193. Probing the Anomeric Effect in O–C–N Systems Theory *vs.* Experiment: MO-*ab initio* Calculations and a Structural-Statistical Analysis[1])

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Dedicated to Professor *Jack D. Dunitz*

(23.VII.90)

A combined computational (MO *ab initio*) and structural-statistical study of molecules containing the O–C–N moiety is presented. Aminomethanol, the simplest member of this series, was computed using GAUSSIAN-82 with the 3-21G and 6-31G* basis sets and with complete geometry optimization, as well as with MP3//6-31G*. A set of carefully selected molecules containing the O–C–N unit was retrieved from the *Cambridge Structural Database* (CSD), and its structural parameters were analyzed according to an established procedure. Comparison between experimental and computational data was thus made possible. Results are consistent with the co-existence of two unequal anomeric effects in this system: a strong n_N-σ^*_{C-O} anomeric interaction, and a weak $n_{\pi O}$-σ^*_{C-N} one. The ability of the two basis sets to reproduce the energies and structural characteristics of the stereoelectronic effects is assessed, including the significance of using polarization functions and the inclusion of correlation energy.

Introduction. – We have recently described a series of results [1–5] from an approach towards the study of stereoelectronic effects in saturated systems containing the O–C–O and N–C–N moieties, using mainly the structural manifestations of these effects. The approach consists of two complementary sets of calculations: *i*) statistical analysis of a carefully selected collection of structural data from crystallographic studies, retrieved from the most useful and reliable of the available sources, namely the *Cambridge Structural Database* (CSD) [6] and *ii*) high-level MO-*ab initio* calculations on small model molecules containing the moiety of interest. The general approach of comparing calculated with experimentally available structural parameters is, of course, long in use, in particular in the difficult task of constructing force fields for molecular mechanics. In previous studies [2] [4], we had reparameterized MM2 [7] [8] for such purposes. We have sought to increase the reliability of the experimental data, by subjecting them to computerized data retrieval and statistical analysis, and used them in conjunction with calculated results for the reparameterization of MM2 for stereoelectronic effects in OCO and NCN systems. The mutual complementarity of the results from the two methods is bound to help in both characterizing the structural trends and explaining them.

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[1]) Structure and Conformation of Heterocycles, Part 19. Part 18: [1a].

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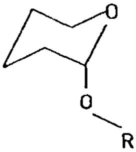
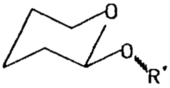
The above approach was first applied to the investigation of the stereoelectronic features of O–C–O systems [2] and in particular of the *anomeric effect* in carbohydrates [3], then to the study of N–C–N systems [4], with particular attention to 1,4,5,8-tetraazadecalins [1] [5]. We wish to apply it now to the investigation of the same features of O–C–N containing systems.

The anomeric effect has been observed more than 30 years ago in carbohydrate derivatives [9] [10] and has since become an intensively studied and documented topic [11]3)). Phenomenologically, it consisted of a preference of the α-axial form **1** over the β-equatorial one **2**, contrary to what is expected on steric considerations alone. In fact, this applies also to the second half of the anomeric moiety, *i.e.*, viewed from outside (R′–O–C–O) and named the *exo-anomeric effect* [12f]. This is tantamount to a tendency of a R–X–C–Y–R′ moiety to assume a *gauche-gauche* (**4**) rather then an *anti-gauche* (**3**) conformation around the X–C–Y bonds. Theoretically, this behaviour was first interpreted in terms of electrostatic interactions (*e.g. destabilization* of **2** relative to **1** by repulsive parallel dipoles) [9] [10] and later on [13] in terms of MO theory. The latter interpretation was well endorsed by quantum-chemical calculations at various levels [14–18] and consists in a 2 electrons 2 orbitals n_π-σ^* *stabilizing* interaction (*cf.* **4**), the magnitude of which depends on the overlap (*i.e.* relative orientation) of the two orbitals and on the energy gap between them. In terms of valence-bond theory, one may invoke equivalently, double bond – no bond resonance (**4**↔**4′**) [12c,d,h] or hyperconjugation [12j,k] [16]. These MO arguments account well for the structural characteristics of the anomeric effect, in contrast to the electrostatic rationale.



1



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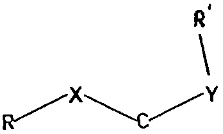

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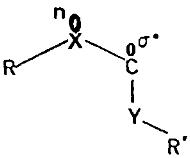

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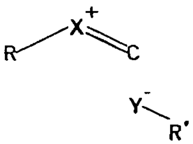

4′

The existence of an anomeric effect in a system is manifest in its properties as follows: *1*) structure, *e.g.* shorter or longer anomeric bonds and larger anomeric bond angles; *2*) energy, *i.e.*, greater stability of *gauche* (axial) forms **1** over *anti* (equatorial) ones **2**; *3*) reactivity, *i.e.*, variation of rates of attack at or around the anomeric center, all those as a function of geometry.

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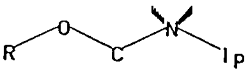
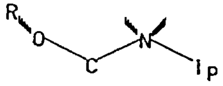
3) For reviews on or including anomeric effect, see [12].

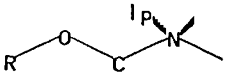
In symmetrical R–X–C–Y–R′ moieties with X=Y and R=R′, *viz.*, C–O–C–O–C or C–N–C–N–C, only four conformations have to be considered [2] [4]. However, in the present case, where X=O ≠ Y=N, there are five relevant conformers: *aa*; ag^+; g^+a; g^+g^+, and g^-g^+, each of the last 4 of those having another enantiomeric form[4]. We consider the R–O–C–N–R′ anomeric unit to be the most interesting, since it incorporates a good (N) donor adjacent to an excellent (O) acceptor and is, thus, capable of exhibiting two unequal anomeric effects: a strong $n_{\pi N}$-σ^*_{C-O} anomeric interaction, and a weak $n_{\pi N}$-σ^*_{C-N} one.



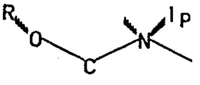
aa



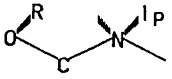
g^+a



ag^-

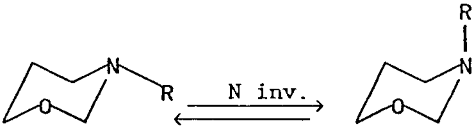


g^+g^+



g^-g^+

Experimental Background. The main molecular systems containing the O–C–N moiety, which have undergone experimental conformational analysis, are of the tetrahydro-1,3-oxazine type. The position of the equilibrium **5**⇆**6** is determined by a balance between anomeric and steric interactions, the former favouring the axial conformer, the latter the equatorial one. The relative stabilities of the different conformers in solution have been analyzed by various methods including IR spectroscopy [19] [20], dipole moment measurements [20–22], and various NMR techniques. The latter, in particular ^{13}C-NMR, seems to give the most reliable results.



