Electrostatic interactions in cations and their importance in biology and chemistry

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Electrostatic effects exert strongly stabilizing influences on cations, in many cases controlling the conformational preferences of these cations. The lowest energy conformers are ones where the positive charge is brought closest to substituents bearing partial negative charges. These conformational biases, along with stereoelectronic effects, can control the stereoselectivity of reactions involving carbocationic intermediates.

Introduction

Attractive electrostatic interactions between oppositely charged atoms exert powerful influences on the courses of chemical reactions. These interactions are particularly important in biological systems, where electrostatic effects govern the specificity and reactivity of various processes.[1–4] For example, electrostatic effects operate at the active site of enzymes to lower activation barriers and guide protein interactions.[5–7] A detailed understanding of uncatalyzed processes in the gas phase and in solution have elucidated the factors that lower the energy barriers of the chemical reaction within an enzyme pocket.[5] Electrostatic effects also influence the efficacy of enzyme inhibitors. For example, exchange of a hydrogen atom with an electronegative fluorine on an inhibitor adds an attractive interaction with a polarized carbonyl functionality at the active site of the target enzyme.[8,9] Electrostatic attractions can also be used as a tool to confer specificity to macromolecular organization in non-biological systems.[10]

Electrostatic effects operate not only between molecules, but also within a molecule. These electrostatic effects can control both the structure and reactivity of certain systems. This account will describe examples of how intramolecular electrostatic effects control the structures and reactivities of organic molecules. An overview of our work on the stereoselective reactions of oxocarbenium ions will highlight how attractive electrostatic interactions provide a powerful new approach to controlling stereochemistry in synthetic organic chemistry.

Electrostatic effects and conformational analysis

Electrostatic effects can exert a dramatic effect on the conformational preferences of small organic molecules. For example, 4-methoxycyclohexanone favors the pseudoaxial conformation **2** in a number of solvents (eqn 1).[11,12] Similar conformational preferences are exhibited by 4-halocyclohexanones, with the fluoro derivative having the highest axial preference.[13,14] This

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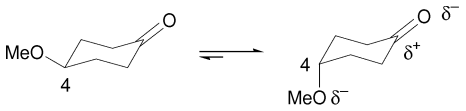
trend indicates that electrostatic forces between the partially negatively charged substituent and the partially positively charged carbonyl carbon atom are most likely the origin of the contrasteric conformational preference.[15] The stabilization provided from this interaction compensates for the steric repulsions associated with bringing the two polar groups in proximity to each other.[16,17] Other cyclic carbonyl compounds bearing heteroatom substituents also favor axial conformers.[18–23]

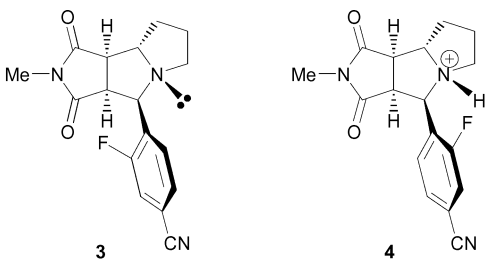


(1)

1 **2**

favored by 0.4 kcal/mol ($CDCl_3$)

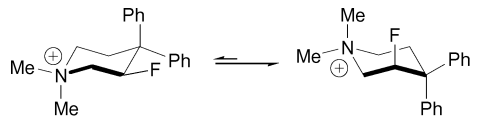
Electrostatic effects exert an even more dramatic effect on the conformational preferences of charged organic molecules. For example, the formal charge of a bicyclic nitrogen atom governs the substituent orientation of the fluorinated derivatives **3** and **4**.[24] The neutral amine **3** resides in the exo conformation, positioning the fluorine atom away from the nitrogen lone pair and alleviating unfavorable steric interactions. Upon protonation of the nitrogen atom to form ammonium ion **4**, the conformational preference changes to position the fluorine substituent in the opposite direction. This reversal in the structural stability of **4** is attributed to a favorable through-space interaction between the electronegative fluorine and the acidic hydrogen.[24]



3 **4**

exo favored by 3.4 kcal/mol *endo favored by 4.1 kcal/mol*

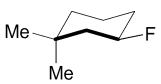
The conformational preferences of piperidinium ions are strongly influenced by electrostatic effects.[25,26] For example, investigations involving fluorine-substituted piperidinium ions[27,28] revealed an unusual affinity for the fluorine atom to reside in the axial position of the chair conformation **6**, despite the presence of destabilizing 1,3-diaxial interactions (eqn 2).[29] The preference for the axial conformer **6** results from attractive forces between the positively charged hydrogen atoms on the axial *N*-methyl group and the electronegative fluorine substituent. In the absence of a cationic center, the fluorine substituent of cyclohexane **7** weakly prefers the equatorial position.



