A COMPUTATIONAL EXAMINATION OF THE ANOMERIC EFFECT IN 1,3-DIAZANES

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Abstract- The anomeric effect was examined for several 1,3-diazane molecules, with computations carried out at the HF/6-31G, HF/6-31G*, MP2-FC/6-31G*, and HF/6-311G** levels. Results were analyzed using the NBO method, and concepts of steric hindrance. The effect of $n \rightarrow \sigma^*$ donation to C-N antibonds appears to control the conformation of diazane systems in which nitrogens are monosubstituted. The computed and experimental results show that specific $n \rightarrow \sigma^*$ donation to C-N antibonds is irrelevant to the conformations of 1,3-diazane systems in which the nitrogens are trisubstituted. Lone pair electron repulsion would normally operate in the same sense as $n \rightarrow \sigma^*$ donation, but extensive delocalization of the lone pairs in the σ orbitals appears to diminish this effect to insignificant levels. In the methyl substituted molecules, a generalized and subtle type of steric hindrance seems to be dominant over $n \rightarrow \sigma^*$ electron donation in determining conformational preference.

I. Introduction

The anomeric effect is a description of situations where the geometry of the lowest energy molecular conformers cannot be fully explained by simple steric hindrance arguments. The anomeric effect is important in the stereochemistry of sugars and has been extensively studied and reviewed.[1] The effect is most clearly demonstrated in the predominance of an axial conformation for a 2-methoxy-tetrahydropyran, rather than the equatorial conformation expected from analogy with 2-methoxycyclohexane. Identification of the occurrence of the effect has remained elusive since estimation of the equilibria for γ-pyranose derivatives cannot be characterized by a single value for the free energy difference between axial and equatorial conformers.[2] Kirby has summed up the debate on the origin of the effect:[2] "There is a stereo electronic preference for conformations in which the best donor lone pair or bond is antiperiplanar to the best acceptor bond."

Three major explanations for the anomeric effect have been advanced. In the first,[3] the antiperiplanar conformation and associated shortening of the carbon-heteroatom bond is attributed to stabilizing interaction between a lone pair of

electrons and the antibonding sigma orbital of the opposing bond. This effect is also known as negative hyperconjugation, or $n \rightarrow \sigma^*$ donation. In the second explanation,[4] the anomeric effect is attributed to repulsion between lone pairs on atoms attached to the anomeric center. Box[4] has argued that bond shortening is not a characteristic effect. The third explanation says that molecular conformation depends on minimization of unfavorable dipole-dipole interactions between bonds formed from the anomeric carbon and adjacent heteroatoms.[5]

The present examination of static systems does not contribute to the discussion of dynamic effects underlying explanations of the anomeric effect in terms of least nuclear motion.[6] Sinnot[6] has criticized explanations based on molecular orbital interactions on the ground of conceptual confusion and lack of agreement with experiment.

II. Computational Details

Simple cyclic and linear diamine systems were examined to avoid the complexities associated with oxygen geminal lone pair descriptions, and to allow comparison of computed and experimental results. Computations were carried out using Gaussian92, revisions C and D,[7] executed on a Cray C90 at the Minnesota Supercomputer Center. All molecular geometries were optimized to standard G92 tolerances, using the 6-31G[8] and 6-31G*[9] basis sets. Molecular sketches of low energy conformers are given in Figure 1. For the low energy conformers, additional geometry optimizations were performed at the MP2-FC/6-31G*[10] and 6-311G**[11], levels. It is always hard to know how far to climb up professor Pople's ladder of basis sets, since the small additional accuracy gained by larger basis sets may not be worth the large additional computational effort. However in the present study we were examining small differences in energy and electron density between similar conformers, so it seemed preferable to use a basis set with added polarization functions on both heavy atoms and hydrogens. For each optimized geometry, Weinhold's natural bond orbital (NBO)[12] method was used to quantify the extent and energetic importance of stereo-electronic effects (i.e. the "hyperconjugative delocalizations", or $n \rightarrow \sigma^*$ donations).

