

Application of ab Initio Molecular Orbital Calculations to the Structural Moieties of Carbohydrates. 4¹

G. A. Jeffrey* and J. H. Yates

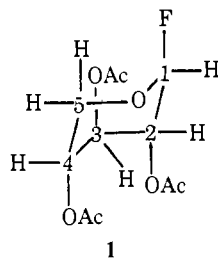
Contribution from the Department of Crystallography, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. Received June 5, 1978

Abstract: Ab initio RHF/4-31G level molecular orbital calculations have been carried out on methoxymethyl fluoride and methoxymethyl chloride as models for examining the *anomeric effect* in glycosyl halides. The calculations indicate that the sequence of anomeric energies for anomeric substitution is $F > OH > Cl > OCH_3$. The optimized bond lengths show good agreement with the limited experimental data available from X-ray crystal structure analyses, except for the C-Cl bond lengths, which are calculated about 5 pm longer than those observed. These, and previous calculations, predict that the torsional force constant for the ring O(5)-C(1) bond in pyranose, pyranosyl, or pyranoside molecules will be greater in the α -(4C_1) than in the β -(4C_1) anomers. This could account for the observation that the pyranose rings of the α anomers have a lesser range of deviations from the ideal chair conformations than do those of the β anomers.

The Anomeric Effect

The *anomeric effect* is a descriptor which has developed within the context of carbohydrate chemistry²⁻⁴ to describe the consequences of the electronic structure in the vicinity of a particular carbon atom in a pyranose or furanose sugar. This *anomeric carbon atom* is unique in these molecules in that it is bonded to *two* atoms which are more electronegative. This feature of electronic structure is of general interest, since it will occur, to a more or less degree, in all molecules where an atom is covalently bonded to two or more atoms which are to the right of it in the periodic table. In this more general context, the departure from ideal electron pair bonding⁵ is sometimes referred to as *back-bonding*. It is one of the factors responsible for the *gauche effect*.^{6,7} The magnitude of this *back-bonding* depends not only upon the atomic electronegativity differences but also upon the conformation of the -X-C-X- or -C-Y-C- bonds, relative to that of the lone-pair or vacant atomic orbitals on the X or Y atoms.⁸

It might be inferred that the greater the electronegativity difference of the heteroatoms, X or Y, from that of carbon, the larger the effect. In pyranose or furanose sugars the anomeric carbon is flanked by the ring heteroatom and the first atom of the glycosyl substituent. The most electronegative divalent atom is oxygen; the most electronegative glycosyl substituent is fluorine. Therefore, it was no accident that some of the most convincing experimental evidence leading to the recognition of the structural consequences of the *anomeric effect* was on the halogeno-1,4-dioxanes⁹ and the acetylpyranosyl halides.¹⁰ A typical example is provided by 2,3,4-tri-*O*-acetyl- β -D-xylopyranoside fluoride (**1**) and chloride, which have



been shown to exist predominantly in the all-axial 1C_4 conformation *in solution*,¹¹ despite the resulting syn-diaxial steric interactions between the acetyl groups on C(2) and C(4) and the halide and acetyl group on C(3).

A standard text⁴ on carbohydrate stereochemistry quotes that the importance of the anomeric effect in determining the configuration of reaction products follows the sequence halogen > benzyloxy > acetoxy > methoxy, etc., but does not quote

evidence relating to the sequence within the halides themselves. Recent theoretical work on fluoro- and chloromethanol using ab initio minimum basis set Hartree-Fock MO methods¹² leads to the prediction that the anomeric effect will, in fact, be greater for pyranosyl chlorides than fluorides, contrary to the conceptual view stated above.

We follow the procedure of modeling the relevant part of the carbohydrate molecules with a smaller molecule and exploring this problem using ab initio RHF/4-31G level molecular orbital calculations. As in the previous papers in this series,¹³⁻¹⁵ we test the credibility of the molecular-orbital descriptions by optimizing the bond lengths and comparing the results with those available from single crystal structure determinations.