5 **6**

Booth and *Lemieux* [23] have used ^3J(H,H) values to show that tetrahydro-1,3-oxazine itself exists mainly in the N-axial form (**6**, R=H). *N*-Alkyltetrahydro-1,3-oxazines were studied mainly by ^{13}C-NMR techniques, utilizing the γ-gauche effect to distinguish between the N-axial and N-equatorial conformers. Thus, *Katritzky et al.* [24] have shown that for R=Me the axial form is favoured by 0.10±0.05 kcal/mol (a similar value, *ca.* 0.16 kcal/mol was obtained by *Ferguson et al.* [25] using ^{1}H-NMR spectroscopical observation of the Me protons), while, for R = Et, it is favoured by 0.50±0.05 kcal/mol. Introduction

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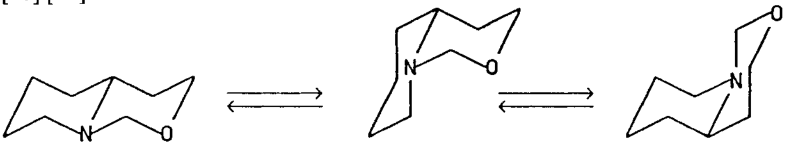
[4] The following definitions are used throughout this work: *a* = *anti* (antiperiplanar), *g* = *gauche* (synclinal), *lp* = lone-pair. Due to the substitution pattern of the R–O–C–N–R′ unit (two substituents on N and only one on O), conformers are defined by the two dihedral angles: D1 = R–O–C–N; D2 = O–C–N–*lp*. The location of the Nlp is determined according to the following procedure: 3 unit vectors are drawn from the N along its 3 bonds. The lp is located along the negative direction of the vector sum of these 3 vectors.

of additional substituents at different positions of the oxazine ring, was also studied [24] [26] [27].

A variety of conformers is available for the fused system perhydropyrido[1,2-*c*]-[1,3]oxazine and its derivatives. Steric interactions favour the *trans*-conformer **7**, while anomeric interactions favour the *cis*-O-inside one (**8**). *Crabb* and *Newton* [28] have studied the IR and ^{1}H-NMR spectrum of perhydropyrido[1,2-*c*][1,3]oxazine and found the *trans*-fused conformer **7** to be 0.34 kcal/mol more stable than the *cis*-fused ones. Substitution of the A or B ring by an alkyl group influences the position of this equilibrium [28] [29].



7 (*trans*) **8** (O-inside) **9** (O-outside)

Pinto and *Wolfe* used ^{1}H-NMR spectroscopy to study the conformational equilibrium of 5-amino-D-glucopyranose [30]. They found an enhanced preference for the axial conformer relative to D-glucopyranose and concluded that 'the anomeric effect in 5-amino-D-glucopyranose in water solvent is greater than that in D-glucopyranose by approximately 0.7 kcal/mol', in accord with the predictions of qualitative molecular orbital theory.

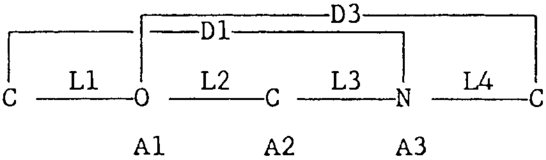
Theoretical Background. Aminomethanol (AME) has been calculated *ab initio* with a variety of basis sets and different levels of geometry optimization [14f,i]. The most detailed work was done by *Schafer et al.* [14i], who computed four conformers of AME at 4–31G//4–31G level with complete geometry optimization. Other studies concerned its heat of formation [31], relative stability of conformers (both *in vacuo* and in aqueous solution) [14i] [31] and potential surface (using small basis sets with no geometry optimization) [32] [33]. No complete analysis of the anomeric effect in this system has been done, to the best of our knowledge, using a large basis set with inclusion of polarization functions. Most recently, *Rios* and coworkers [34] have calculated at 4–21G level with complete geometry optimization a number of substituted AMEs. This actually prompts us to publish at this stage our own results in this interesting area.

Results. – *Statistical Analysis of Structural Parameters.* All three manifestations of the anomeric effect (*i.e.* energy, structure, and reactivity) can, in principle, be used as a probing ground for investigating its nature and characteristics. The structural criterion, however, seems to be the most reliable, less subject to misleading interpretations, and by far, the most quantitative. In this work, designed along the lines developed in previous studies [3], the structural criterion is probed in a statistical analysis of a large set of molecules in the solid state, containing the R–O–C–N–R′ unit. We seek a statistically valid correlation between the conformation of the anomeric moiety and its geometric parameters, based on a large data set of crystal structures from various laboratories. This should allow the assumption that errors due to variations in precision and accuracy are not systematic, and they, along with random interference of crystal forces with molecular parameters, may cancel out in the background noise. Hence, no qualification should be necessary concerning the juxtaposition of crystallographic data to those in other phases.

It is the *correlation* between conformation and geometrical parameters [35] that is of interest and not the conformations as such.

Thus, 1817 structures containing the C–O–C–N–C moiety were retrieved from the *Cambridge Structural Database* (CSD, January 1989 edition) [31], using connectivity criteria and the QUEST89 program, to produce a crude preliminary data set. These data were then subjected to a classifying and purging procedure. Structures having an *R* factor higher than 0.1 or appreciable disorder within or near the anomeric unit were discarded. So were structures containing double bonds, triple bonds, or C=O groups attached to the anomeric moiety, as well as heteroatoms connected to the anomeric N-atom. Finally, structures containing metal ions or having a charged anomeric unit were removed, leaving a total of 102 entries in the 'pure' data set. The CSD GEOM89 program was used to obtain the structural parameters within the anomeric unit, as defined in the *Scheme*, and to perform basic statistics on the pure data set and on selected cuts through it. Each of the entries was individually checked and recorded on specially designed ID cards (*Fig. 2*). An overview of the entire data set is shown in three-dimensional histogram form in *Fig. 1*.

Scheme



Definitions of Structural Parameters in the R–O–C–N–R' Anomeric Unit. L: bond length, A: bond angle, and D: dihedral angle. D2 is defined as O–C–N–*lp*.