Natural Bond Orbital (NBO) Analysis

Natural bond orbital (NBO)[12] analysis is a set of methods for localization and analysis of molecular wavefunctions, based on the one particle density matrix. The NBO method was developed by Weinhold and coworkers, and is derived from the Brunck-Weinhold[13] study of internal rotation barriers. It can be used to analyze the one particle density matrix produced by any numerical quantum mechanics method. The NBO method is a standard feature of the Gaussian92 program.[14]

The basic NBO method transforms delocalized molecular orbitals into a set of localized "bond orbitals". The NBO method is not a least squares parameter fitting procedure, rather it is a well defined algorithm for obtaining the one, two, and three center orbitals which have maximal electron occupancy (i.e. 2.0 or slightly less). The one center orbitals include both the core and lone pair orbitals. The two center orbitals are the normal bonds. Double and triple bonds arise naturally from the NBO procedure, when present in the molecule. Three center orbitals are obtained only in special cases, such as the allyl radical. Together the occupied core, lone pair, and bond orbitals make up the standard Lewis structure description of each molecule. In addition, at higher energies, there are empty, or nearly empty antibonding and Rydberg orbitals. The label "Rydberg" only implies that these orbitals are primarily formed from the outer shells of split valence or triple zeta basis sets; it does not imply "Rydberg" in the spectroscopic sense.

The steps of NBO analysis involve: 1) natural populations analysis (NPA),[12a] which finds atomic populations and partial charges based on natural atomic orbitals (NAOs), 2) formation of strictly localized natural bond orbitals (NBOs), each of which is composed of one, two, or three natural hybrid orbitals (NHOs),[12b] and 3) the formation of natural localized molecular orbitals (NLMOs),[12c] by allowing the natural bond orbitals to delocalize to full occupancy. All of the orbital sets, NAOs, NHOs, NBOs, and NLMOs are unitary transformations of the canonical molecular orbitals.

The NBO method is ideally suited to analyze and understand energy stabilization effects which determine molecular conformations. Energy stabilizations are examined in terms of small shifts, or delocalizations, of electron density from almost filled orbitals to neighboring almost empty orbitals. A small shift of electron density to neighboring atoms is equivalent to an expansion, or delocalization, of the orbital, which always lowers the orbital energy. In most cases, the actual computed molecular orbitals result from many minor electron delocalizations out of hypothetical pure Lewis orbitals, where electrons are restricted to pure core, lone pair, and bond NBOs. Energy effects of delocalizations are expressed as perturbations to the Fock matrix. In the case of anomeric effects the delocalization, or so called negative hyperconjugation, is a lone pair$\rightarrow \sigma^*$ density shift. Thus in the present work, only delocalizations with nitrogen lone pairs as donors are considered.

The NBO method has previously been used to study a variety of intra- and intermolecular bonding and delocalization situations,[15] including anomeric effects with central atoms other than carbon.[16]

III. **Results for Diaminomethanes**

Dimethylaminomethane and bis(dimethylamino)methane have been discussed by Senderowitz and coworkers.[17] The nomenclature system adopted here follows the scheme used by those authors; the tetrahedral geometry of the nitrogen atoms

allows the conformations to be conveniently labeled by the relationships of the bisectors of the obtuse angles between the methyl groups. The variation of $n\rightarrow\sigma^*$ donation from the lone pair to the opposing C-N antibond in the NBO analysis supports the assumption that the bisector corresponds to the lobe of an approximately sp^3 hybridized lone pair, which is the donor orbital.

The potential surface for rotation about the central C-N bonds has been examined previously, and conformers occupying potential minima have been identified.[18] In this work, stable conformers occupying potential wells were further optimized at the 6-311G** level and analyzed using NBOs. In agreement with earlier work,[18] we find the antiperiplanar, antiperiplanar *(ap,ap)* conformation to be at the lowest energy, followed by the antiperiplanar, synclinal gauche *(ap,sc)*, and the +synclinal gauche, +synclinal gauche *(+sc,+sc)* conformations. The total energies are given in Table 1, and sketches of the conformers are given in Figure 1.

The NBO Fock matrix perturbation results for stabilization by delocalization from nitrogen lone pairs are given in Table 2. Strong $n\rightarrow\sigma^*$ donation from both lone pairs to the respective antiperiplanar C-N antibonding orbital is found for the *(ap,ap)* conformer. In the *(ap,sc)* conformer, strong donation from one lone pair to the antiperiplanar C-N antibond contrasts with weak donation from the other lone pair to the synclinal C-N antibond. The weaker donation to C-N σ^* is only partially compensated by increased donation to the opposing C-H σ^*. In the *(+sc,+sc)* conformer, specific donations to the synclinal C-N antibonds are weak. These results are in very good agreement with the hypothesis of $n\rightarrow\sigma^*$ donation as the foundation of the anomeric effect. However, the results also agree with the hypothesis that conformation is controlled by repulsion between lone pairs, since the *(ap,ap)* conformation should minimize this interaction.

