more reactive, unless the corresponding transition state were also lower in energy (*cf.* the discussion in section **3**).

In principle, the observed stereochemical results can be explained under two categories, depending on whether the transition states for the reactions of the α and β anomers would be similar in energy or not: an interesting application of the CHP is now possible. (That the two anomeric transition states are energetically similar was assumed in the case of the reactions of the restricted models **3** and **4,** *cf.* section **2.1**).[12] In fact, if reaction were to occur with inversion of configuration in both the anomers, two different products would be produced, so eqn. 1 may be employed. However, if the transition states are similar, $\Delta G_o^{\dagger} \sim 0$ (corresponding to $P_1 \sim P_2$), so the two (inverted) products should be formed nearly equally!

In other words, the CHP leads to the intriguing result that reactions at a rapidly equilibrating anomeric centre should lead to almost equal amounts of α and β products! (The caveat is that $\Delta G_o^{\dagger} \sim 0$; the above conclusion may also be reached by applying eqns. 2 and 3: essentially, the relatively higher reactivity – deriving from a correspondingly higher ground state energy – of the β anomer, is offset by the preponderance of the α anomer.) Clearly, therefore, the basis for the observed high α selectivity in these reactions is far from simple, but an interesting possibility is as follows.

6.4.2 Do the anomers react *via* different mechanisms (inversion and retention)?

The above reasoning leads to the conclusion that reaction occurs from both the anomeric substrates (Scheme 11). This, and the fact that predominant α selectivity is observed, indicate that the two anomeric substrates cannot both be reacting by the same mechanism. It also seems likely that the α anomer could be reacting *via* the ion pair mechanism, but with predominant retention of configuration: this is because the exploded transition state model would lead to inversion of configuration (*cf.* **25**), whereas predominant α selectivity is observed in the reaction. On the other hand, the β anomeric substrate likely reacts *via* the exploded transition state mechanism with inversion of configuration to yield the α anomeric product. (As argued above, the ion pair mechanism apparently leads to predominant retention, so cannot apply to the reaction of the β anomeric substrate.)

The alternative possibility mentioned above – that the transition states are energetically different – may now be considered. There are, of course, two further possibilities: the transition state leading from the α anomer being lower (required by ALPH) or higher in energy than that leading from the β anomer. The former case clearly implies that the major fraction of the reaction occurs by the ALPH route (as the α anomer is predominant): and, again, the observed predominant α selectivity requires that retention of configuration be the predominant mode. On the other hand, if the transition state leading from the β anomer is relatively lower in energy,

inversion of configuration should be the predominant mode: this, of course, would totally invalidate ALPH!

6.4.3 The *in situ* anomerisation procedure: how does it work?

Intriguingly, in fact, the apparent success of the *in situ* anomerisation procedure (mentioned above),[9,34,35] appears to indicate that this is probably the major pathway, thus posing a major challenge to ALPH! On the other hand, the studies on the restricted models **3** and **4** (*cf.* section **2.1**)[12] demonstrate that the α anomer is nearly as reactive as the β anomer. On this basis, therefore, it seems more likely that both the α and β anomers react in parallel, *via* transition states that are closely similar in energy. Therefore, the acceleration observed in the *in situ* anomerisation procedure must have a non-stereochemical basis, possibly electrostatic assistance to the ionization by the tetraalkylammonium ion.

6.4.4 Possible reasons for the different mechanisms of the anomers

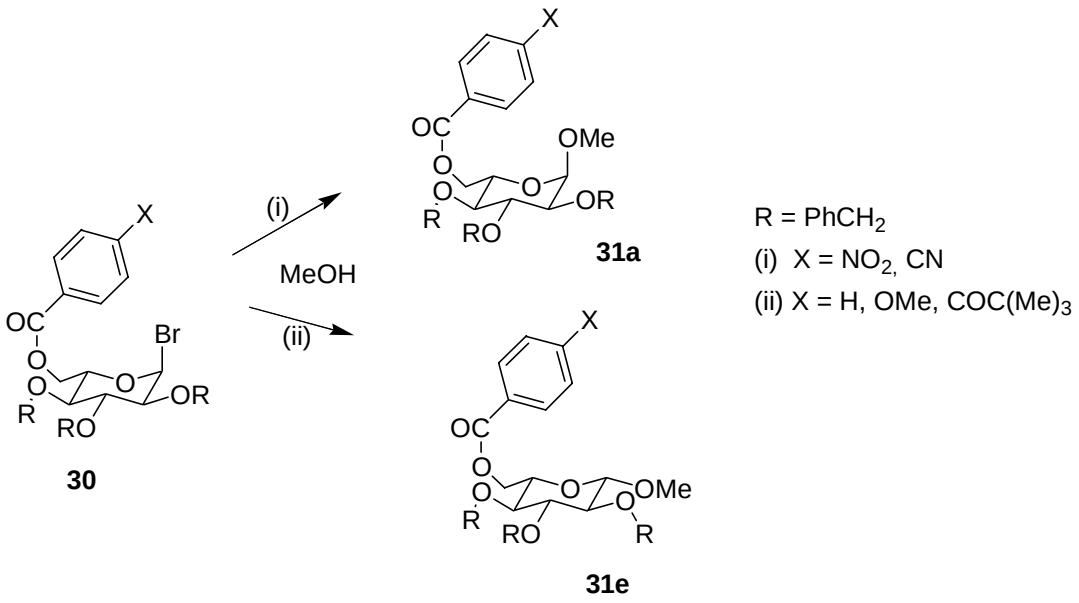
The reasons for the possibly different mechanisms of the anomeric substrates may now be considered. To begin with, it would appear that ALPH is more in accord with the oxocarbenium ion pair mechanism (*cf.* **23**) than with the exploded transition state model (*cf.* **25**): the formation of the ion pair is relatively more dependent on the stabilization by the oxygen lone pair, whereas the exploded transition state is electrostatically stabilized by both the nucleophile and the nucleofuge. On this basis, the α anomeric substrate – which is stereoelectronically pre-aligned – would react *via* the ion pair. The β anomeric substrate, however, is not stereoelectronically set up to produce the oxocarbenium ion pair, but needs the assistance of the nucleophile to ionize (at the exploded transition state).