(2)

5 **6**

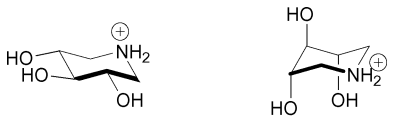
only observable conformer



7

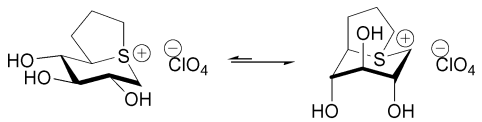
favored by 0.64 kcal/mol

The presence of oxygen-containing substituents also exerts a powerful influence on the conformational preferences of charged species. Piperidinium ions bearing substituents such as hydroxyl or acetoxy groups adopt conformations that place the partially negatively charged substituent close to the positively charged ammonium group.[25,26] This effect modifies the acidities of piperidinium ions **8** and **9** bearing hydroxyl substituents.[30,31] The pK_a values for these piperidines reflect the lower acidity of the all-axial piperidinium conformer **9** that possesses a stabilizing electronic interaction between the partial negative charge on the substituents and the formal positive charge residing on nitrogen. This interaction is not present in the all-equatorial conformer **8**. The preference of a charged species for the all-axial conformer **9** is related to the conformational preferences of hydroxylated sulfonium salts that have been employed as glycosidase inhibitors.[32–35] Although the axial conformer **11** is destabilized by numerous 1,3-diaxial interactions, this conformer is preferred both in solution and in the solid state (eqn 3).[32,33] The axial hydroxyl groups maximize the through-space electrostatic stabilization of the sulfonium ion.



8 **9**

pK_a = 7.5 pK_a = 9.5

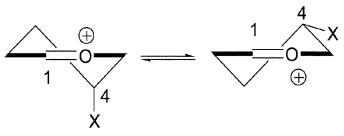


(3)

10 **11**

While the conformational analysis of stable compounds has been examined in detail, determining the conformational preferences of reactive intermediates is more challenging. For example, knowledge of the three-dimensional structures of cyclic oxocarbenium ions is important to understanding both uncatalyzed and enzymatic reactions of carbohydrates, since these reactions often involve oxocarbenium ion intermediates.[36–40] It is not possible, however, to observe oxocarbenium ions, particularly in aqueous environments, because the charged intermediates are much too reactive.[41,42]

Theoretical studies of oxocarbenium ions suggested that electrostatic effects control the conformational preferences of these reactive intermediates.[43–46] Computational studies of carbohydrate-derived oxocarbenium ions revealed that methyl substituents favor equatorial positions in oxocarbenium ions, while hydroxyl groups assume axial positions preferentially at certain positions (eqn 4).[43] These conclusions were reinforced by *ab initio* calculations (RHF/6-31G**) on C-4 alkoxy-substituted oxocarbenium ions.[46] These authors conclude that a through-space electrostatic effect,[47,48] not anchimeric assistance, stabilizes the axial conformation **12** (X = OMe) by about 4 kcal mol^{-1} relative to the equatorial conformer **13** (eqn 4).[46] It is important to note that although oxocarbenium ions are typically drawn with a formal positive charge on the oxygen atom (as shown in eqn 4), it is the carbon atom that bears positive charge, not the oxygen atom.[47,48]

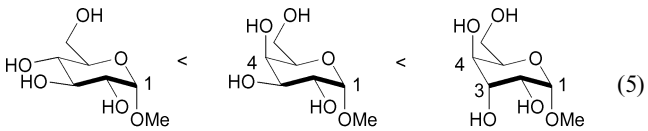


12 **13**

X = OH, $\Delta G° = +4.7$ kcal/mol
X = Me, $\Delta G° = -0.7$ kcal/mol

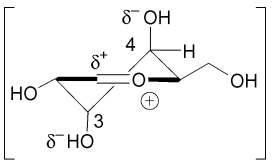
(4)

Consideration of the preferences for alkoxy groups to adopt axial conformers at certain positions, as shown in eqn 4, explains the relative rates of monosaccharide hydrolysis.[43,46] For example, the reactivity pattern exhibited by methyl pyranosides **14**–**16** showed a trend that the more axial hydroxyl groups present in the acetal, the faster the rate of hydrolysis (eqn 5).[49,50] Since the transition state structures of exocyclic C–O bond cleavage resemble the oxocarbenium ion intermediates, favorable interactions that stabilize the charged intermediates would facilitate hydrolysis.[51] The pyranoside **16** bearing axial substituents at C-3 and C-4 reacted at the highest rate *via* an oxocarbenium ion **17** stabilized by two partially negatively charged oxygen atoms positioned near the positively charged carbon atom of the oxocarbenium ion.[47,48]



14 **15** **16**

(5)