The relative energies of bis(dimethylamino)methane are also shown in Table 1. The most stable conformation is the *(+sc,+sc)*, for all levels of basis set, in agreement with the experimental result.[19] Other conformers, the antiperiplanar, synperiplanar *(ap,sp)*, the *(ap,sc)*, and the *(ap,ap)* occupy shallow potential wells on the energy surface. These undergo changes in relative energies on going from the 6-31G to the HF/6-31G* level.

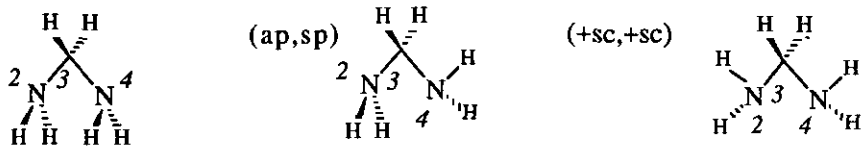
Values for the NBO Fock matrix perturbation analysis of nitrogen lone pair interactions are shown in Table 3. The absence of strong $n\rightarrow\sigma^*$ donation to specific C-N antibonds in the *(+sc,+sc)* conformer, compared to strong donation to antiperiplanar C-N antibonds in the *(ap,sp)* conformer, indicates that such donation does not control the minimum energy geometry in this molecule. Donation to C-H antibonds is in evidence, as shown in Table 3. Summation of the HF/6-31G* delocalization energies shows that the stabilization is greatest for the highest energy (ap,ap) conformer, 110.4 Kcal/mole for all $n\rightarrow\sigma^*$ delocalizations. In comparison, the total HF/6-31G* $n\rightarrow\sigma^*$ delocalization energies of *(+sc,+sc)*, *(ap,sc)*, and *(ap,sp)* conformers are 88.3, 98.4, and 95.0 Kcal/mole, respectively.

Figure 1. Sketches of Low Energy Conformations

(For clarity, unimportant ring hydrogens are not drawn)

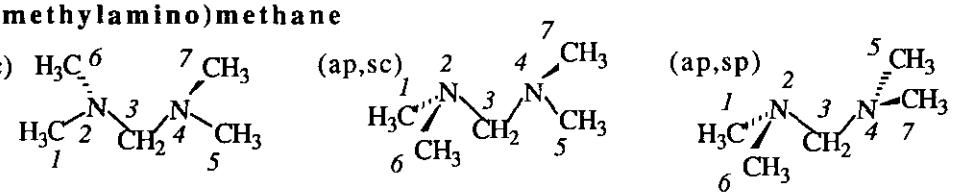
Diaminomethane

(ap,ap) (ap,sp) (+sc,+sc)



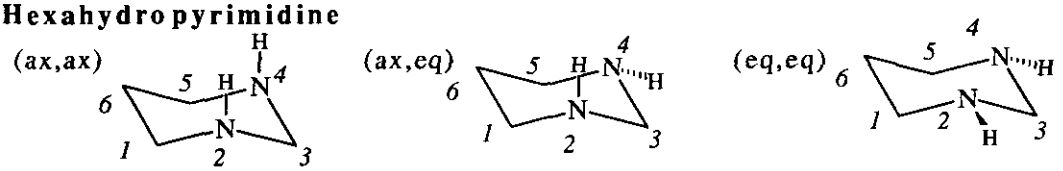
Bis(dimethylamino)methane

(+sc,+sc) (ap,sc) (ap,sp)



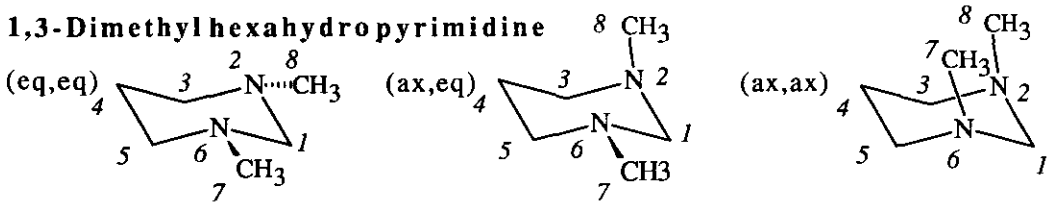
Hexahydropyrimidine

(ax,ax) (ax,eq) (eq,eq)



