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Note

An attempt to derive the potential function for evaluation of the energy associated with the exo-anomeric effect

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The influence of the exo-anomeric effect on the conformational preference of glycosidic linkages[1,2] is well documented by theoretical calculations for dimethoxymethane[3,4] and 2-methoxytetrahydropyran[5], as well as by a survey of the crystal structures of glycosides[6,7]. The procedure employed customarily for calculating the conformational properties of oligosaccharides consists of expressing the conformational energy as a sum of important, intramolecular energy terms. The terms usually represent contributions from non-bonded interactions, electrostatic interactions, hydrogen bonding, torsional terms, bond stretching, and valence-angle bending terms. The exo-anomeric effect has an order of magnitude comparable to those of the above contributions[5]. Therefore, a suitable and simple function to represent the intramolecular mechanism responsible for the exo-anomeric effect should be added to the potential-energy scheme. There have been several attempts in this respect[8–12]. However, since the origin of the anomeric and exo-anomeric effects involves interactions of the lone pairs of electrons on oxygen[13], the expression of conformational dependences of these interactions by a potential function is still far from being solved. An interesting approach to this problem was presented by Lemieux and co-workers. In the first version of the HSEA (hard-sphere, exo-anomeric) method[14], they added the *ab initio* potential energy for internal rotation in dimethoxymethane, derived by Jeffrey *et al.*[4], to the energy changes estimated by calculation of the non-bonded interaction term. The authors were aware that this was a crude approach and subsequently[15] they presented the exo-anomeric effect as the difference between the course of rotational energy in dimethoxymethane (calculated by the *ab initio* method[4]) and the potential of non-bonded interactions. Thus, two formulae to describe the exo-anomeric term of HSEA calculations were developed, depending on the orientation of the aglycon:

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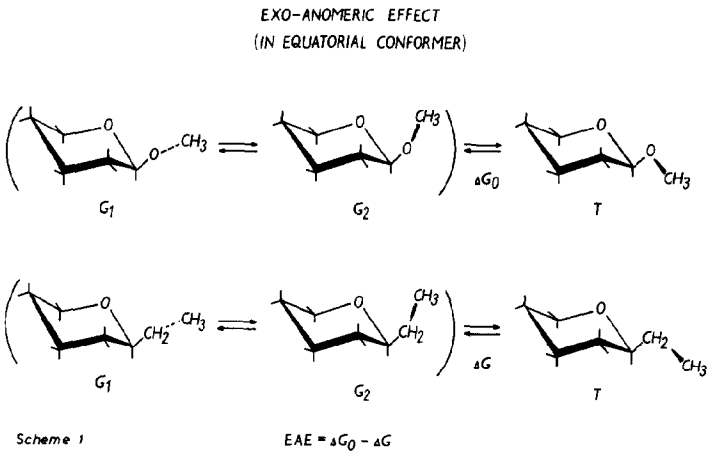
for α anomers,

$$EAE^{\alpha} = 6.61\,(1 - \cos\phi) - 3.10\,(1 - \cos 2\phi) - 2.93\,(1 - \cos 3\phi) + 7.20;$$

and, for β anomers, $EAE^{\beta} = 1.66\,EAE^{\alpha}$.

In spite of the fact that the conformations of some oligosaccharides calculated by HSEA methods are consistent with the results obtained by an n.m.r. study of these molecules[14,15], the HSEA method has shortcomings caused by the inherent properties of dimethoxymethane when used as a model of the glycosidic linkage. Most importantly, the course of rotational energy in dimethoxymethane does not correspond to the situation in glycosides[5]. For example, from the energy difference of 10.05 kJ.mol^{-1} between the *gauche-gauche* and *gauche-trans* conformers of dimethoxymethane, ~98.3% of the axial anomer of glycosides would be expected, whereas n.m.r. measurements of 2-methoxytetrahydropyran[16] gave a value of 83% for solutions in carbon tetrachloride. The exo-anomeric effect calculated in this way comprises, besides the interactions responsible for the exo-anomeric effect, contributions from torsional, potential, and electrostatic interactions that are often included in computing schemes and, therefore, such an exo-anomeric effect cannot be used in methods other than the original HSEA approach.