Unfortunately, the crystal data on the glycosyl halides is not as plentiful, nor as precise, as for the simple pyranoses and methyl pyranosides discussed in the previous papers in this series.¹³⁻¹⁵ Glycosyl halides tend to be hygroscopic and are difficult to crystallize unless all the hydrogen-bonding potential of the hydroxyl groups is blocked by substitution, for example, by acetylation or benzylation. This makes the diffraction crystal structural analysis more demanding for comparable accuracy. The acetylation of the three hydroxyls in a pentopyranose sugar increases the number of structural parameters to be determined by 105 for an X-ray diffraction study (45 positional, 54 anisotropic thermal, 6 isotropic thermal), or 135 for a neutron diffraction study (45 positional and 90 anisotropic thermal). Thus, the molecule **1** is a 231-parameter X-ray diffraction problem (at least) vs. a 126-parameter problem for the unacetylated derivative. Although the number of experimental diffraction data increases, because of the reduction in the dimensions of the reciprocal lattice, the observation to parameter ratio generally deteriorates with increasing molecular weight. The experimental data on the glycosyl halides is not as definitive as we would wish, but it does permit a useful comparison with the theoretical results.

The Molecular Orbital Method

As in the previous work with methanediol,¹³ methoxymethanol,¹⁴ and dimethoxymethane,¹⁵ we have selected as small molecules as possible to be representative of the components of the carbohydrate structure that we are interested in. In this case, the molecules are methoxymethyl fluoride (CH_3OCH_2F) and methoxymethyl chloride (CH_3OCH_2Cl). The *sc* conformation, **2**, then represents an α -glycosyl halide, with ring conformation 4C_1 (or β , with 1C_4); the *ap* conformation, **3**, represents the β epimer with ring conformation 4C_1 (or α , with 1C_4).

Table I. Total and Relative Energies of Methoxymethyl Fluoride and Chloride Conformations (RHF/4-31G) in hartrees and kcal/mol, Respectively

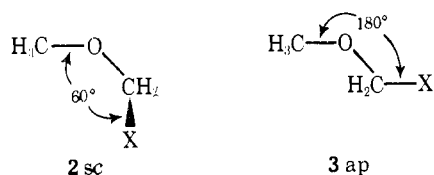
	standard bond lengths (standard C-O-C-Hal torsion angle)	standard bond lengths (minimum C-O-C-Hal torsion angle) ^a	optimized bond lengths (standard C-O-C-Hal torsion angle)	optimized bond lengths (optimized C-O-C-Hal torsion angle)
Fluorides				
sc	-252.572 208 0.0 (60°)	0.0 (67°)	-252.574 080 0.0 (60°)	-252.574 205 0.0 (64°)
ap	-252.565 326 4.3 (180°)	4.5 (180°)	-252.565 968 5.1 (180°)	-252.565 968 5.2 (180°)
Chlorides				
sc	-612.239 125 0.0 (60°)	0.0 (79°)	-612.242 274 0.0 (60°)	-612.244 362 0.0 (74°)
ap	-612.236 862 1.4 (180°)	3.7 (180°)	-612.237 685 2.9 (180°)	-612.237 685 4.2 (180°)

^a The values of the torsional angle minima and the corresponding energy value were interpolated from the three-term Fourier decomposition of the 60° energy grid, shown in Figures 1 and 2.

Table II. The Effect of Basis Set on the Difference between *Gauche,sc* and *Trans,ap* Conformational Energies for Fluoro- and Chloromethanol (in hartrees Except Where Stated)

		basis set		
		STO-3G	4-31G	6-31G
Cl-CH ₂ -O-H	sc	-567.552 025	-573.279 172	-573.864 997
	ap	-567.544 375	-573.270 569	-573.856 849
	Δ, kcal/mol	4.80	5.4	5.1
F-CH ₂ -O-H	sc	-211.004 554	-213.669 315	-213.820 389
	ap	-210.999 555	-213.599 492	-213.810 599
	Δ, kcal/mol	3.14	6.2	6.1

^a Calculated values in ref 12. Our values were calculated at the same geometry given in ref 12 except for the C-O-H angle, which we assumed to be tetrahedral and ref 12 assumed to be 105°. This accounts for the slight discrepancy. The conversion factor used in this paper is 1 hartree = 627.544 kcal/mol.