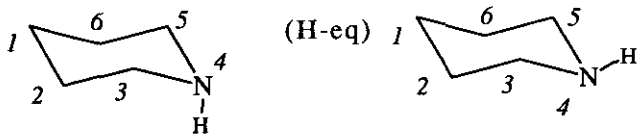
1,3-Dimethylhexahydropyrimidine

(eq,eq) (ax,eq) (ax,ax)



Piperidine

(H-ax) (H-eq)



1-Methyl-2-dimethylaminopiperidine

(ax,ax) (eq,eq) (ax,eq)

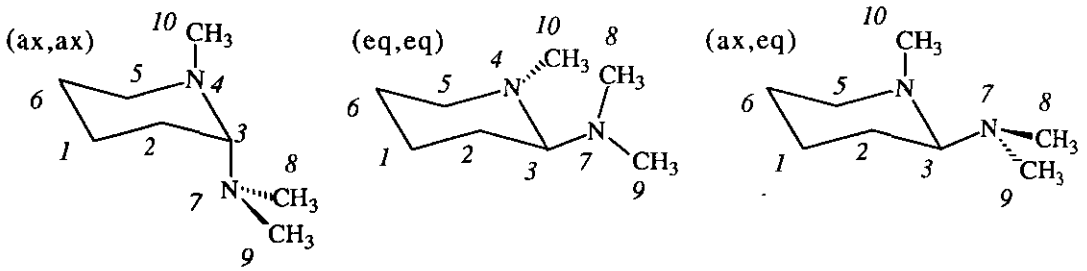


Table 1.	Total Molecular Energies (au)			
Conformer	HF/6-31G	HF/6-31G*	MP2-FC/6-31G*	HF/6-311G**
Diaminomethane				
(ap,ap)	-150.17593	-150.23712	-150.69653	-150.28922
(ap,sc)	-150.17422	-150.23647	-150.69543	-150.28842
(+sc,+sc)	-150.17378	-150.23599	-150.69440	-150.28773
Bis(Dimethylamino)methane				
(+sc,+sc)	-306.20834	-306.35076	-307.33764	-306.43014
(ap,sp)	-306.20490	-306.34560		-306.42478
(ap,sc)	-306.20495	-306.34492		
(ap,ap)	-306.20542	-306.34308		
Hexahydro pyrimidine				
(ax,eq)	-266.05131	-266.17193		-266.24223
(ax,ax)	-266.05140	-266.17168		-266.24193
(eq,eq)	-266.04607	-266.16723		-266.23811
1,3-Dimethylhexahydro pyrimidine				
(eq,eq)	-344.06769	-344.22917	-345.34019	-344.31374
(ax,eq)	-344.06962	-344.22916	-345.34127	-344.31316
(ax,ax)	-344.06528	-344.22234		
Piperidine				
equatorial	-250.08055	-250.18871	-251.00298	-250.25173
axial	-250.07898	-250.18741	-251.00208	-250.25032
1-Methyl-2-dimethylamino piperidine				
(eq,eq)	-422.10608	-422.29538		-422.39811
(ax,ax)	-422.10138	-422.29033		-422.39311
(ax,eq)	-422.10035			
(eq,ax)	-422.09986			

A similar reversal of total $n \rightarrow \sigma^*$ delocalization energies is seen at the 6-311G** level, 98.5 Kcal/mole for higher energy *(ap,sc)* vs. 91.3 Kcal/mole for the lower energy *(+sc,+sc)* conformer. The higher relative energies of the *(ap,sp)* and *(ap,ap)* conformers, with lone pairs widely separated, show that minimization of lone pair repulsion does not control molecular geometry either. The relatively small difference between dipole moments for the *(+sc,+sc)* and *(ap,sp)* conformers (0.32 and 0.34 Debye respectively, at the 6-311G** level) is insufficient to support the hypothesis that the anomeric effect is related to the molecular dipole.

Attempts to quantify an energy for repulsion between lone pairs have been unfruitful. At higher levels of computational model the approximately localized lone pairs are replaced by extensively delocalized molecular orbitals, so simple intuitive pictures become difficult to develop. Relationships utilizing orbital energies and atomic coefficients failed to produce consistent patterns, and

quantitative results were inextricable. This failure suggests that the concept of repulsion between lone pairs is not viable.