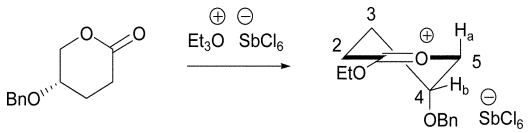


17

Investigations and applications of electrostatically stabilized intermediates

Our laboratory became interested in applying the concept of electrostatic stabilization of conformations to stereoselective bond-forming reactions. We reasoned that if electrostatic effects controlled the conformational preferences of alkoxy-substituted cations, then reactions *via* these low-energy conformers should lead to stereoselective reactions. A benefit of using electrostatic effects rather than steric effects to control conformations arises from the fact that the stereochemical controlling element, a protected hydroxyl group, would be amenable to a myriad of synthetic manipulations after the stereochemistry-determining event. Our investigations have required defining the magnitude of the conformational biases imposed by these electronic effects as well as understanding their origin. In addition, we have needed to analyze the interactions that develop in the transition states of reactions to understand the outcomes of these reactions.

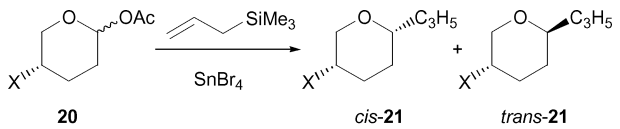
Recent studies from our laboratory provided unambiguous evidence for the preferred axial orientation of a partially negatively charged substituent in an oxygen-substituted carbocation.[52] The isolable but unstable benzyloxy-substituted cation **19** was prepared by ethylation of the corresponding lactone **18** (eqn 6).[53] Spectroscopic analysis of the dioxocarbenium ion **19** revealed that H_b exhibited a splitting pattern characteristic of an equatorial proton, suggesting that the C-4 alkoxy substituent preferred the axial position in solution (eqn 6). An X-ray crystal structure of cation **19** confirmed that the low energy ground state conformer orients the alkoxy substituents proximal to the electron-deficient carbon. The distance between C-4 oxygen substituent and the cationic carbon (3.301 Å) is consistent with a through-space Coulombic interaction, excluding stabilization from covalent bond formation between the two charged atoms.[54] We prepared the corresponding alkyl-substituted cation, which displayed the alkyl group equatorially both in solution and in the solid state.[55]



18 **19**

(6)

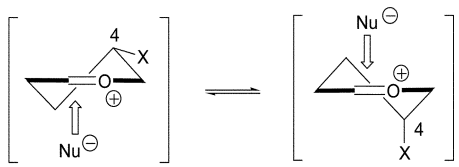
The strong preference for an alkoxy substituent to reside in an axial position (eqn 4 and 6) can be utilized to control the conformation of oxocarbenium ions, permitting the formation of carbon–carbon bonds in a contrasteric manner. Nucleophilic substitution of the acetate **20** (X = OBn) in the presence of a Lewis acid afforded the 1,4-*trans* product *trans*-**21** with high diastereoselectivity (eqn 7);[54,56] similar selectivities have been observed with vinyl oxocarbenium ions.[57,58] Control experiments indicate that these reactions proceed *via* free oxocarbenium ions and not contact ion pairs.[59] This *trans*-selective outcome can be understood by considering that the alkoxy-substituted oxocarbenium ion favors the axial conformer **23**, in accord with the structural data[52] of the dioxocarbenium ion **19** (eqn 6) as well as computational predictions (eqn 4).[43,46] Nucleophilic addition to the lower energy conformer **23** (eqn 8) through the stereoelectronically preferred chair-like transition structure[60–62] leads to the observed *trans* product. This explanation can be used to understand the reactions of related *N*-acyliminium ions.[63–65] Reaction of the corresponding alkyl-substituted acetate **20** (X = Me) in the presence of a Lewis acid afforded the 1,4-*cis* product *cis*-**21**, consistent with an equatorial preference for the substituent at C-4 (namely **22**) followed by stereoelectronically controlled nucleophilic addition.[60–62]



20 *cis*-**21** *trans*-**21**

(7)

X	*cis*-**21** : *trans*-**21**
OBn	1 : 99
Me	94 : 6



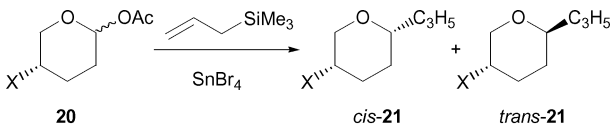
favored for X = Me *favored for X = OBn*

22 **23**

(8)

Examination of halogen-substituted C-4 analogs confirmed that stabilization of the C-1 center does not occur through anchimeric