For the energy calculations we have used closed-shell Hartree-Fock theory with a 4-31G basis set.¹⁶ The calculations were carried out on a DEC KI-10, using a version of GAUSSIAN 74, which was converted from the program used on a UNIVAC 1108. The first calculations were with standard geometry: $R_{CO} = 143$ pm, $R_{CH} = 109$ pm, $R_{CF} = 136$ pm, tetrahedral valence angles with the methyl group in the staggered orientation relative to the O-C bond. For R_{C-Cl} a value of 180 pm was used; this is the average between the *short* bonds of 178 pm in chloroform¹⁷ and the *long* bonds of 182 pm in *tert*-butyl chloride.¹⁸ The C-hal bond lengths were optimized first, then the two C-O bond lengths. For the fluoride, the C-F bond length was then reoptimized, and found not to be significantly different. For the chloride, the C-Cl distance was not reoptimized. Parabolic fits were used to predict the optimum C-hal bond lengths for fixed C-O lengths. Fits to the expression $E = a(C-O)^2 + b(C-O) + c(C'-O)^2 + d(C'-O) + e(C-O)(C'-O) + f$ were used to determine the optimum C-O and C'-O bond distances by setting the two first derivatives equal to zero. (The C-H bond lengths were not varied.) The valence angles were fixed at their tetrahedral values and not optimized. The change in energy with valence angles is much smaller than the change with bond distance and should not significantly affect the optimum bond lengths; for this reason the additional computer use did not seem justifiable. Finally, the values of the CH₃-O-CH₂-X torsion angles were optimized.

In the case of the chloride, there was difficulty obtaining

initial convergence of the density matrix for the β conformer with GAUSSIAN-74. The density matrix and the energy values exhibited a nonconvergent oscillatory behavior. This was overcome by a method, well-known in crystallography,¹⁹ of damping.²⁰

We did not extend our calculations to the methoxymethyl bromide because GAUSSIAN-74 does not provide for atomic basis sets where the d orbitals are necessary.

Results

The results of the energy calculations are given in Table I. The anomeric energy is given by the difference between the *sc* and *ap* conformations for optimized bond lengths and torsion angles. The values obtained support the hypothesis that the fluoride has a greater anomeric energy than the chloride. The difference between the models for the α -fluoride (*sc*) and the β -fluoride (*ap*) is 5.2 kcal/mol, as compared with 4.2 kcal/mol for the chloride.²¹

The energies for optimized torsion angles with standard geometry for CH₃O-CH₂-OH and CH₃-O-CH₂-O-CH₃ were interpolated from a Fourier decomposition of the 60° energy grid reported previously.^{12,13} These values are 4.0 (torsion angle, 74°) and 3.1 kcal/mol (torsion angle, 76°), respectively.²² They are calculated with the same assumptions as the values in column 2 of Table I for the methoxymethyl halides. The sequence of comparable anomeric energies is therefore F (4.5) > OH (4.0) > Cl (3.7) > OCH₃ (3.1). This result is different from the conclusions obtained from *ab initio* STO-3G molecular orbital calculations of fluoromethanol and chloromethanol.¹² We therefore repeated these calculations and extended them to the 4-31G and 6-31G basis sets. The explanation of this discrepancy is apparent from the results given in Table II, showing a reversal in the difference of calculated energies in going to the more sophisticated description of the atomic orbitals.

Table III. Bond Lengths in O-Acetylated Pyranosyl Halides

compd ^d	C(1) configuration	bond distances, pm			ref
		C(5)-O(5)	O(5)-C(1)	C(1)-F	
I	α	145.0	136.2	138.9	<i>a</i>
II	β	142.8	140.6	136.9	<i>a</i>
theory	sc (α)	144.7	139.6	139.5	
	ap (β)	143.7	140.5	137.6	
(III)	axial	146.6	139.4	181.9	<i>b</i>
IV	α	145.9	141.5	182.4	<i>c</i>
V	α	144.3	136.6	185.6	<i>c</i>
VI	quasi-equatorial	145.1	138.3	185.9	<i>d</i>
(II)	equatorial	147.3	142.5	178.1	<i>b</i>
VII	β	142.6	141.5	175.5	<i>e</i>
VIII	β	143.7	133.1	178.0	<i>f</i>
theory	sc (α)	144.9	140.5	188.6	
	ap (β)	143.9	141.0	183.7	
		C(5)-O(5)	O(5)-C(1)	C(1)-Cl	
IX	α	145.8	134.7	200.2	<i>g</i>
X	α	145.9	137.1	200.3	<i>h</i>
XI	α	142	137	199	<i>i</i>