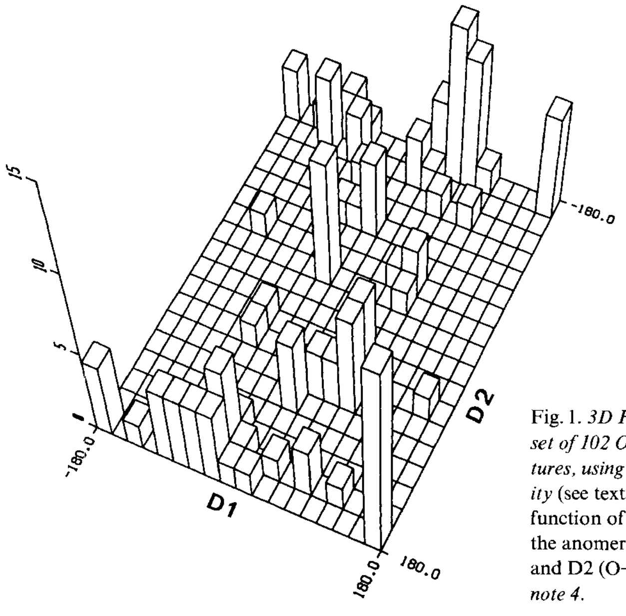


Fig. 1. *3D Histogram of a 'crude' data set of 102 O–C–N containing structures, using C–O–C–N–C connectivity* (see text). Occurrence is shown as function of the two dihedral angles in the anomeric moiety, D1 (C–O–C–N) and D2 (O–C–N–*lp*). *Cf.* also *Footnote 4*.

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*   Anomeric Effect   *
*   O-C-N Data Base   *
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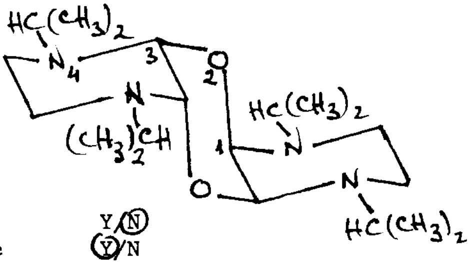

1. Acronym - DEBTOT

2. Classification :

2.1 Compound type:

2.1.1 1,3-dioxazine Y/[✓ N]
2.1.2 dioxanodiazane [✓ Y]/N
2.1.3 morpholinomorpholine Y/[✓ N]

2.2 Cyclicity:

Acyclic X
Monocyclic (ring size) X ( )
Bicyclic (ring1/ring2) [✓ X] (6/6)
Semicyclic (ring s.) X ( )

2.3 Angular N - Y/[✓ N]

3. Perturbations :
3.1 Central carbon substitution - Sec. X Tert. [✓ X] Quat. X
3.2 Double bond - None [✓ X] Attached X (C/T/M) Conjugated X (C/T/M)
3.3 Triple bond - None [✓ X] Attached X (C/T/M) Conjugated X (C/T/M)
3.4 Carbonyl - None [✓ X] Attached X (C/T/M) Conjugated X (C/T/M)
3.5 Overlap - None X Linear [✓ X] Orthoamide X Multiple X
3.6 Conjugation - None X Linear X Thru central C X Multiple [✓ X]

4. Geometrical parameters:

L1- 1.458 L2- 1.415 L3- 1.455 L4- 1.464 L5- 1.461
A1- 113.93 A2- 111.12 A3- 109.69 A4- 114.83 A5- 115.09
D1- -67.61 D2- 59.85 D3- -52.10 D4- 176.47

5. X-ray data:
R-factor- 0.08 Low temp.- Y/[✓ N]
Thermal Corr.- Y/[✓ N]

6. Remarks ____________________

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Fig. 2. *Sample ID card for entries in the local C–O–C–N–C database after retrieval from the* Cambridge Structural Database

The following definitions should be kept in mind (*cf.* also *Footnote 4*): *1*) Five conformations of the basic R–O–C–N–*lp* unit are considered and defined: *aa*, ag^+, g^+a, g^+g^+, and g^+g^- (and the enantiomers of the last four, *i.e.* with + signs substituted by –). *2*) *a* = *anti* was defined as a ±160–180° range; *g* = *gauche*, as ±30–90°. *3*) Statistics on dihedral angles were performed on absolute values thus giving a measure of the deviation from a standard anomeric effect geometry (60° for D1, 180° for D2, based on sp^3 hybridization of both O(2) and N(4)).

Within and following these qualifying conditions, the four populated groups (*aa*, g^+a, g^+g^+, and g^+g^-) are listed in *Table 1*, which gives the average structural parameters after further removal of cases deviating in more than 3σ from the mean values.

Table 1. *Mean Values of Geometrical Parameters and Their Standard Deviations* (σ) *in the Various Conformations of C–O–C–N–C Containing Structures Retrieved from the CSD, after Removal of Cases Deviating in More Than* 3σ *from the Mean Values* (bond lengths in Å, bond and torsional angles in degrees). *Cf. Scheme.*

Entries	*aa*	g^+a	g^+g^+	g^-g^+	*Entries*	*aa*	g^+a	g^+g^+	g^-g^+
	17	22	16	2		17	22	16	2
L1	1.426	1.438	1.445	1.458	A1	113.63	110.61	108.70	113.93
σ	0.012	0.017	0.016	0.000	σ	1.97	4.69	4.30	0.00
L2	1.443	1.439	1.415	1.415	A2	109.07	111.39	106.14	111.11
σ	0.018	0.016	0.009	0.000	σ	1.34	4.66	3.68	0.00
L3	1.434	1.447	1.467	1.455	A3	112.93	111.29	109.26	109.69
σ	0.012	0.022	0.015	0.000	σ	1.25	6.24	4.44	0.00
L4	1.465	1.471	1.459	1.464	D1	179.81	62.04	51.46	67.60
σ	0.014	0.032	0.021	0.000	σ	4.34	18.38	12.85	0.00
					D2	175.88	171.60	67.75	59.85
					σ	3.37	5.32	9.78	0.00

The resulting, leaner but reliable set of 57 cases is shown also in three-dimensional histogram form in *Fig. 3*. The following trends are observed: *1*) there is a marked preference for a *gauche* rather than an *anti* D1 (40 *vs.* 17 entries, respectively). At the same time, D2 prefers the *anti*-orientation (39 *vs.* 18 entries for *a* and *g*, respectively).

2) The ag^+ group is not populated.

3) Only two entries are found for the $g^\pm g^\mp$ conformation. Hence, no meaningful statistical analysis could be performed and these data are presented only for the sake of completeness.

4) There are relevantly distinct differences in the average structural parameters of the various conformations, which can be interpreted in terms of stereoelectronics, *i.e.*, the anomeric effect in these systems, as discussed below.