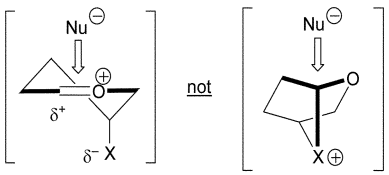
assistance, but is instead more consistent with an electrostatic effect (eqn 9). The *trans*-selectivity of substitution decreased as the halogen atom became less electronegative (F > Cl > Br > I, eqn 9). If the high *trans* selectivities were attributable to anchimeric assistance through formation of a bond as shown in **25**, the iodine substituent should lead to the highest *trans* selectivity. Instead, the iodinated acetate **20** (X = I) provided mostly the *cis* product *cis*-**21**, similar to the outcome for the alkyl-substituted substrate **20** (X = Me, eqn 7). This outcome requires the iodine to favor an equatorial position in the oxocarbenium ion. The highly selective reaction of the fluorinated substrate **20** (X = F) suggests that the conformational preference for the halogen atom is caused by electrostatic effects holding the electronegative atom closer to the oxocarbenium ion (as in **24**). The more negatively charged the halogen atom, the greater the preference for the axial conformation.



20 *cis*-**21** *trans*-**21**

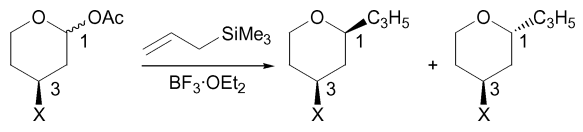
X	*cis*-**21** : *trans*-**21**
F	5 : 95
Cl	14 : 86
Br	31 : 69
I	72 : 28

(9)



24 **25**

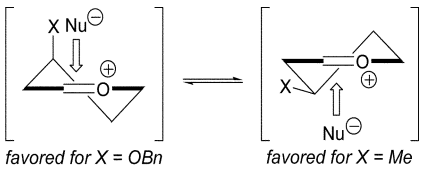
Conformational control through electrostatic stabilization is also observed with an alkoxy substituent at the C-3 position of a six-membered ring oxocarbenium ion intermediate. In contrast to the *trans* product obtained with an alkyl substituent, nucleophilic addition to **26** (X = OBn) in the presence of a Lewis acid afforded the contrasteric 1,3-*cis* product *cis*-**27** (eqn 10). The *cis* product arises from addition of the nucleophile to the psuedoaxial conformer **28**, which would be favored for X = OBn.[43] The high selectivity for the contrasteric *cis* product indicates that the electrostatic stabilization compensates for the development of steric interactions between the C-3 alkoxy substituents and the approaching nucleophile in the chair-like transition structure.[66] Without the electrostatic stabilization, substituents at the C-3 position reside in the pseudoequatorial position of the oxocarbenium ion (**29**) to give the sterically preferred 1,4-*trans* product *trans*-**27**.



26 *cis*-**27** *trans*-**27**

X	*cis*-**27** : *trans*-**27**
Me	<1 : >99
OBn	89 : 11

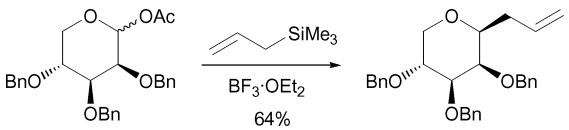
(10)



28 **29**

(11)

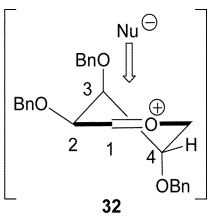
The conformational preferences exerted by a single alkoxy substituent can be manifested in systems with several alkoxy groups. In our studies of carbohydrate oxocarbenium ions that serve as models for enzyme inhibitors,[67] we treated the pentose acetal **30** with allyltrimethylsilane in the presence of a Lewis acid to provide the product **31** with high diastereoselectivity (eqn 12).[68] This stereochemical outcome can be analyzed by considering that the cation prefers the conformation **32**, where the alkoxy groups at C-2, C-3, and C-4 are all in their favored orientations.[43,54,56]



30 **31**

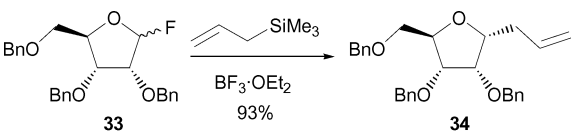
92 : 8 diastereoselectivity

(12)



32

Analyzing the reactions involving highly oxygenated five-membered ring oxocarbenium ions added another level of complexity. For example, analyzing the *C*-glycosylation reactions of ribose derivatives (eqn 13)[69] required not only understanding the conformational preferences of the intermediate carbocations but also the preferred direction of nucleophilic attack. A reliable, predictive stereochemical model would be necessary to analyze which face of the cation would be attacked. Unfortunately, few systematic studies of stereoselective reactions of five-membered ring oxocarbenium ions were available,[70–72] and it was not clear how to adapt the available models to analyze the selectivity shown in eqn 13.