The similar reactivities of the restricted anomers **3** and **4,**[12] apparently indicate that the above transition states for retention and inversion are energetically similar. In fact, the retentive transition state may be represented by **28,** indicating the front-side displacement of the nucleofuge by the nucleophile. Likewise, the inverting exploded transition state may be represented by **29.** The likely reason for the formation of **28** (in preference to a rear-side displacement) in the case of the α anomer, is the shielding of one face of the oxocarbenium ion moiety by the overlapping oxygen lone pair. The similar energy content of the retentive and exploded transition states (**28** and **29** respectively), is indeed intriguing, but may arise because both apparently involve the electrostatic stabilization of the oxocarbenium centre by the nucleofuge-nucleophile combination. The relative spatial orientation of these moieties is apparently of little energetic consequence, presumably because the stabilization is largely electrostatic.

It is also interesting to note that the exploded mechanism (*cf.* **25**) would be impossible at the bridgehead centre in **5,** although the (retentive) ion pair mechanism (*cf.* **23**) would still be possible in principle (*i.e.* if ALPH were to be overruled)!

6.4.5 Apparent departures

Interestingly, on the other hand,[9,33] the methanolyses of the series of glycosidic α bromides **30** (Scheme 12), display stereochemical trends that depend on the nature of the protecting acyl group at C_6. Now, high β selectivity is observed in the case of relatively electron-rich acyl groups [X = OMe or H; also the 6-*O*-pivaloyl (not shown)], whereas high α selectivity is observed in the case of electron-poor acyl groups (X = NO_2 or CN).



Scheme 12

A mechanism involving relatively rapid anomeric equilibration was proposed, but again, the stereochemical course cannot be explained on the basis of ground state effects: this would violate the CHP, analogously to the arguments proposed above. (The anomeric equilibration involves a relatively rapid epimerization, rather than a conformational inversion, but the arguments would be analogous to the CHP case.)

The reactions of **30,** in fact, possibly occur *via* an exploded transitions state (*cf.* **25** and **29**). This is because the electron-withdrawing acyl protecting group at C_6 would disfavour the formation of an oxocarbenium ion pair (*cf.* **23**). And this would also explain the predominant inversion of configuration observed (in the electron-rich cases). The reactions of the electron-poor esters, however, necessitate a considerable departure from the norm, as the observed predominant α selectivity cannot be explained on the above bases (the ion pair mechanism being even less likely in this case).

An interesting possibility is that in the electron-poor cases (**30,** X = NO_2, CN), the ground state anomeric effect is absent (to varying extents), because of the presence of a highly electron-withdrawing moiety adjacent to the anomeric oxygen atom. If so, prior equilibration – fast relative to the retarded glycosidic transfer – would lead to a predominance of the (now) more

stable β anomeric bromide (not shown); this could react *via* an exploded transition state (*cf.* **25** and **29,** *via* inversion) to afford predominant α selectivity. This assumes that the anomeric effect 'reappears' at the transition state, because of the enhanced electron demand at the anomeric centre: this is not unlikely, as the oxygen lone pair could be 'partitioned' between the inductive effect of the C_6 benzoate group and the δ+ at the anomeric centre. Note that the δ+ would be far greater at the transition state than the ground state.

Interestingly, the corresponding chloride shows high β selectivity, presumably because the anomeric equilibration is retarded by the poor nucleofugacity of chloride, reaction thus occurring from the α anomer. On the other hand, reactions with carbohydrate acceptors displayed exclusively α selectivity,[9] regardless of the protecting group at C_6. This most likely indicates a change in mechanism to the oxocarbenium ion pair pathway, because of the reduced reactivity – for both steric and electronic reasons – of the acceptors. (In any case, these and similar results cannot be explained on the basis of competitive anomeric equilibration, as it violates the CHP as discussed at length above.)