Scheme 1. Illustration of the proposed definition of the exo-anomeric effect on the conformations of models for β-glycosides.

We now report on functions, describing the exo-anomeric effect, derived by analogy with the anomeric effect and based on calculations of cyclic models of glycosides[5,17,18]. The magnitude of the anomeric effect is usually defined as the difference between the conformational free-energy for the axial–equatorial equilibrium of a substituted pyranoid ring (*e.g.*, 2-methoxytetrahydropyran) and the con-

formational free-energy for the corresponding equilibrium for an analogously substituted cyclohexane. The magnitude of the exo-anomeric effect can be similarly defined. Since the conformational changes around the glycosidic bond are being considered, 2-ethyltetrahydropyran is used as the reference molecule (Scheme 1). On the basis of the above definition of the exo-anomeric effect and the results of PCILO quantum-chemical calculations of the conformational properties of 2-methoxytetrahydropyran[5,17] (MTHP) and 2-ethyltetrahydropyran[18] (ETHP), expressions can be constructed for evaluation of the energy associated with the exo-around the C-C bond in ETHP (Figs. 1 and 2; curves A-ETHP and E-ETHP) from the conformational energy of the rotation around the C-O bond in MTHP (curves tions. The procedure was to subtract the conformational energy of the rotation around the C-C bond in ETHP (Figs. 1 and 2; curves A-ETHP and A-ETHP) from the conformational energy of the rotation around the C-O bond in MTHP (curves A-MTHP and E-MTHP). Calculation of the conformational energies for MTHP and ETHP were performed by the PCILO quantum-chemical method while the geometry of each conformer was optimised[5,17,18]. The resulting difference curves represent changes in energy expected to arise from the changes in exo-anomeric effect and are presented for α-glycosides in Fig. 1 (curve EAE^{α}) and for β-glycosides in Fig. 2 (curve EAE^{β}). For comparison, the curves of EAE calculated by the equations derived by Thøgersen *et al.*[15] are presented in Figs. 1 and 2. In order to take into consideration the asymmetry of EAE curves, a potential function of the type

$$EAE(\phi) = \sum_{i=1}^{3} V_i/2\,(1 - \cos i\phi) + V_4 \sin\phi + V_5 \sin 2\phi$$

was used. The five points on the EAE curve (60°, 120°, 180°, −120°, and −240°) and a reference point at 0° for both anomers (Figs. 1 and 2) were used to set up five expressions of the type mentioned above. Solution of these five simultaneous equations yielded the values of the V_j constants and gave the following expression for the exo-anomeric effect in α-glycosides,

$$EAE^{\alpha}(\phi) = -5.57(1 - \cos\phi) - 2.59(1 - \cos 2\phi) + 1.49(1 - \cos 3\phi) - \\ - 12.23\sin\phi - 3.11\sin 2\phi;$$

and, in β-glycosides,

$$EAE^{\beta}(\phi) = 0.3\,(1 - \cos\phi) - 1.54\,(1 - \cos 2\phi) + 2.40\,(1 - \cos 3\phi) - \\ - 4.01\sin\phi + 0.41\sin 2\phi.$$

These equations express a different conformational dependence of the exo-anomeric effect in α- and β-glycosides. These properties of the exo-anomeric effect are due to the different conformational dependence of the oxygen lone-pair interactions in the two anomers[13]. No simple relationship has been found between

the exo-anomeric effect in α- and β-glycosides, as has been assumed by Thøgersen *et al.*[15]. Since the above expressions of the exo-anomeric effect were obtained without any assumption about the potential function for computing the conformational energy, the proposed functions can be used as an additional term in different potential-energy schemes. For example, if the given empirical scheme includes contributions from the van der Waals (V_{NB}), hydrogen bond (V_{HB}), and torsional (V_{TORS}) terms, the conformational potential-energy of a molecule requires evaluation of these conventional contributions and a correcting term that takes into account the influence of the exo-anomeric effect EAE (EAE^{α} or EAE^{β}), and is thus written as