Table 2. Second Order Perturbation Analysis of Fock Matrix Energies in NBO Basis: (in Kcal/mole; threshold=1.00): Diaminomethane

NBO Interaction	6-311G** Conformers		
	(ap,ap)	*(ap,sc)*	*(+sc,+sc)*
n (N2) → Ry*2 H1	1.09		1.36
n (N2) → Ry*1 C3	1.17	1.64	1.17
n (N2) → Ry*2 H8	1.10	1.19	1.06
n (N2) → σ* C3 - N4	14.87	13.11	2.91
n (N2) → σ* C3 - H6	2.34	3.35	10.86
n (N2) → σ* C3 - H7	2.37	1.41	2.03
n (N4) → Ry*1 C3	1.17		1.17
n (N4) → Ry*2 H5	1.10	1.28	1.36
n (N4) → Ry*2 H9	1.10	1.07	1.06
n (N4) → σ* C3 - N2	14.84	3.71	2.91
n (N4) → σ* C3 - H6	2.35	1.30	2.03
n (N4) → σ* C3 - H7	2.35	9.97	10.86
Total n → σ* Δ Energies	39.1	32.8	31.6
Total Δ Energies	45.8	38.0	38.8

No simple reason can be advanced for the higher energy of the *(ap,sp)* and *(ap,ap)* conformers of bis(dimethylamino)methane relative to the *(+sc,+sc)* conformer. A speculative reason is the effect of steric interaction between the hydrogens of the methyl groups. Thus, in this case, the minimum energy geometries are a result of subtle interactions of all three factors, plus steric interactions.

The results from these two molecules encapsulate some of the difficulties in quantifying the anomeric effect. The computed geometry of diaminomethane offers an elegant example of conformation apparently controlled by $n \rightarrow \sigma^*$ donation; the conformation of the tetramethyl analog is at complete variance with this effect. This may be because $n \rightarrow \sigma^*$ donation to C-H bonds provides an alternative means for electron delocalization. However, this is hardly relevant to the anomeric effect, since such non-specific delocalization is available in a wide range of molecules and conformations.

Table 3. Second Order Perturbation Analysis of Fock Matrix Energies in NBO Basis: (in Kcal/mol; threshold=1.00): Bis(dimethylamino)methane

NBO Interaction	6-311G** Conformers	
	(+sc,+sc)	*(ap,sc)*
n (N2) → Ry*2,4 C1, C3	1.88	3.91
n (N2) → Ry*1 C6	2.03	1.61
n (N2) → σ* C1 - H8	2.08	1.92
n (N2) → σ* C1 - H9	2.25	2.57
n (N2) → σ* C1 - H10	11.38	11.07
n (N2) → σ* C3 - N4	4.20	15.08
n (N2) → σ* C3 - H11	10.83	2.57
n (N2) → σ* C3 - H12	2.56	
n (N2) → σ* C6 - H16	1.60	1.91
n (N2) → σ* C6 - H17	2.49	2.58
n (N2) → σ* C6 - H18	10.84	11.09
n (N4) → Ry*2 C3		2.34
n (N4) → Ry*1 C5		1.04
n (N4) → Ry*2 C5	1.88	1.63
n (N4) → Ry*1 C7	2.03	1.04
n (N4) → Ry*2 C7		1.62
n (N4) → σ* C3 - N2	4.19	9.60
n (N4) → σ* C3 - H11		2.52
n (N4) → σ* C3 - H12	10.84	2.65
n (N4) → σ* C5 - H13	2.08	1.93
n (N4) → σ* C5 - H14	2.25	2.59
n (N4) → σ* C5 - H15	11.38	11.66
n (N4) → σ* C7 - H19	1.60	1.90
n (N4) → σ* C7 - H20	2.49	2.61
n (N4) → σ* C7 - H21	10.84	11.65
Total n → σ* Δ Energies	91.3	98.5
Total Δ Energies	99.2	111.6

IV. Results for Pyrimidines

Hexahydropyrimidine is related to the diaminomethane system and the 6-31G* and 6-31G** optimized geometries show the similarity. Minimum energy values for all conformers are given in Table 1. Values for the NBO Fock matrix perturbation analysis of nitrogen lone pair interactions are shown in Table 4 for hexahydropyrimidine, and Table 5 for 1,3-dimethylhexahyhdropyrimidine.