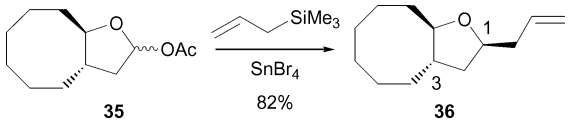
33 **34**

α-isomer only

(13)

Our studies of the reactions of five-membered ring oxocarbenium ions culminated in a stereoelectronic model to explain these processes.[73–76] This model is illustrated by analyzing the stereoselective reaction of the bicyclic lactol acetate **35** (eqn 14).[74] The intermediate oxocarbenium ion was constrained to one possible envelope conformation (as shown in **37**, eqn 15).[74] Although this system provides no impediment to approach from either inside or outside the envelope, the reaction was highly selective (eqn 14). Formation of the 1,3-*trans* diastereomer demonstrated that an inherent stereoelectronic preference directs nucleophilic addition from the inside face of the five-membered ring oxocarbenium ion

envelope structure. This preference arises from the development of destabilizing eclipsing interactions upon nucleophilic attack from outside the envelope conformation (as shown in **39**, eqn 15). Inside attack instead provides a staggered product **38**, so transition states leading to this favored product should be lower in energy.



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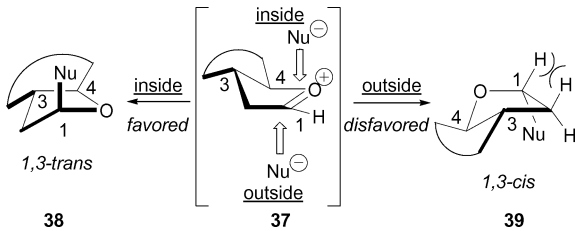
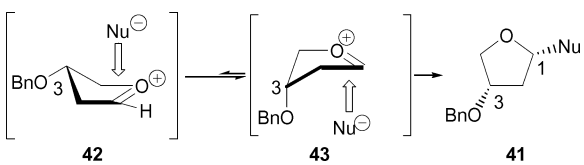


(15)

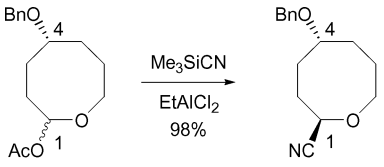
With this stereoelectronic model in hand, the reactions of alkoxy-substituted five-membered ring acetals can be understood.[76] We recently completed a detailed study analyzing the counter-intuitive α-selective *C*-glycosylation reactions of substituted five-membered ring oxocarbenium ions related to ribose and deoxyribose (eqn 13).[76] This study was achieved by preparing approximately 20 substrates with a range of substituents at different positions on the ring to establish their effects on selectivities. These experiments revealed that the reactions of furanose oxocarbenium ions are governed by the stereoelectronic effect embodied in eqn 14 along with the electronic effects established during our studies of six-membered ring oxocarbenium ions.[54,56] For example, the reaction of the 3-benzyloxy-substituted acetal **40** provided high stereoselectivity for the 1,3-*cis* product **41** (eqn 16). This result can be understood by considering that a through-space electrostatic effect stabilizes conformer **43**, and addition of the nucleophile to this conformer from the stereoelectronically preferred inside face of the oxocarbenium ion affords the observed 1,3-*cis* product **41** (eqn 17). A related analysis explains the selective reactions in the corresponding oxygen-substituted *N*-acylpyrrolidinium ion[77,78] as well as the ribose case (eqn 13).

(16)

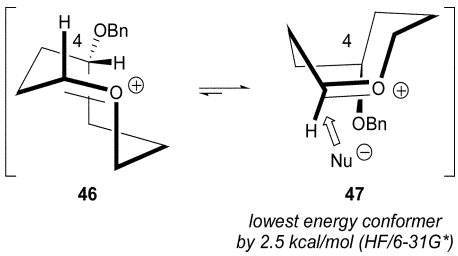


(17)

Electrostatic effects between heteroatom substituents and cationic carbon atoms are also powerful enough to control the reactions in medium-ring systems,[79] which can reside in many more conformations compared to the smaller six- and five-membered rings.[80] We prepared the eight-membered ring acetal **44** and subjected it to nucleophilic substitution according to eqn 18. The cyanohydrin product **45** was obtained with high selectivity. The stereochemistry of the product, which was proven by X-ray crystallography, is consistent with reaction through the sterically disfavored conformer **47**, which benefits from stabilizing electrostatic effects between the benzyloxy group and the carbocationic center (as determined by computational methods).[79] In contrast, the 4-methyl analogue of **44** provided a nearly 1 : 1 mixture of two diastereomeric products.