^a G. Kothe, P. Luger, and H. Paulsen, *Acta Crystallogr.*, in preparation. ^b Reference 8. ^c P. Herpin, R. Famery, J. Auge, S. David, and L. Guibe, *Acta Crystallogr., Sect. B*, 32, 209 (1976). ^d P. Luger, G. Kothe, and H. Paulsen, *Chem. Ber.*, 109, 1850 (1976). ^e G. Kothe, P. Luger, and H. Paulsen, *Carbohydr. Res.*, 37, 283 (1974). ^f J. Hjortas, private communication. ^g M. Takei, H. Watanabe, J. Hayashi, and S. Watanabe, *Bull. Fac. Eng., Hokkaido Univ.*, 99, 101 (1976). ^h P. Luger, P. L. Durette, and H. Paulsen, *Chem. Ber.*, 107, 2615 (1974). ⁱ P. W. R. Corfield, J. D. Mokren, P. L. Durette, and D. Horton, *Carbohydr. Res.*, 23, 158 (1972). ^j 1, 2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl fluoride (conformation is ¹C₄, with the C-F bond axial, i.e., α as defined in the text). II, 2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl fluoride (conformation is ⁴C₁, with C-F equatorial). III, *cis*-2,3-dichloro-1,4-dioxane, which has the C-O-C-Cl sequences with C-Cl bonds in both axial and equatorial configurations on a ²C₅ chair. Although this was an accurate analysis for its time at -140 °C, it was, nevertheless, based on two-dimensional X-ray diffraction data recorded on film. IV, 2,3,4-tri-*O*-acetyl- α -L-mannopyranosyl chloride. V, 2,3,4,5-tetra-*O*-acetyl- α -D-mannopyranosyl chloride. VI, 2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl chloride (conformation ²S₀ with the C-Cl bond quasi-equatorial). The C(5)-O(5)-C(1)-Cl torsion angle is -89°. VII, 2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl chloride, form A. VIII, 2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl chloride, form B. IX, 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide. X, 2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl bromide (conformation ¹C₄). XI, 2,3,4-tri-*O*-acetyl- β -D-arabinopyranosyl bromide (conformation ¹C₄).

The anomeric energies, given in Table I, for the isolated model molecules at rest are larger than those estimated from equilibrium compositions of aqueous solutions of pyranose sugars by factors between 2 and 5.^{4,23} This is not unexpected. There is good evidence that the effect of the anomeric energy on the epimeric equilibrium in solution is modified by solvent interactions.²⁴ The differences in the solvation energies of the two anomers is therefore an intangible quantity in this type of comparison between experimental and theoretical configurational energies.

In comparing molecular dimensions, we have on the one hand an isolated molecule at rest, on the other a molecule undergoing thermal motion within the constraints of the intermolecular forces of a crystal lattice. Again there is a gap, about which we do not have much quantitative experience. It is the success of our earlier comparisons¹³⁻¹⁵ which provides the justification for using bond length agreement as a criterion for testing the validity of the theoretical calculations. The calculated and observed bond lengths are given in Table III.

For the *pyranosyl fluorides*, the calculations predict that the anomeric configuration has the longest C(5)-O(5) and the shortest O(5)-C(1) bonds. This agrees with the experimental data from the two recent structure determinations, although the calculated difference of 5.1 pm is less than that observed, i.e., 8.8 pm. For the β configuration, the C(5)-O(5) bond length is predicted to be greater than that of O(5)-C(1) by a smaller amount, 3.2 pm, in good agreement with the 2.2 pm observed. The theory also predicts that the β C-F bond is 1.9 pm shorter than the α bond, in excellent agreement with the experimental difference of 2.0 pm.