The above discussion indicates that the alternative formulations of the mechanism of glycosidic displacements – the ion pair and the exploded mechanisms – represent extreme variants, either of which may be valid under different conditions. Although much remains to be elucidated – the above discussion being speculative rather than definitive – a few general comments are noteworthy. The ion pair mechanism would appear to be favoured in the case of normal glycosyl donors and good leaving groups; when the glycosyl donor is deactivated (by the presence of electron-withdrawing groups), or if the leaving group is poor, the 'exploded mechanism' would be favoured. Good leaving groups are generally halide ions, and in these cases, the α and β anomers possibly react *via* different mechanisms, as discussed above.

6.4.6 General cases: complex synthetic reactions

Complex synthetic work,[9,35,36] however, hardly ever employs the glycosyl halides under anomeric equilibrating conditions. Generally, glycosyl donors of defined anomeric configuration are employed under controlled conditions: these involve donors such as halides, trichloacetimidates, etc., at relatively low temperatures and solvents of medium polarity. In the majority of such cases, inversion of the anomeric configuration is apparently observed. (Exceptions almost always involve neighbouring group effects, usually by 2-*O*-acyl groups leading to dioxolinium intermediates, in manno- and glucopyranosides.) It would appear, therefore, that most of these reactions occur *via* the 'exploded mechanism', rather than the ion pair mechanism, leading to the observed configurational inversion. (This is understandable, as the leaving groups are of moderate nucleofugacity and the solvent of low ionizing power.)

It is finally noteworthy, that both the ion pair and 'exploded' mechanisms indicate that ALPH is not 'taken to its logical conclusion', but is curtailed at the oxocarbenium ion pair stage. (Therefore, the kinetic anomeric effect would mediate the formation of the oxocarbenium ion pair or the exploded transition state, rather than the free ion!) As discussed above, this does not necessarily mean that the free oxocarbenium ion is unstable, but only that the preceding ion pair

reacts with nucleophiles much too rapidly, to allow the free ion to form. Whether the free ion can be formed in the absence of nucleophiles (including nucleophilic solvents) is an interesting question for further studies. Also, it is presently not clear whether dioxocarbenium and trioxocarbenium ions can exist free.[37] Although these would be relatively more stable thermodynamically, it is also likely that the nucleophilic capture of the corresponding ion pairs would be even faster than in the oxocarbenium case. If this were to be borne out experimentally, it would mean that the free oxocarbenium ion is indeed chimerical.

Conclusions

ALPH has stimulated a generation of physical organic chemists, and inspired a magnificent research effort spread over a quarter of a century (not to mention several continents).[1,2,38] Although it has remained controversial, the following conclusions are reasonably justified.

Although ALPH was poorly manifested (if at all) in several restricted model systems, it was reasonably well-established in the bicyclic system reported by Kirby and coworkers. (However, the early suspicions that ALPH conflicted with the Curtin-Hammett principle were unfounded.) Other objections to ALPH – apparently supported by impressive and extensive studies – are apparently not unambiguous. The recent claims that the reverse anomeric effect (RAE) has been disproved are also ambiguous, as the results apparently may also be interpreted to support the RAE, thus reviving the classical electrostatic model of the anomeric effect. This has fundamental implications and suggests that the bases of the ground state and kinetic anomeric effects are different. Thus, ALPH would operate predominantly at the transition state, as supported by the observed reactivity-pK_a correlations. A rigorous consideration of the reactions at anomeric centres in glycosyl systems, leads to the conclusion that the α anomers possibly react with retention of configuration whereas the β anomers react with inversion of configuration. It also appears that the oxocarbenium ion pair mechanism and the alternative 'exploded transition state' mechanism, represent extreme variants, either of which would be valid depending on the reaction conditions. Interestingly, however, the fact that the fully-fledged oxocarbenium ion has been shown not to exist, indicates that the 'ALPH effect' is never fully consummated.

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Biography

Sosale Chandrasekhar obtained B.Sc. (Hons.) (Bangalore University, 1971) and M.Sc. (I.I.T. Mumbai, 1973) in India. For Ph.D. (1977) he worked on sulphur-nitrogen heterocycles of pharmaceutical interest, with D. E. Ames at the University of London (U.K.). This was followed by postdoctoral work at the University of Cambridge with A. J. Kirby, F.R.S., where he was privileged to carry out the first experimental tests of ALPH. Further postdoctoral work notably at the Max-Planck Institut für Strahlenchemie, Mülheim-Ruhr, Germany (with M. Demuth) and Université de Montréal, Canada (with J. D. Wuest) laid the foundations of his future career. He joined the Indian Institute of Science in 1984, where he is now Professor and Chairman of the Department of Organic Chemistry. His research interests are centred around mechanistic organic chemistry, notably stereochemistry, bioorganic chemistry and synthetic methodology. His diverse interests include such topics as the mechanism of enzyme action, the origin of molecular homochirality, and the nature of olfactory chemoreception. On the fringes of philosophy, he has contributed to the controversy on the meaning and significance of the structural theory. His frequently provocative views on many of these topics are to be found in several recent papers, which may be located via the www. He lives in Bangalore, not far from the IIS campus, with his wife and two daughters.