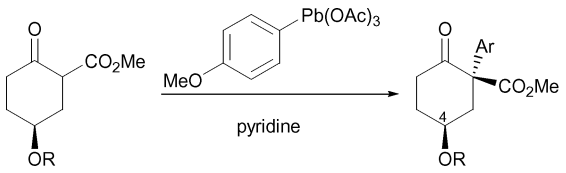
(18)



(19)

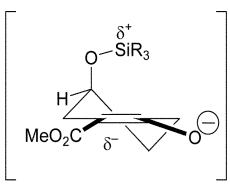
Future directions

Although numerous studies in the area of carbocationic chemistry can be considered, future studies of the application of electrostatic effects in organic synthesis could also address the reactivities of anionic intermediates. A demonstration that electrostatic effects operate in enolates was recently reported.[81] Arylation of enolates derived from β-ketoesters **48** provided products where the electrophile approached from the face opposite to the substituent at C-4, and the selectivities were highest for silyl-protected alcohols (eqn 20).[81] Computational studies suggested that electrostatic interactions between the negatively charged enolate moiety and the positively charged silicon atom stabilized conformer **50**, where the large silyl group blocked one face.



(20)

R	diastereoselectivity
Me	80 : 20
t-BuMe$_2$Si	95 : 5



Conclusions

Electrostatic effects are powerful forces that can be used to control the structures and reactivities of organic compounds. These forces play a dramatic role in biological systems, influencing the interactions between small molecules and proteins as well as the stabilities of reactive intermediates in biological processes. Our work has shown that these systems provide a potent stereochemical control element that can be used for stereoselective synthesis. In the future, additional new phenomena as well as application of these phenomena will lead to new approaches for the analysis of stereoselective reactions.