For the *pyranosyl chlorides*, there are more experimental data, with some conflicting results. The large differences in the O(5)-C(1) bond lengths between IV and V of 4.9 pm and between VII and VIII of 8.4 pm corresponds to about five times

the estimated standard deviations, indicating that the errors in one or both of these pairs of analyses are larger than generally observed in modern high-precision work.

The calculated differences in the C-O bond lengths for the chlorides parallel those of the fluorides. Very good agreement is observed with the structure analyses of IV and VII. Further experimental data is clearly required to test the validity of the short C(1)-O(5) distances observed in V and VIII. The calculated difference in the α and β C-Cl bonds of 4.9 pm is in the direction of those observed but smaller, as with the C-F bond lengths. The calculated values of the C-Cl bond lengths are about 5 pm greater than those observed. This is a greater difference than is generally observed for calculations involving first-row elements and could be due to a deficiency in the basis set used for the chlorine atom.

We have no calculations for the bromide analogue,²⁵ but the experimental data shown in Table III are provocative. The observed C-Br bond lengths are long, as compared with 192 pm in CH₂Br₂ and 194 pm in CBr₄,²⁶ and the C-O distances show bigger differences, ~9 pm, than for the fluorides or chlorides.

The sections of the potential energy surface for internal rotation for H₃C-O-CH₂-F and H₃C-O-CH₂-Cl (with standard geometry) are shown in Figures 1 and 2, together with a three-term truncated Fourier decomposition, $V(\theta) = \frac{1}{2}V_1(1 - \cos \theta) + \frac{1}{2}V_2(1 - \cos 2\theta) + \frac{1}{2}V_3(1 - \cos 3\theta)$. These curves can be compared with those for H₃C-O-CH₂-OH and H₃C-O-CH₂-O-CH₃ given in Figures 3 and 4 as calculated from the standard geometry data given in ref 14 and 15, respectively.²⁷ The most significant differences are in the V_3 potentials. In the discussion of the methanediol molecule, this term was the major component associated with a large dipole-dipole interaction¹³ of the lone-pair electrons, as originally suggested by Edward.²⁸ Since then this concept has ap-

Table IV. Calculated Force Constants, k_θ (mdynÅ/(rad)²) for Rotation about the Central C-O Bond in H₃C-O-C-X^a

	α -(⁴ C ₁) sc	β -(⁴ C ₁) ap
CH ₃ -O-CH ₂ -F		
standard geometry, $\theta_{\min} = 67, 180^\circ$	0.16	0.06
optimized geometry, $\theta_{\min} = 64, 180^\circ$	0.18	0.04
CH ₃ -O-CH ₂ -Cl		
standard geometry, $\theta_{\min} = 79, 180^\circ$	0.25	0.09
optimized geometry, $\theta_{\min} = 74, 180^\circ$	0.24	0.05
CH ₃ -O-CH ₂ -OCH ₃		
standard geometry, $\theta_{\min} = 76, -161^\circ$	0.20	0.10
CH ₃ O-CH ₂ -OH		
standard geometry, $\theta_{\min} = 74, -178^\circ$	0.22	0.09
[CH ₃ -CH ₂ -CH ₂ -F] ^b		
standard geometry	0.15	0.14

^a For standard geometry, k_θ is calculated from $\Delta E = \frac{1}{2}k_\theta(\Delta\theta)^2$, where $\Delta\theta$ is $\pm 3^\circ$ from the minima in the truncated Fourier expansion of the potential. For the optimized geometry, k_θ is the corresponding harmonic constant calculated from a fit of the several lowest points calculated during the torsion angle optimization. ^b Calculated from the Fourier decomposition curve given in ref 28.

chloride than for the fluoride and this contributes to offset the large steric interaction and provide a minimum at close to $\theta = 60^\circ$.

In summary, the Fourier decomposition of the potential energy surfaces for rotation about the central C-O bond of the model compounds suggest that in the pyranosyl fluorides, the dipole-dipole and steric interactions almost cancel and the anomeric energy difference ($E_{\theta, \sim 70^\circ} - E_{\theta, 180^\circ}$) is determined mainly by the *back-bonding*, V_2 , potential. In the pyranoses, pyranosyl chlorides, and methyl pyranosides, the steric interactions become increasingly important, overriding any dipole-dipole effect. Were it not for corresponding increases in the back-bonding V_2 potential, the anomeric effect would not exist except in the glycosyl fluorides. In the pyranosyl bromides, we can expect a further increase in the V_1 potential. However, the experimental bond length data given in Table III suggest that this is accompanied by a comparable increase in the back-bonding V_2 component.