MO-ab initio *Calculations.* In this work, we present results of more elaborate calculations for AME. A first set was obtained using the GAUSSIAN-82 program [34] at both 3–21G//3–21G and 6–31G*//6–31G* levels with complete geometry optimization (*Tables 2* and *3*, respectively). Five starting points were used for the optimization process. These are the fully staggered conformers: *aa*, ag^+, g^+a, g^+g^+, and g^+g^-. Optimization was carried out with no constraints (unless mentioned otherwise), until a stationary point was

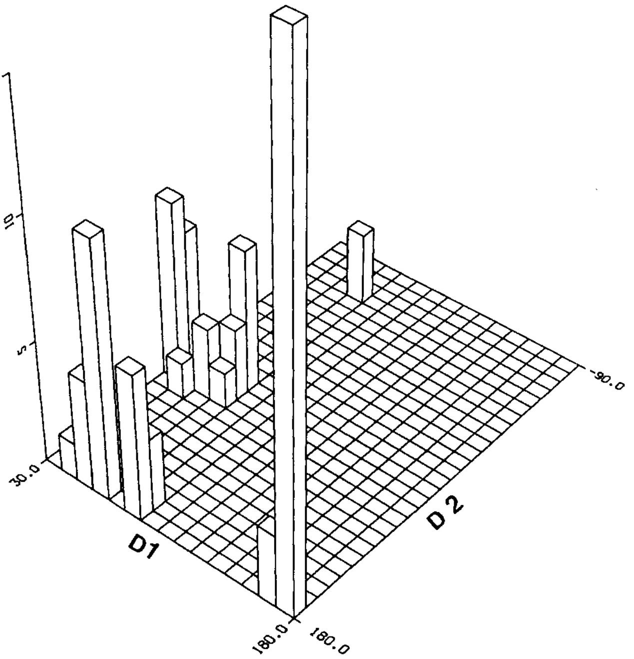
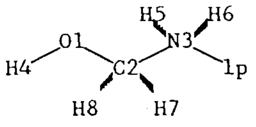
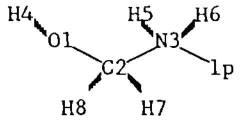


Fig. 3. *3D Histogram of 57 carbohydrate structures using C–O–C–N–C connectivity and after suitable purging and 'normalization' to one enantiomer in each case* (see text). Occurrence is shown as function of the two dihedral angles in the anomeric moiety, Dl (C–O–C–N) and D2 (O–C–N–*lp*). *Cf.* also *Footnote 4.*

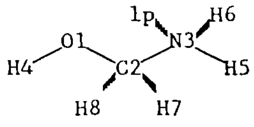
reached. Each such point was examined using the FREQUENCIES command and its nature determined. *Tables 2* and *3* present the results in terms of relative energies and covalent bond parameters along with some electronic properties of interest.



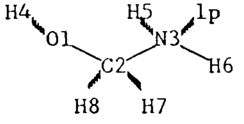
aa



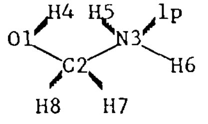
g^+a



ag^-



g^+g^+



g^-g^+

D1=H(4)-O(1)-C(2)-N(3) and D2=O(1)-C(2)-N(3)-*lp*

Table 2. *Selected Structural Parameters and Population Analysis Data for AME Calculated at 3-21G Level.* 4-21G results (in parentheses) [14 h] are cited for comparison: relative energy (E_{rel}) in kcal/mol; bond lengths (L) in Å, bond angles (A) and dihedral angles (D) in degrees.

	aa[a])	g^+a[a])	ag^-[b])	g^-g^+[a])	g^+g^+[c])
E_{rel}	1.40	0.00	7.89	1.25	7.69
	(1.12)	(0.00)	(7.69)	(1.26)	
L(C–O)	1.447	1.444	1.435	1.435	1.429
	(1.455)	(1.452)	(1.443)	(1.438)	
L(C–N)	1.434	1.438	1.447	1.441	1.463
	(1.439)	(1.443)	(1.449)	(1.454)	
L(C–H(7))	1.082	1.082	1.084	1.081	1.076
	(1.081)	(1.081)	(1.083)	(1.082)	
L(C–H(8))	1.082	1.076	1.092	1.083	1.091
	(1.081)	(1.076)	(1.091)	(1.083)	
A(O–C–N)	110.4	115.9	105.7	112.00	111.6
	(110.0)	(115.5)	(105.6)	(109.9)	
D(H–O–C–N)[d])	-179.6	62.9	178.8	-39.7	67.5
	(180.0)	(-63.5)	(178.0)	(-43.9)	
D(O–C–N–*lp*)[d])	179.9	173.5	-67.7	28.3	64.1
	(180.0)	(-174.2)	(63.3)	(43.3)	
Overlap population					
L(C–O)	0.22	0.24	0.24	0.25	0.25
L(C–N)	0.27	0.23	0.26	0.22	0.23
L(C–H(7))	0.37	0.37	0.36	0.38	0.38
L(C–H(8))	0.37	0.39	0.35	0.37	0.35
Total atomic charges					
O(1)	8.70	8.69	8.68	8.68	8.67
C(2)	5.86	5.88	5.83	5.84	5.86
N(3)	7.81	7.84	7.81	7.87	7.81

[a]) Minimum energy point (no special mention was made in [14i] of the exact nature of the stationary points obtained during the minimization process).

[b]) First-order saddle point. The dihedral angle O(1)–C(2)–N(3)–H(6) was frozen at 180° to maintain the conformer.

[c]) First-order saddle point. The dihedral angle O(1)–C(2)–N(3)–H(5) was frozen at 180° to maintain the conformer.

[d]) g^-a and ag^+ conformers were calculated in [14i], rather than the enantiomeric g^+a and ag^- in this work.

The use of polarization functions, such as with the 6–31G* basis set in the present study (*Table 3*), causes severe bond shortening [36] [37]. Electron correlation can help offset this [37]; with this in mind, MP3 [36] calculations of AME were also performed. These were point calculations, using the 6–31G* output for starting geometries but optimizing the O–C–N bond lengths and bond angle at the MP3 level. The results are given in *Table 4*, whereas *Table 5* compares selected structural parameters obtained from both statistics and calculations as well as relative energies of the different conformers.

Discussion. – Our entire approach relies on the expectation that trends found in the calculated structural parameters should match those observed in the structural statistics, with the reserve that the former are obtained for the small parent, unsubstituted AME system, whereas the latter for large O- and N-substituted molecules. This means that only the O–C–N bond lenghts (L2 and L3) and bond angle (A2) can be meaningfully compared.