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References

1 P. H. Maccallum, R. Poet and E. J. Milner-White, *J. Mol. Biol.*, 1995, **248**, 361–373.
2 D. Morikis and J. D. Lambris, *J. Immunol.*, 2004, **172**, 7537–7547.
3 Y. L. Jiang, Y. Ichikawa, F. Song and J. T. Stivers, *Biochemistry*, 2003, **42**, 1922–1929.
4 A. R. Dinner, G. M. Blackburn and M. Karplus, *Nature*, 2001, **413**, 752–755.
5 A. Warshel, *Acc. Chem. Res.*, 1981, **14**, 284–290.
6 A. Shurki, M. Strajbl, C. N. Schutz and A. Warshel, *Methods Enzymol.*, 2004, **380**, 52–84.
7 B. Honig and A. Nicholls, *Science*, 1995, **268**, 1144–1149.
8 J. A. Olsen, D. W. Banner, P. Seiler, U. Obst Sander, A. D'Arcy, M. Stihle, K. Müller and F. Diederich, *Angew. Chem., Int. Ed.*, 2003, **42**, 2507–2511.
9 R. Paulini, K. Müller and F. Diederich, *Angew. Chem., Int. Ed.*, 2005, **44**, 1788–1805.
10 J.-P. Bourgeois, M. Fujita, M. Kawano, S. Sakamoto and K. Yamaguchi, *J. Am. Chem. Soc.*, 2003, **125**, 9260–9261.
11 R. D. Stolow and T. W. Giants, *J. Chem. Soc. D*, 1971, 528–529.
12 K. W. Baldry, M. H. Gordon, R. Hafter and M. J. T. Robinson, *Tetrahedron*, 1976, **32**, 2589–2594.
13 L. Dosen-Micovic, D. Jeremic and N. L. Allinger, *J. Am. Chem. Soc.*, 1983, **105**, 1723–1733.
14 M. P. Freitas, C. F. Tormena, P. R. Oliveira and R. Rittner, *THEOCHEM*, 2002, **589–590**, 147–151.
15 For an explanation invoking orbital effects, see: Y. Nagao and M. Goto, *Heterocycles*, 1995, **41**, 883–888.
16 E. L. Eliel and F. Alcudia, *J. Am. Chem. Soc.*, 1974, **96**, 1939–1941.
17 E. L. Eliel and H. D. Banks, *J. Am. Chem. Soc.*, 1972, **94**, 171–176.
18 J. P. Bowen and N. L. Allinger, *J. Org. Chem.*, 1987, **52**, 1830–1834.
19 Y. Nagao, M. Goto, M. Ochiai and M. Shiro, *Chem. Lett.*, 1990, 1503–1506.
20 N. Boudreault, R. G. Ball, C. Bayly, M. A. Bernstein and Y. Leblanc, *Tetrahedron*, 1994, **50**, 7947–7956.
21 Y. Morimoto and H. Shirahama, *Tetrahedron*, 1997, **53**, 2013–2024.
22 S. Brandänge, M. Färnbäck, H. Leijonmarck and A. Sundin, *J. Am. Chem. Soc.*, 2003, **125**, 11942–11955.
23 These counterintuitive conformational preferences are likely involved in the unusual stereochemical courses of reactions of alkoxy-substituted ketones: C. Cianetti, G. Di Maio, V. Pignatelli, P. Tagliatesta, E. Vecchi and E. Zeuli, *Tetrahedron*, 1983, **39**, 657–666; G. Di Maio, W. Li and E. Vecchi, *Tetrahedron*, 1985, **41**, 4891–4896; Y. Nagao, M. Goto and M. Ochiai, *Chem. Lett.*, 1990, 1507–1510; Y.-D. Wu, J. A. Tucker and K. N. Houk, *J. Am. Chem. Soc.*, 1991, **113**, 5018–5027; Z. Shi and R. J. Boyd, *J. Am. Chem. Soc.*, 1993, **115**, 9614–9619; V. K. Yadav and D. A. Jeyaraj, *J. Org. Chem.*, 1998, **63**, 3474–3477; S. Tomoda and T. Senju, *Tetrahedron*, 1999, **55**, 3871–3882; G. Di Maio, M. G. Mascia and E. Vecchi, *Tetrahedron*, 2002, **58**, 3313–3318; G. Catanoso and E. Vecchi, *Tetrahedron*, 2003, **59**, 5555–5561.
24 J. Olsen, P. Seiler, B. Wagner, H. Fischer, T. Tschopp, U. Obst-Sander, D. W. Banner, M. Kansy, K. Müller and F. Diederich, *Org. Biomol. Chem.*, 2004, **2**, 1339–1352.
25 M.-L. Stien, G. Chiurdoglu, R. Ottinger, J. Reisse and H. Christol, *Tetrahedron*, 1971, **27**, 411–423.
26 Y. Terui and K. Tori, *J. Chem. Soc., Perkin Trans. 2*, 1975, 127–133.
27 D. C. Lankin, N. S. Chandrakumar, S. N. Rao, D. P. Spangler and J. P. Snyder, *J. Am. Chem. Soc.*, 1993, **115**, 3356–3357.
28 D. C. Lankin, G. L. Grunewald, F. A. Romero, I. Y. Oren and J. P. Snyder, *Org. Lett.*, 2002, **4**, 3557–3560.
29 A. Sun, D. C. Lankin, K. Hardcastle and J. P. Snyder, *Chem.–Eur. J.*, 2005, **11**, 1579–1591.
30 H. H. Jensen, L. Lyngbye, A. Jensen and M. Bols, *Chem.–Eur. J.*, 2002, **8**, 1218–1226.
31 A. Gregersen, C. M. Pedersen, H. H. Jensen and M. Bols, *Org. Biomol. Chem.*, 2005, **3**, 1514–1519.
32 L. Svansson, B. D. Johnston, J.-H. Gu, B. Patrick and B. M. Pinto, *J. Am. Chem. Soc.*, 2000, **122**, 10769–10775.
33 M. G. Szczepina, B. D. Johnston, Y. Yuan, B. Svensson and B. M. Pinto, *J. Am. Chem. Soc.*, 2004, **126**, 12458–12469.
34 A. Siriwardena, H. Strachan, S. El-Daher, G. Way, B. Winchester, J. Glushka, K. Moremen and G.-J. Boons, *ChemBioChem*, 2005, **6**, 845–848.
35 J. Gonzalez-Outeiriño, J. Glushka, A. Siriwardena and R. J. Woods, *J. Am. Chem. Soc.*, 2004, **126**, 6866–6867.
36 D. L. Zechel and S. G. Withers, *Acc. Chem. Res.*, 2000, **33**, 11–18.
37 B. Allart, M. Gatel, D. Guillerm and G. Guillerm, *Eur. J. Biochem.*, 1998, **256**, 155–162.
38 N. S. Banait and W. P. Jencks, *J. Am. Chem. Soc.*, 1991, **113**, 7951–7958.
39 J. Zhu and A. J. Bennet, *J. Am. Chem. Soc.*, 1998, **120**, 3887–3893.
40 A. Vasella, G. J. Davies and M. Böhm, *Curr. Opin. Chem. Biol.*, 2002, **6**, 619–629.
41 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 7888–7900.
42 J. P. Richard, K. B. Williams and T. L. Amyes, *J. Am. Chem. Soc.*, 1999, **121**, 8403–8404.
43 R. J. Woods, C. W. Andrews and J. P. Bowen, *J. Am. Chem. Soc.*, 1992, **114**, 859–864.
44 T. Nukada, A. Bérces and D. M. Whitfield, *Carbohydr. Res.*, 2002, **337**, 765–774.
45 T. Nukada, A. Bérces, L. Wang, M. Z. Zgierski and D. M. Whitfield, *Carbohydr. Res.*, 2005, **340**, 841–852.
46 M. Miljkovic, D. Yeagley, P. Deslongchamps and Y. L. Dory, *J. Org. Chem.*, 1997, **62**, 7597–7604.
47 R. J. Woods, C. W. Andrews and J. P. Bowen, *J. Am. Chem. Soc.*, 1992, **114**, 850–858.
48 T. J. Dudley, I. P. Smoliakova and M. R. Hoffmann, *J. Org. Chem.*, 1999, **64**, 1247–1253.
49 C. McDonnell, O. López, P. Murphy, J. G. F. Bolaños, R. Hazell and M. Bols, *J. Am. Chem. Soc.*, 2004, **126**, 12374–12385.
50 D. Crich and N. S. Chandrasekera, *Angew. Chem., Int. Ed.*, 2004, **43**, 5386–5389.
51 H. H. Jensen and M. Bols, *Org. Lett.*, 2003, **5**, 3419–3421.
52 S. Chamberland, J. W. Ziller and K. A. Woerpel, *J. Am. Chem. Soc.*, 2005, **127**, 5322–5323.
53 K. B. Wiberg and R. F. Waldron, *J. Am. Chem. Soc.*, 1991, **113**, 7705–7709.
54 L. Ayala, C. G. Lucero, J. A. C. Romero, S. A. Tabacco and K. A. Woerpel, *J. Am. Chem. Soc.*, 2003, **125**, 15521–15528.
55 The alkoxy- and alkyl-substituted cations are topographically similar except for the orientation of the substituent.