Torsion Angle Potentials and Pyranose Ring Conformations

The energy potential for torsional rotation about the central C-O bonds in CH₃-O-CH₂-OH, H₃C-O-CH₂-OCH₃, CH₃-O-CH₂-F, and CH₃-O-CH₂-Cl is of special interest in carbohydrate stereochemistry because it influences the rigidity of the pyranose or furanose rings. The central -O-CH₂-bonds in these molecules are analogous to the O(5)-C(1) ring bond in an aldopyranose or furanose sugar. Thus, any difference in the torsional force constant for this bond between the α and β configurations, due to the *anomeric effect*, will affect the ease with which ring conformational changes can take place.

The force constants given in Table IV were calculated by simple harmonic fits to the potential energy surface minima. The notable feature is the marked difference between the values for sc and ap conformations, the former being about 30% greater than those calculated for propyl fluoride³⁰ and the latter about 30% less.

Analysis of the detailed ring conformations of pyranose rings is complex because the six-membered chair conformation is not *flexible*.³¹ Therefore, any differences in ring torsional angles must be accompanied by energetically comparable differences in bond lengths and valence angles, and vice versa. Nevertheless, there is evidence that the differences in the torsion-angle force constants between the α and β models given in Table IV are reflected in the ring shapes of the pyranoses

Table V. Comparison of θ Puckering Parameters^a and α - β -(⁴C₁-D) Pyranosides

	α anomer	β anomer
Pyranoses		
galactose	1.9 ^b	5.2 ^c 4.8 ^{c,d}
glucose	3.6 ^c	6.9 ^f
hydrate	4.9 ^g 3.6 ^h	
urea complex	1.9 ⁱ	
Methyl Pyranosides		
arabinoide ⁴ C ₁ (L)	1.8 ^j	1.5 ^j
galactoside	4.6 ^k	6.1 ^l
glucoside	2.4 ^m	7.0 ⁿ
xyloside	3.0 ^o	8.8 ^p

^a The θ puckering parameter [D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975)] for six-membered rings is a measure of the deviation of the ideal chair. $\theta = 0^\circ$ corresponds to a perfect ⁴C₁ chair, $\theta = 90^\circ$ corresponds to a boat or twist conformation depending upon the value of the parameter, and $\theta = 180^\circ$ corresponds to a ¹C₄ chair. ^b B. Sheldrick, *Acta Crystallogr., Sect. B*, **32**, 1016 (1976). ^c J. Ohanessian and H. Gillier-Pandraud, *Acta Crystallogr., Sect. B*, **32**, 2810 (1976). ^d F. Longchambon, J. Ohanessian, D. Avenel, and A. Neuman, *ibid.*, **31**, 2623 (1975). ^e G. M. Brown and H. A. Levy, *Science*, **147**, 1038 (1965). ^f S. S. C. Chu and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, **24**, 830 (1968). ^g R. C. G. Killean, W. G. Ferrier, and D. W. Young, *Acta Crystallogr.*, **15**, 911 (1962). ^h E. Hough, S. Neidle, D. Rogers, and P. G. H. Troughton, *Acta Crystallogr., Sect. B*, **29**, 365 (1973). ⁱ R. L. Snyder and R. D. Rosenstein, *ibid.*, **27**, 1969 (1971). ^j Shozo Takagi and G. A. Jeffrey, *ibid.*, **34**, 1591 (1978). ^k B. M. Gatehouse and B. J. Poppleton, *ibid.*, **27**, 654 (1971). ^l B. Sheldrick, *ibid.*, **33**, 3003 (1977). ^m H. M. Berman and S. H. Kim, *ibid.*, **24**, 897 (1968). ⁿ G. A. Jeffrey and Shozo Takagi, *ibid.*, **33**, 738 (1977). ^o Shozo Takagi and G. A. Jeffrey, *ibid.*, **34**, 3104 (1978). ^p Shozo Takagi and G. A. Jeffrey, *ibid.*, **33**, 3033 (1977).

and methyl pyranosides as they are observed in the crystalline state.