Table 3. *Selected Structural Parameters for AME Calculated at 6-31G* Level.* Relative energy (E_{rel}) in kcal/mol, bond lengths (L) in Å, bond angles (A), and dihedral angles (D) in degrees.

	aa[a])	g^+a[a])	ag^-[a])	g^-g^+[a])	g^+g^+[b])
E_{rel}	0.14	0.00	5.08	0.51	5.27
L(C–O)	1.408	1.404	1.396	1.390	1.391
L(C–N)	1.424	1.433	1.435	1.443	1.447
L(C–H(7))	1.086	1.085	1.087	1.086	1.093
L(C–H(8))	1.086	1.080	1.094	1.087	1.080
A(O–C–N)	110.9	115.6	106.9	110.0	111.4
D(H–O–C–N)	180.0	68.5	–172.4	–48.4	72.4
D(O–C–N–*lp*)	–179.4	174.1	–67.7	48.5	60.2
Overlap population					
L(C–O)	0.21	0.23	0.23	0.24	0.24
L(C–N)	0.34	0.31	0.30	0.28	0.28
L(C–H(7))	0.41	0.41	0.41	0.42	0.42
L(C–H(8))	0.41	0.41	0.41	0.41	0.41
Total atomic charges					
O(1)	8.75	8.74	8.72	8.73	8.72
C(2)	5.85	5.86	5.82	5.82	5.83
N(3)	7.83	7.84	7.83	7.86	7.84

[a]) Minimum-energy point.

[b]) Probably a first-order saddle point. The dihedral angle C(1)–C(2)–N(3)–H(5) was frozen at 180° to maintain this conformer.

Table 4. *Selected Structural Parameters for AME as Calculated by MP3//6-31G* and Optimized for the Shown Parameters.* Bond lengths (L) in Å, bond angles (A), dihedral angles (D) in degrees, and relative energy (E_{rel}) in kcal/mol.

	aa[a])	g^+a[a])	ag^-[a])	g^-g^+[a])	g^+g^+[b])
E_{rel}	0.31	0.00	5.57	0.71	5.74
L(C–O)	1.431	1.425	1.417	1.405	1.409
L(C–N)	1.431	1.442	1.444	1.452	1.458
A(O–C–N)	110.57	115.89	106.04	109.57	111.02
D(H–O–C–N)	180.0	68.5	–172.4	–48.4	72.4
D(O–C–N–*lp*)	–179.4	174.1	–67.7	48.5	60.2

[a]) Minimum-energy point.

[b]) First-order saddle point (the dihedral angle C(1)–C(2)–N(3)–H(5) was frozen at 180° to maintain this conformer).

Following our previous studies of stereoelectronics, we anticipated a certain order of stability of the different conformers in the R–O–C–N–lp unit, namely: $ga > aa > g^-g^+ > g^+g^+ > ag$. This was based mainly on the interesting complementarity of the two partners in the anomeric interactions, *viz.*, the excellent n_π donating properties but poor accepting ability of N and *vice versa* for O. Thus, *f. ex.* in the g^+a form of R–O–C–N–lp, a strong lp_N- σ^*_{C-O} anomeric interaction operates along with a weak $n_{\pi O}$-σ^*_{C-N} one. Geometrical parameters should then be affected more by the strong n_N- σ^*_{C-O} anomeric effect than by the weak $n_{\pi O}$-σ^*_{C-N} one. Finally, the n_N-σ^*_{C-O} anomeric and $n_{\pi O}$-σ^*_{C-N} anomeric interactions should also be reflected in C–H bond lengths.

Table 5. *A Comparison of Relative Energies and Selected Geometrical Parameters Obtained from Statistical and* ab initio *(3-21G and 6-31G*) Calculations for AME.* Relative energy (E_{rel}) in kcal/mol, bond lengths (L) in Å, bond angles (A) in degrees.

	L(O–C)	L(C–N)	A(O–C–N)	E_{rel}
aa				
statistics	1.443	1.434	109.07	
3-21G	1.447	1.434	110.40	1.40
6-31G*	1.408	1.424	110.93	0.14
MP3//6-31G*	1.431	1.431	110.57	0.31
g^+a				
statistics	1.439	1.447	111.39	
3-21G	1.441	1.438	115.94	0.00
6-31G*	1.404	1.433	115.62	0.00
MP3//6-31G*	1.425	1.442	115.89	0.00
g^+g^-				
statistics	1.415	1.455	111.11	
3-21G	1.435	1.441	111.96	1.25
6-31G*	1.390	1.443	110.02	0.51
MP3//6-31G*	1.405	1.452	109.57	0.71
g^+g^+				
statistics	1.415	1.467	106.14	
3-21G	1.429	1.463	111.63	7.69
6-31G*	1.391	1.447	111.36	5.27
MP3//6-31G*	1.409	1.458	111.02	5.74

Moreover, in AME and larger molecules with H-atoms on O and/or on N, an enhanced stabilization of g^+g^- relative to g^+g^+ was expected, due to H-bond like attractive interactions in the former, *i.e.*, N–H···O and H–H···N, and repulsive (N)H···H(O) and (N)*lp*···*lp*(O) interactions in the latter.

All these expectations were, in fact, borne out by the results of this study. The predicted order of stability is reflected in the relative energies of AME conformations as computed with all three methods as well as in the relative populations of the four different groups observed in the statistical study. All calculations indicate g^+a to be the most stable conformer. This is also the most populated group (22 entries). The difficulty in defining *a priori* the next most stable conformer (one strong anomeric interaction in *aa vs.* a weak one but with the possibility to form OH···N H-bonds in g^+g^-), is well reflected in the ambiguous results obtained from computations, albeit with marginal differences: 6–31G* and MP3 establish *aa* to be the next most stable conformation whereas 3–21G opts for g^+g^-. The stability of the *aa* conformer finds its expression in the population of this group (17 entries), while the g^-g^+ group is rather small (2 entries), perhaps because there are no more examples with secondary NH. All methods calculate *ag* and g^+g^+ to be the least stable conformers. The instability of the *ag* conformer is in accord with the absence of such group in the structural data base. The large population of the g^+g^+ group there is, however, readily understood when taking into account ring formation by joining the C–O–C–N–C termini (*e.g.* 1,3-oxazine or 1,3-oxazoline).

The mean structural parameters obtained from statistics show (*Table 1*) that the *aa* conformer exhibits a long C–O bond (L2 = 1,443 Å) and a short C–N bond (L3 = 1.434 Å) corresponding with an $n_{\pi N}$- σ^*_{C-O} anomeric interaction. As expected [3], a moderately small O–C–N bond angle (A2 = 109.07°) is observed. A3 in this conformer is large, as expected for a strong anomeric effect, while A1 is similarly but unexpectedly wide.

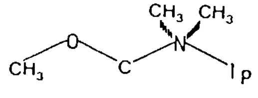
In the *ga* conformer, the O–C bond is shorter and the C–N bond longer than those found in the *aa* conformer (L2 = 1.443 *vs.* 1.439; L3 = 1.434 *vs.* 1.447 Å), due to a mutual cancellation of the two (unequal) stereoelectronic effects. This is in accord with the earlier postulated [3] notion of cross-hyperconjugation in such conformations. The C–O–C, C–N–C, and O–C–N bond angles are all rather large, as expected [2–4].