The axial, axial *(ax,ax)* conformer of hexahydropyrimidine has the lone pairs in the same relationship as the *(ap,ap)* conformer of diaminomethane, while the axial, equatorial *(ax,eq)* conformer has the lone pairs in the *(ap,sc)* relationship. These conformers differ by only 0.5 Kcal/mole for diaminomethane at the 6-311G** level, and for hexahydro pyrimidine the *(ax,ax)* and *(ax,eq)* differ by only 0.2 Kcal/mole. For comparison, in piperidine the calculated energies show the axial hydrogen conformer to be 0.56 Kcal/mole higher energy than the equatorial hydrogen conformer at the MP2-FC/6-31G* level, and 0.88 Kcal/mole higher at the 6-311G** level. Experimental values for piperidine have resolved in favor of the equatorial hydrogen by values ranging from 0.2 to 0.6 Kcal/mole.[20] The energy penalty for axial hydrogens in hexahydro pyrimidine is expected to be small and stabilization by $n\rightarrow\sigma^*$ donation appears to be the dominant effect.

For 1,3-dimethylhexahydro pyrimidine the computed *(eq,eq)* conformer is favored over the *(ax,ax)* conformer by 4.3 Kcal/mole at the HF/6-31G* level. This is similar to results for bis(dimethylamino)methane for which the *(+sc,+sc)* conformer is favored over the *(ap,ap)* conformer by 4.8 Kcal/mole. The computations find the *(eq,eq)* conformer to be 0.0011 au (0.7 Kcal/mole), above the *(ax,eq)* conformer at the MP2-FC/6-31G* level, which does not agree with the experimental finding of 88% *(eq,eq)* at -150 °C. However, at the 6-311G** level the *(eq,eq)* conformer is 0.0006 au (0.4 Kcal/mole) below the *(ax,eq)* conformer, which corresponds to 82% *(eq,eq)* at -150 °C. In both cases the energy difference is small, and determination of the relative energies of the *N,N'*-dimethylhexahydropyrimidine has taxed experimental methods.[21] A variety of experiments have investigated the equilibrium, with important work carried out by ^{13}C-nmr spectroscopy.[22] The similarity between the energies of the *(eq,eq)* and *(ax,eq)* shows that repulsion between the nominally axial lone pairs in the *(eq,eq)* conformer is insufficient to lower the molecular energy and push equilibrium toward the *(ax,eq)* conformer.

The *(ax,eq)* and *(eq,eq)* conformations of *N,N'*-dimethylhexahydropyrimidine respectively correspond to the *(ap,sc)* and *(+sc,+sc)* conformations of the bis(dimethylamino)methane. The low stabilization energies for specific $n\rightarrow\sigma^*$ donation to N-C antibonds show the similarity. For the low energy *(eq,eq)* conformer, the total stabilization by $n\rightarrow\sigma^*$ delocalization is 93.7 Kcal/mole at 6-311G** level, which is slightly less than the 94.4 Kcal/mole $n\rightarrow\sigma^*$ delocalization for the *(ax,eq)* conformer. Thus, the *N,N'*-dimethylhexahydropyrimidine shows operation of a stereoelectronic effect, which is neither primarily $n\rightarrow\sigma^*$ donation nor primarily lone pair repulsion.

Table 4. Second Order Perturbation Analysis of Fock Matrix Energies in NBO Basis: (in Kcal/mole; threshold=1.00): Hexahydropyrimidine

NBO Interaction	6-311G** Conformers		
	(ax,eq)	*(ax,ax)*	*(eq,eq)*
n (N2) → Ry*2 C1	1.71	1.06	
n (N2) → Ry*2 C3	1.57	1.53	1.33
n (N2) → Ry*2 H8	1.24	1.23	1.17
n (N2) → σ* C1 - N6	12.48	13.71	2.64
n (N2) → σ* C1 - H9	1.72	1.37	2.10
n (N2) → σ* C1 - H10	2.80	3.42	10.91
n (N2) → σ* C3 - C4	9.73	9.85	1.09
n (N2) → σ* C3 - H11	3.36	3.67	11.30
n (N2) → σ* C3 - H12	1.55	1.42	2.05
n (N6) → Ry*2 C1, C5	1.29	2.60	1.33
n (N6) → Ry*2 H7	1.19	1.23	1.17
n (N6) → σ* C1 - N2	2.83	13.71	2.64
n (N6) → σ* C1 - H9	1.80	1.37	2.10
n (N6) → σ* C1 - H10	10.74	3.42	10.91
n (N6) → σ* C5 - C4	1.16	9.85	1.09
n (N6) → σ* C5 - H15	11.18	3.67	11.30
n (N6) → σ* C5 - H16	1.90	1.42	2.05
Total n → σ* Δ Energies	61.2	66.9	60.2
Total Δ Energies	68.2	74.5	65.2