$$V = V_{NB} + V_{HB} + V_{TORS} + EAE.$$

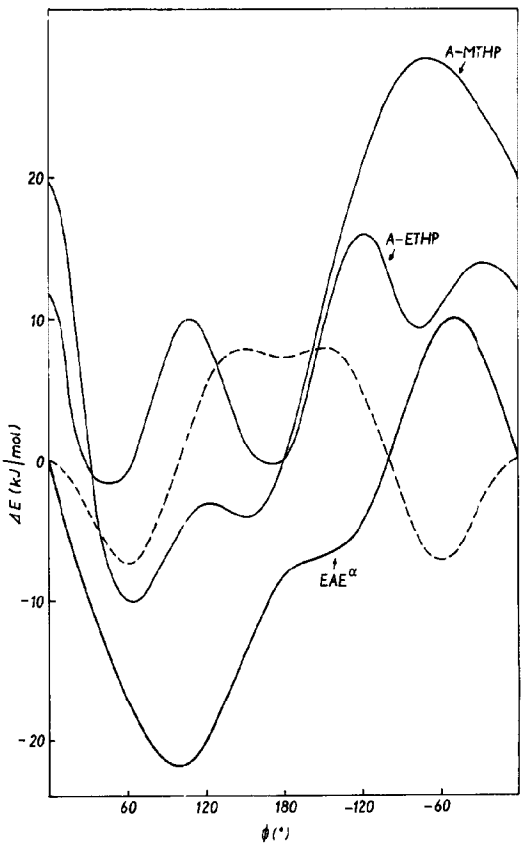


Fig. 1. Relationship between the ϕ torsion angle and the exo-anomeric effect (curve EAE^{α}) for α-glycosides determined from differences of the conformational energies of the rotation around the C-O bond in MTHP (curve A-MTHP) and the corresponding C-C bond in ETHP (curve A-ETHP). For purposes of comparison, the curve for the exo-anomeric effect used in HSEA[15] is also shown (----).

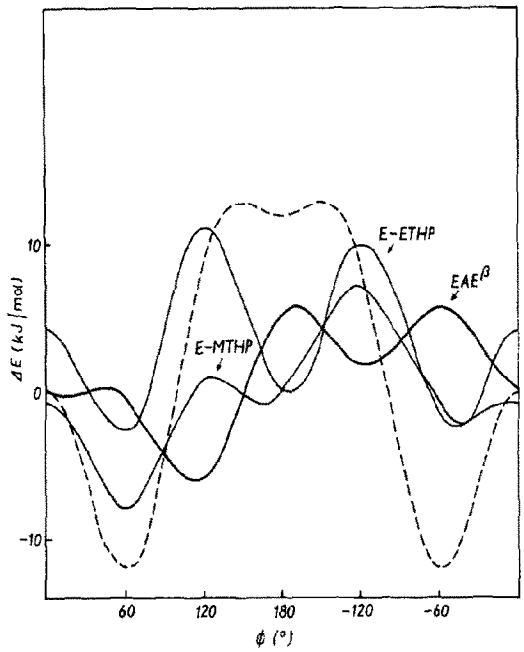


Fig. 2. As in Fig. 1, but for the β-glycosides.

However, it is worth mentioning that the expressions for the exo-anomeric effect determined by this or similar ways always take into account some effects that are not directly connected with the exo-anomeric effect. For example, our definition neglects the differences between the geometry of MTHP and ETHP molecules, but this probably does not lead to a serious inconsistency. Also, it is assumed that the PCILO method quantitatively describes the conformational properties of both molecules. The comparison of the calculated abundances for the MTHP and ETHP conformers with the experimental data[17,18] justifies this assumption. In other words, if the exo-anomeric effect is to be included correctly into calculations using potential functions, it is first necessary to know the nature of this effect and then express the conformational properties of the interactions responsible. One way of solving the problem of the exo-anomeric effect was suggested in previous papers[11–13]. Based on an investigation of the interactions of the lone pairs of electrons on oxygen in dimethoxymethane, a simple method[11] was proposed which consisted of modifying the charge distribution with respect to the presence of hybridisation dipole moments of the lone pairs. The method, when tested with dimethoxymethane[12], properly described its potential surface. The method has a further advantage in that it enables calculation of the conformational dependence of dipole moments, which is important in considering the effect of solvents on conformational equilibria. The application of this method to glycosides is now in progress in our laboratory.

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