The g^+g^+ conformation set exhibits the shortest C–O bond (L1 = 1.415 Å), the longest N–C bond (L3 = 1.467 Å), a small O–C–N bond angle (A2–106.1°), and a small C–N–C bond angle (A3 = 109.3°), all as expected for a O-donor···N-acceptor only interaction. In our set, this interaction occurs, however, in perhydro-1,3-oxazine or -oxazoline ring systems *(vide supra)*, and the relatively small bond angles (A1 = 108.7°) are probably due to ring constraints. Indeed, the g^-g^+ form, with similar stereoelectronics, has similar L2/L3 bond length relationships but wider bond angles.

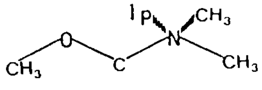
As to C–H bonds, C(2)–H(7) and C(2)–H(8) show the anticipated bond lengthening when *anti* to lone-pairs on any or both hetero-atoms.

We sought but could find no simple correlation between the magnitude of the O–C–N–*lp* dihedral angles and geometrical anomeric parameters. This fits similar findings in a structural statistical study of C–O–C–O–C in carbohydrates [3].

None of the above mentioned results can provide good, unequivocal value for the 'worth' of the N-donor···O-acceptor anomeric effect. In AME, the interplay between the two unequal anomeric effects, steric effects and 'H-bond'-like interactions leads to complications, while the statistical study (as well as the theoretical one) provides only reliable geometrical parameters, as affected by stereoelectronics. One estimate can be from the energy difference between the *aa vs. ag* conformers of 1-(dimethylamino)-1-methoxymethane (**10** and **11** respectively). According to recently published calculations of *Rios* and coworkers (at 4–21G level) [34], this amounts to 4.86 kcal/mol. We corroborated largely this result (4.56) at the 3–21G level, while the MP3 calculations are in course. Another instructive value is that of the *aa vs. ag* energy difference for methoxymethylamine, which we calculated using MP3//6–31G* to be 6.04 kcal/mol (as compared to 6.56 at 4–21G level [34]) [38]; this value includes, however the additional NH···O H-bonding contribution. These values can be compared with those for dimethoxymethane (at comparable levels of theory), *viz.*, $g^+g^+/ag/aa$: 0.0/4.55/10.3 kcal/mol at 4–21G//4–21G [14h] but 0.0/2.42/5.66 at 6–31G*//6–31G* [14l] and 0.00/4.00/6.94 at MP3//6–31G* [14l]. Furthermore, the *aa vs. ag* energy difference in methlyenediamine is 1.6 at 3–21G//3–21G [4], 1.1 at 6–31G*//6–31G* [1b], and 0.55 at MP3//6–31G* [1b].



10 (*aa*)



11 (ag^-)

This trend fits well, in fact, the *lp*-donor *vs.* σ^*-acceptor relationships, envisaged for the anomeric effect, namely, N being a better donor than O but C–N a much poorer acceptor than C–O. Also, it is clear that polarized basis sets reduce appreciably the calculated magnitude of these stereoelectronic effects, but bring about an even stronger shortening effect on bond lengths and that this can be well alleviated by electron correlation, to fit experimental results [141] [37]. Indeed, comparison of the experimentally observed geometrical parameters with the calculated ones (*Table 5*), reveals that 6-31G* consistently gives shorter O—C and C—N bonds and lower energy differences, as discussed above. 3–21G results are closer to the average bond lengths obtained by statistics, but the MP3 calculations yield the closest geometrical parameters and energy differences which are in better accord with common chemical wisdom.

Mulliken population analysis, which had been used once to probe stereoelectronic interactions [18c], yields good inverse correlation between bond lengths and overlap populations (OP) (*cf. Tables 2* and *3*). This is most significant in the O—C—N bonds but less so for C—H bonds. Additional trends observed (*Tables 2* and *3*): total atomic charges vary between different conformers as follows: O(*aa*) is highest and O(*gg*) lowest for oxygen, N(*gg*) is highest and N(*aa*) lowest for nitrogen, and C(*ga*) has the highest electron density among C-atoms. Gross orbital charges are shown in *Table 6*; both O(Py) and N(Py) present a decreased electron density accompanied by an increased charge on C(Py) when an anomeric interaction is possible. These trends are consistent with the picture of the anomeric effect as a depopulation of an *lp* orbital situated on either heteroatoms (Py in both cases) accompanied by population of the adjacent σ^* orbital, the latter being expressed as an increased electron density on C(Py). This is in full agreement with the MO description of this effect.

Conclusions. – We have explored the stereoelectronic features of the R—O—C—N—R entity by high level MO-*ab initio* calculations on the small model molecular unit $HOCH_2NH_2$ and statistical analysis of structural parameters of large systems in the crystal. Both pinpoint the *ga* as the stereoelectronically most preferred form, followed by *aa* and g^-g^+, while *ag* and g^+g^+ have much higher calculated energies. The latter, however, can be observed in suitable ring systems. Anomeric bond lengths and angles are adequate probes for the anomeric effect also in the present case. Trends observed in the total atomic charges and in the gross overlap population of the different conformers of AME are consistent wich the accepted MO picture of the anomeric effect. We consider the generality and reliability of the established structural manifestation of stereoelectronics in O—C—N systems to be a good basis for our ongoing work on parameterization of a suitable force-field (MM2/MM3) for molecular mechanics calculation of such compounds⁵). Further calculations of cyclic molecules (*e.g.* 1,3-oxazine and larger derivatives) are now in course.

The calculations were performed on an *IBM 4381* computer at the Computing Center of Tel-Aviv University, the staff of which provided valuable assistance. We thank Dr. *Leah Schleifer* for help with some calculations and discussions. This work was completed and written up during a sabbatical visit of one of the authors (*B. F.*) for the summer term 1990 at the University of Zurich. The gracious hospitality of the Organisch-Chemisches Institut and its Head, Prof. *H.-J. Hansen*, and in particular of Prof. *W. von Philipsborn*, is gratefully acknowledged.

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5) Prof. *M. A. Rios* has kindly informed us that they have performed a parametrization of MM2, based on *ab initio* calculations only.