It can be inferred, therefore, that the anomeric effect will give rise to a greater rigidity in the pyranose ring of the α -(⁴C₁) anomer relative to that of the corresponding β -(⁴C₁) compound. The experimental observations shown in Table V support this view. The range of distortion from the ideal ⁴C₁ chair conformations, as measured by the parameter θ , is almost twice as large for the β anomers than for the α molecules. No comparable data are available for corresponding α and β pyranosyl halides. The data relating to furanose rings will be discussed elsewhere.

Acknowledgments. This work is supported by NIH Grant GM-24526. The authors are grateful to Professor J. A. Pople for advice on the use of his methodology and to Mr. J. S. Binkley for assistance in transferring GAUSSIAN-74 from a UNIVAC 1108 to a DEC KI-10, and for carrying out the 6-31G calculations on chloromethanol referred to in Table II using an unpublished chlorine basis set.

References and Notes

- For parts 1, 2, and 3 of this series, see ref 13, 14, and 15.
- R. U. Lemieux and N. J. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, No. 31N. See P. de Mayo, Ed., "Molecular Rearrangements", Part 2, Wiley-Interscience, New York, N.Y., 1964, Chapter 12.
- E. L. Eliel, N. L. Allinger, S. J. Angyal, and C. A. Morrison, "Conformational Analysis", Wiley-Interscience, New York, N.Y., 1965, Chapter 6.
- J. F. Stoddart in "Stereochemistry of Carbohydrates", Wiley-Interscience, New York, N.Y., 1971, Chapter 3.
- C. Altona, Ph.D. Thesis, University of Leiden, The Netherlands, 1964.
- S. Wolfe, A. Rauk, L. M. Tel, and J. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971).
- S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972).
- The first observations that bond distances in C-O-C-X systems varied with configuration were made by (a) C. Altona and C. Romers, *Acta Crystallogr.*, **16**, 1225 (1963); (b) M. Sundaralingam, *J. Am. Chem. Soc.*, **87**, 599 (1965);

- (c) H. M. Berman, S. S. C. Chu, and G. A. Jeffrey, *Science*, **157**, 1576 (1967).
- (9) C. Romers, C. Altona, N. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969).
- (10) D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965).
- (11) C. V. Holland, D. Horton, and J. S. Jewell, *J. Org. Chem.*, **32**, 1818 (1967).
- (12) S. Wolfe, M.-H. Whangbo, and D. J. Mitchell, *Carbohydr. Res.*, in press; private communication.
- (13) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, **25**, 117 (1972).
- (14) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, **38**, 81 (1974).
- (15) G. A. Jeffrey, J. A. Pople, J. S. Binkley, and S. Vishveshwara, *J. Am. Chem. Soc.*, **100**, 373 (1978).
- (16) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).
- (17) C. C. Costain, *J. Chem. Phys.*, **29**, 864 (1958).
- (18) R. L. Hilderbrandt and J. D. Wieser, *J. Chem. Phys.*, **55**, 4648 (1971).
- (19) J. S. Rollett, "Computing Methods in Crystallography", Pergamon Press, Elmsford, N.Y., 1965, p 55.
- (20) Convergence for the β -Cl model conformer was obtained by constructing, at each cycle, not an extrapolated density matrix, but one representing 0.7 of the previous density matrix and 0.3 of the current density matrix. This is equivalent to applying a damping factor to the change in each array element of 0.3.
- (21) This anomeric energy may be an overestimate for the glycosyl chlorides, since it assumes that the $\text{CH}_3\text{-O-CH}_2\text{-Cl}$ torsion angle is unrestricted and can have the optimum value of 74° . In a pyranose ring, this angle is constrained by the ring closure to be closer to 60° ; in the two α glycosyl chlorides for which experimental data are available (see Table III), the $\text{C}(5)\text{-O}(5)\text{-C}(1)\text{-Cl}$ torsion angles are 68 and 72° .
- (22) These values represent energy differences between the actual minima and are a refinement of those reported previously (ref 14 and 15), where the standard torsion angles of 60 and 180° gave energy differences of 3.0 and 2.4 kcal/mol for $\text{CH}_3\text{-O-CH}_2\text{-OH}$ and $\text{CH}_3\text{-O-CH}_2\text{-OCH}_3$, respectively.
- (23) S. J. Angyal, *Aust. J. Chem.*, **21**, 2737 (1968).
- (24) R. U. Lemieux, *Pure Appl. Chem.*, **25**, 527 (1971).
- (25) This is presently not practical for us, owing to program and computer limitations.
- (26) E. L. Sutton, Ed., "Tables of Interatomic Distances", *Chem. Soc., Spec. Publ., No. 18* (1965).
- (27) Very different potential energy curves for dimethoxymethane and methoxymethyl chloride were calculated using a lower level semiempirical molecular orbital approximation (CNDO/2) by I. Ivaroska and T. Bleha, *Tetrahedron Lett.*, 249 (1975); *J. Mol. Struct.*, **24**, 249 (1975).
- (28) J. T. Edward, *Chem. Ind. (London)*, 1102 (1955).
- (29) Since the minimal STO-3G basis set is well-known to underestimate the steric repulsions, these results are consistent with the reversal in anomeric energies for the methanol fluoride and chloride on going to the higher level approximation, shown in Table II. An underestimate of the V_1 potential for methoxymethyl chloride could easily reverse our observed $F > Cl$ anomeric energies.
- (30) L. Radom, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **95**, 693 (1973).
- (31) H. Sacchse, *Ber.*, **23**, 1363 (1890).