56 J. A. C. Romero, S. A. Tabacco and K. A. Woerpel, *J. Am. Chem. Soc.*, 2000, **122**, 168–169.
57 S. Hosokawa, B. Kirschbaum and M. Isobe, *Tetrahedron Lett.*, 1998, **39**, 1917–1920.
58 M. Isobe, R. Saeeng, R. Nishizawa, M. Konobe and T. Nishikawa, *Chem. Lett.*, 1999, 467–468.
59 S. R. Shenoy and K. A. Woerpel, *Org. Lett.*, 2005, **7**, 1157–1160.
60 R. V. Stevens and A. W. M. Lee, *J. Am. Chem. Soc.*, 1979, **101**, 7032–7035.
61 R. V. Stevens, *Acc. Chem. Res.*, 1984, **17**, 289–296.
62 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon: New York, 1983, pp. 209–221.
63 T. Shono, Y. Matsumura, O. Onomura and M. Sato, *J. Org. Chem.*, 1988, **53**, 4118–4121.
64 C. Herdeis and W. Engel, *Tetrahedron: Asymmetry*, 1991, **2**, 945–948.
65 M. K. S. Vink, C. A. Schortinghuis, J. Luten, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra and F. P. J. T. Rutjes, *J. Org. Chem.*, 2002, **67**, 7869–7871.
66 K. Ohno, H. Yoshida, H. Watanabe, T. Fujita and H. Matsuura, *J. Phys. Chem.*, 1994, **98**, 6924–6930.
67 N. Asano, *Glycobiology*, 2003, **13**, 93R–104R.
68 C. G. Lucero and K. A. Woerpel, *J. Org. Chem.*, DOI: 10.1021/jo0522963.
69 Y. Araki, N. Kobayashi, Y. Ishido and J. Nagasawa, *Carbohydr.Res.*, 1987, **171**, 125–139.
70 A. Schmitt and H.-U. Reissig, *SYNLETT*, 1990, 40–42.
71 A. Schmitt and H.-U. Reissig, *Chem. Ber.*, 1995, **128**, 871–876.
72 A. Schmitt and H.-U. Reissig, *Eur. J. Org. Chem.*, 2000, 3893–3901.
73 C. H. Larsen, B. H. Ridgway, J. T. Shaw and K. A. Woerpel, *J. Am. Chem. Soc.*, 1999, **121**, 12208–12209.
74 D. M. Smith, M. B. Tran and K. A. Woerpel, *J. Am. Chem. Soc.*, 2003, **125**, 14149–14152.
75 D. M. Smith and K. A. Woerpel, *Org. Lett.*, 2004, **6**, 2063–2066.
76 C. H. Larsen, B. H. Ridgway, J. T. Shaw, D. M. Smith and K. A. Woerpel, *J. Am. Chem. Soc.*, 2005, **127**, 10879–10884.
77 P. Renaud and D. Seebach, *Helv. Chim. Acta*, 1986, **69**, 1704–1710.
78 For other examples exhibiting similar selectivities, see: M. Thaning and L.-G. Wistrand, *Acta Chem. Scand.*, 1989, **43**, 290–295; A. Boto, R. Hernández and E. Suárez, *Tetrahedron Lett.*, 2000, **41**, 2495–2498; H. Yoda, T. Egawa and K. Takabe, *Tetrahedron Lett.*, 2003, **44**, 1643–1646.
79 S. Chamberland and K. A. Woerpel, *Org. Lett.*, 2004, **6**, 4739–4741.
80 W. C. Still and I. Galynker, *Tetrahedron*, 1981, **37**, 3981–3996.
81 J. P. Konopelski, J. Lin, P. J. Wenzel, H. Deng, G. I. Elliott and B. S. Gerstenberger, *Org. Lett.*, 2002, **4**, 4121–4124.