Table 6. *Gross Orbital Charges for Selected Atoms and Orbitals for the Various Conformers of AME as Calculated at 3-21G and 6-31G* Levels*

		aa	$g^{+}a$	ag^{-}	$g^{-}g^{+}$	$g^{+}g^{+}$
3-21G						
O(1)	2PX(I)[a]	0.635	0.605	0.615	0.565	0.597
	2PX(O)[b]	0.873	0.788	0.837	0.733	0.774
	2PY(I)	0.866	0.695	0.872	0.777	0.688
	2PY(O)	1.083	0.885	1.079	0.978	0.871
	2PZ(I)	0.596	0.796	0.612	0.757	0.814
	2PZ(O)	0.749	1.025	0.767	0.981	1.036
C(2)	2PX(I)	0.445	0.447	0.450	0.455	0.453
	2PX(O)	0.265	0.288	0.247	0.281	0.266
	2PY(I)	0.591	0.602	0.579	0.592	0.593
	2PY(O)	0.530	0.558	0.506	0.534	0.539
	2PZ(I)	0.501	0.486	0.505	0.487	0.487
	2PZ(O)	0.268	0.233	0.278	0.226	0.246
N(3)	2PX(I)	0.751	0.758	0.584	0.725	0.583
	2PX(O)	1.035	1.058	0.698	0.996	0.706
	2PY(I)	0.552	0.552	0.736	0.602	0.718
	2PY(O)	0.642	0.647	0.993	0.751	0.964
	2PZ(I)	0.546	0.546	0.533	0.543	0.538
	2PZ(O)	0.617	0.627	0.607	0.624	0.627
6-31G*						
O(1)	2PX(I)[a]	0.904	0.875	0.888	0.834	0.867
	2PX(O)[b]	0.604	0.559	0.579	0.518	0.543
	2PY(I)	1.148	0.945	1.150	1.017	0.939
	2PY(O)	0.808	0.636	0.799	0.694	0.623
	2PZ(I)	0.854	1.086	0.871	1.060	1.104
	2PZ(O)	0.549	0.761	0.557	0.733	0.770
C(2)	2PX(I)	0.572	0.577	0.728	0.586	0.582
	2PX(O)	0.142	0.152	0.150	0.158	0.155
	2PY(I)	0.740	0.751	0.728	0.738	0.742
	2PY(O)	0.338	0.372	0.311	0.341	0.346
	2PZ(I)	0.637	0.621	0.640	0.626	0.625
	2PZ(O)	0.175	0.137	0.173	0.131	0.134
N(3)	2PX(I)	0.963	0.961	0.820	0.844	0.803
	2PX(O)	0.769	0.778	0.556	0.613	0.541
	2PY(I)	0.759	0.755	0.905	0.875	0.913
	2PY(O)	0.477	0.474	0.686	0.654	0.700
	2PZ(I)	0.760	0.764	0.751	0.758	0.756
	2PZ(O)	0.433	0.441	0.428	0.438	0.439

[a] I = inner functions.

[b] O = outer functions.

REFERENCES

[1] a) R. Müller, W. von Philipsborn, L. Schleifer, P. Aped, Benzion Fuchs, *Tetrahedron*, in press; b) Taken in part from the Ph. D. Thesis of *H. S.*, to be submitted.

[2] P. Aped, Y. Apeloig, A. Ellencweig, B. Fuchs, I. Goldberg, M. Karni, E. Tartakovsky, *J. Am. Chem. Soc.* **1987,** *109,* 1486.

[3] a) L. Schleifer, H. Senderowitz, P. Aped, E. Tartakovsky, B. Fuchs, *Carbohydr. Res.*, in press; b) B. Fuchs, L. Schleifer, E. Tartakovsky, *Nouv. J. Chim.* **1984,** *8,* 275.

[4] P. Aped, L. Schleifer, B. Fuchs, S. Wolfe, *J. Comput. Chem.* **1989,** *10,* 265.

[5] a) B. Fuchs, A. Ellencweig, *Recl. Trav. Chim. Pays-Bas* **1979,** *98,* 326; b) B. Fuchs, S. Weinman, U. Shmueli, A. R. Katritzky, R. C. Patel, *Tetrahedron Lett.* **1981,** *22,* 3541.

[6] a) F.H. Allen, S. Bellard, M.D. Brice, B.A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, B.G. Hummelink-Peters, O. Kennard, W.D.S. Motherwell, J.R. Rodgers, D.G. Watson, *Acta Crystallogr., Sect. B* **1979,** *35,* 2331; b) F.H. Allen, O. Kennard, R. Taylor, *Acc. Chem. Res.* **1983,** *16,* 146.

[7] a) N.L. Allinger, *J. Am. Chem. Soc.* **1977,** *99,* 8127; b) N.L. Allinger, S.H.M. Chang, D.H. Glaser, H. Honig, *Isr. J. Chem.* **1980,** *20,* 5; c) L. Nørskov-Lauritsen, N.L. Allinger, *J. Comput. Chem.* **1984,** *5,* 326.

[8] a) N.L. Allinger, U. Burkert, S. Profeta, Jr., *J. Comput. Chem.* **1980,** *1,* 281; b) S. Profeta, Jr., N.L. Allinger, *J. Am. Chem. Soc.* **1985,** *107,* 1907; c) MM2-87, QCPE, Program 395, University of Indiana, Bloomington, In.

[9] J.T. Edward, *Chem. Ind. (London)* **1955,** 1102.

[10] R.U. Lemieux, N.J. Chu, *Abstr. Papers Am. Chem. Soc. Meeting* **1958,** *133,* 31N.

[11] a) W.A. Szarek, D. Horton, Eds., 'Anomeric Effect. Origins and Consequences', ACS Monograph, Washington, D.C., 1979, Vol. 87; b) A.J. Kirby, 'The Anomeric Effect and Related Stereoelectronic Effects at Oxygen', Springer, Berlin, 1983; c) P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry', Wiley, New York, 1983.

[12] a) R.U. Lemieux, in 'Molecular Rearrangements', Ed. P. de Mayo, Interscience, New York, 1964, Vol. III, p. 709; b) S.J. Angyal, *Angew. Chem. Int. Ed.* **1969,** *8,* 157; c) C. Romers, C. Altona, H.R. Buys, E. Havinga, *Topics Stereochem.* **1969,** *4,* 39; d) E.L. Eliel, *Acc. Chem. Res.* **1970,** *3,* 1; *Angew. Chem. Int. Ed.* **1972,** *11,* 739; *Kem Tidskr.* **1969,** *81,* 22; e) J.C. Martin, *Ann. Chim. Res.* **1971,** *6,* 205; f) R.U. Lemieux, *Pure Appl. Chem.* **1971,** *25,* 527 and previous ref.; g) N.S. Zefirov, N.M. Schechtman, *Usp. Khim.* **1971,** *40,* 593; h) J.F. Stoddard, 'Stereochemistry of Carbohydrates', Wiley, New York, 1971; i) S. Wolfe, *Acc. Chem. Res.* **1972,** *5,* 102, and ref. cit. therein; j) H. Paulsen, *Starch* **1975,** *27,* 397; k) I. Tvaroska and T. Bleha, *Chem. Papers* **1985,** *39,* 805; l) I. Tvaroska and T. Bleha, *Adv. Carbohydr. Chem.* **1989,** *47,* 45.