Theoretical Studies of Drug-Dinucleotide Interactions. Empirical Energy Function Calculations on the Interaction of Ethidium, 9-Aminoacridine, and Proflavin Cations with the Base-Paired Dinucleotides GpC and CpG

Merrill E. Nuss, Frederick J. Marsh, and Peter A. Kollman*

Contribution from the Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143. Received April 12, 1978

Abstract: We present empirical potential function calculations on the interaction of the cationic intercalators ethidium, proflavin, and 9-aminoacridine with the base-paired dinucleotide phosphates GpC and CpG. The calculations find reasonable base-paired structures for the GpC- and CpG-intercalator complexes and relative binding energies in the same order as the experimental free energies of association to DNA for ethidium and proflavin. The calculations are consistent with a low activation energy (<20 kcal/mol) for "opening up" the dinucleotide phosphate base pair from the DNA structure to one into which the intercalator can fit. The calculations are able to reproduce and rationalize the pyrimidine-3',5'-purine specificity of these intercalators.

Introduction

One of the best characterized prototypal "drug-receptor" interactions is that between planar drugs and nucleotides. There is a wealth of physical chemical information on the interaction of planar aromatic dyes with DNA, RNA, and other nucleotides supporting an intercalated structure¹ for the dye-nucleotide complex.

Compared to the relatively large number of empirical potential energy calculations on peptides and nucleotides, there have been relatively few such studies of nucleotide-intercalator interactions. Sobell has used his X-ray structures of drug-nucleotide complexes as a basis for building molecular models of the drug-dinucleotide complex.² Alden and Arnott have used constrained model building to construct a stereochemically reasonable drug-decanucleotide complex.³ Pack and Loew have carried out quantum mechanical calculations on fragments of the dinucleotide intercalator complex.⁴ A very important study by Gilbert and Claverie,⁵ using empirical potential functions, compared the interaction energy of

proflavin, 9-aminoacridine, and acridine using a fixed geometrical model and focusing on base-intercalator interactions.

To our knowledge, no one has carried out an empirical potential function calculation on a *base-paired* dinucleotide phosphate and its complex with an intercalator varying all the torsional (14) and intermolecular (12) degrees of freedom. We describe such a study below.

The first goal of this study was to see whether these empirical energy calculations could find qualitatively reasonable structures for both base-paired dinucleotides and their intercalated complexes. The results of our calculations indicate that such methods can be successfully used in structure prediction of intercalated complexes.

A second goal was to calculate the energetics of drug intercalation, and, by examining the components of this process, gain insight into the important interactions which determine the kinetics and thermodynamics of drug intercalation. We discuss these insights below.

We carried out our calculations on the interaction of the