[13] a) C. Altona, Ph.D. Thesis, University of Leiden, 1964; *cf.* also E.A.C. Lucken, *J. Chem. Soc.* **1959,** 2954.

[14] a) S. David, O. Eisenstein, W.J. Hehre, L. Salem, R. Hoffmann, *J. Am. Chem. Soc.* **1973,** *95,* 3806; b) O. Eisenstein, Nguyen T. Anh, Y. Jean, A. Devaquet, J. Cantacuzene, L. Salem, *Tetrahedron* **1974,** *30,* 1717; c) G.A. Jeffrey, J.A. Pople, L. Radom, *Carbohydr. Res.* **1974,** *38,* 81; d) G.A. Jeffrey, J.A. Pople, S. Binkley, S. Vishveshwara, *J. Am. Chem. Soc.* **1978,** *100,* 373; e) D.G. Gorenstein, J.B. Findlay, B.A. Luxon, D. Kar, *J. Am. Chem. Soc.* **1977,** *99,* 3473; D.G. Gorenstein, D. Kar, *ibid.* **1977,** *99,* 672; f) S. Wolfe, M.-H. Whangbo, D.J. Mitchell, *Carbohydr. Res.* **1979,** *69,* 1; g) A. Pross, L. Radom, N.V. Riggs, *J. Am. Chem. Soc.* **1980,** *102,* 2253; h) C. Van Alsenoy, L. Schafer, J.N. Scarsdale, J.O. Williams, H.J. Geise, *J. Mol. Struct. THEOCHEM.* **1981,** *86,* 111; i) L. Schafer, C. Van Alsenoy, J.O. Williams, J.N. Scarsdale, H.J. Geise, *ibid.* **1981,** *76,* 349; j) P.v.R. Schleyer, A.J. Kos, *Tetrahedron* **1983,** *39,* 1141; k) P.v.R. Schleyer, E.D. Jemmis, G.W. Spitznagel, *J. Am. Chem. Soc.* **1985,** *107,* 6393; l) K.B. Wiberg, M.A. Murcko, *ibid.* **1989,** *111,* 4821.

[15] a) L. Radom, in 'Molecular Structure and Conformation', Ed. I.D. Csizmadia, Elsevier, Amsterdam, 1982; b) R. Hoffman, L. Radom, J.A. Pople, P.v.R. Schleyer, W.J. Hehre, L. Salem, *J. Am. Chem. Soc.* **1972,** *94,* 6221.

[16] N.D. Epiotis, W.R. Cherry, S. Shaik, R.L. Yates, F. Bernardi, *Topics Curr. Chem.* **1977,** *70,* 1.

[17] a) I. Tvaroska, T. Kozar, *Carbohydr. Res.* **1981,** *90,* 173; b) *J. Am. Chem. Soc.* **1980,** *102,* 6929; c) *Theor. Chim. Acta* **1979,** *53,* 9.

[18] a) H.B. Bürgi, J.-M. Lehn, G. Wipff, *J. Am. Chem. Soc.* **1974,** *96,* 1956; b) J.-M. Lehn, G. Wipff, *ibid.* **1974,** *96,* 4048; c) J.-M. Lehn, G. Wipff, *Helv. Chim. Acta* **1978,** *61,* 1274.

[19] R.A.Y. Jones, A.R. Katritzky, A.C. Richards, S. Saba, A.J. Sparrow, D.L. Trepanier, *J. Chem. Soc., Chem. Commun.* **1972,** 673.

[20] A.R. Katritzky, M. Moreno-Manas, A.C. Richards, A.J. Sparrow, D.L. Trepanier, *J. Chem. Soc., Perkin Trans. 2* **1973,** 325.

[21] R.A.Y. Jones, A.R. Katritzky, D.L. Trepanier, *J. Chem. Soc. (B)* **1971,** 1300.

[22] a) D. Gurne, T. Urbanski, *J. Chem. Soc. (B)* **1959,** 1912; b) D. Gurne, L. Stefaniak, T. Urbanski, M. Witanowski, *Tetrahedron Suppl.* **1964,** *46,* 1211.

[23] H. Booth, R. U. Lemieux, *Can. J. Chem.* **1971,** *49,* 777.

[24] A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, *J. Chem. Soc., Perkin Trans. 2* **1980,** 1739.

[25] I. J. Ferguson, A. R. Katritzky, D. M. Read, *J. Chem. Soc., Perkin Trans. 2* **1977,** 818.

[26] Y. Allingham, R. C. Cookson, T. A. Crabb, S. Vary, *Tetrahedron* **1968,** *24,* 4625.

[27] F. G. Riddell, J. M. Lehn, *J. Chem. Soc. (B)* **1968,** 1224.

[28] T. A. Crabb, R. F. Newton, *Tetrahedron* **1968,** *24,* 4423.

[29] I. D. Blackburne, A. R. Katritzky, D. H. Read, P. J. Chivers, T. A. Crabb, *J. Chem. Soc., Perkin Trans. 2* **1976,** 418.

[30] B. M. Pinto, S. Wolfe, *Tetrahedron Lett.* **1982,** *23,* 3687.

[31] L. Radom, J. Hehre, J. A. Pople, *J. Am. Chem. Soc.* **1971,** *93,* 1289.

[32] G. Alagona, R. Bonaccorsi, C. Ghio, J. Tomassi, *J. Mol. Struct. THEOCHEM.* **1986,** *137,* 1263.

[33] P. Kallianan, S. Vishveshwara, V. S. R. Rao, *J. Mol. Struct. THEOCHEM.* **1983,** *105,* 1359.

[34] L. Carballeira, B. Fernandez, R. A. Mosquera, M. A. Rios, *J. Mol. Struct. THEOCHEM.* **1990,** *205,* 235.

[35] H. B. Bürgi, J. D. Dunitz, *Acc. Chem. Res.* **1983,** *16,* 153 (*cf.* p. 154).

[36] GAUSSIAN 82, J. S. Binkley, M. J. Frisch, D. J. DeFrees, K. Rahgavachari, R. A. Whiteside, H. B. Schlegel, E. M. Fluder, J. A. Pople, Department of Chemistry Carnegie-Mellon University, Pittsburgh, PA.

[37] S. Wilson, 'Electron Correlation in Molecules', Oxford University Press, Oxford, 1984, p. 57.

[38] M. G. Krol, C. J. M. Huige, C. Altona, *J. Comput. Chem.* **1990,** *11,* 765 (reference added in proof).