Table 5. Second Order Perturbation Analysis of Fock Matrix Energies is NBO Basis: (in Kcal/mol; threshold=1.00): 1,3-Dimethylhexahydropyrimidine

NBO Interaction	6-311G** N-H Bond Conformers	
	(eq,eq)	*(ax,eq)*
n (N2) → Ry*2 C1		1.16
n (N2) → Ry*2 C3	1.02	1.98
n (N2) → Ry*3 C3	1.12	
n (N2) → Ry*2 C8	2.13	1.77
n (N2) → σ* C1 - N6	2.45	13.75
n (N2) → σ* C1 - H9	2.22	1.55
n (N2) → σ* C1 - H10	11.68	3.47
n (N2) → σ* C3 - C4	1.02	10.03
n (N2) → σ* C3 - H17	2.25	4.00
n (N2) → σ* C3 - H18	11.58	1.29
n (N2) → σ* C8 - H11	2.14	2.02
n (N2) → σ* C8 - H12	2.22	2.50
n (N2) → σ* C8 - H13	11.31	10.93
n (N6) → Ry*2 C1		1.05
n (N6) → Ry*2 C5	1.02	1.11
n (N6) → Ry*3 C5	1.12	
n (N6) → Ry*2 C7	2.13	2.23
n (N2) → σ* C1 - N2	2.45	2.69
n (N2) → σ* C1 - H9	2.22	1.69
n (N2) → σ* C1 - H10	11.68	10.56
n (N2) → σ* C5 - C4	1.02	1.03
n (N2) → σ* C5 - H21	2.25	11.37
n (N2) → σ* C5 - H22	11.58	2.07
n (N2) → σ* C7 - H14	2.14	2.05
n (N2) → σ* C7 - H15	2.22	2.19
n (N2) → σ* C7 - H16	11.31	11.17
Total n → σ* Δ Energies	93.7	94.4
Total Δ Energies	102.3	103.7

V. Results for 1-Methyl-2-dimethylaminopiperidine

The conformations of 1-methyl-2-dimethylaminopiperidine were examined to provide closer comparison to 2-methoxytetrahydropyran, the archetypal anomeric system. No previous experimental or computational results were found for this molecule. Four conformers are possible for 1-methyl-2-dimethylaminopiperidine: both substituents equatorial, both substituents axial, and two with one group axial and the other equatorial. All four conformers are minima on the potential energy surface, and were optimized at the 6-31G level. The two lowest energy conformers were further optimized at the HF/6-31G* and 6-311G** levels. For comparison, similar computations were carried out with H-axial and H-equatorial piperidine. Minimum energy values for all conformers are given in Table 1. Values for the NBO Fock matrix perturbation analysis of nitrogen lone pair interactions are shown in Table 6 for piperidine, and Table 7 for 1-methyl-2-dimethylaminopiperidine.

At all levels, the most stable conformer had both the 1-methyl and the 2-dimethylamino groups in equatorial positions. At the 6-311G** level, a second conformer with both 1-methyl, and 2-dimethylamino axial was 0.005 au (3.1 Kcal/mole) above this. Nitrogens in both these conformers are in the (+sc,+sc) relationship found in bis(dimethylamino)methane. As expected, the NBO analysis shows relatively weak donation from lone pairs to C-N antibonds. Attempts to minimize the geometry of conformers with the nitrogens in *(ap,ap)* and *(ap,sp)* relationships were not successful at the 6-31G level, because these geometries are not potential energy minima.

Table 6. Second Order Perturbation Analysis of Fock Matrix Energies in NBO Basis: (in Kcal/mol; threshold=1.00): Piperidine

NBO Interaction	6-311G** N-H Bond Conformers	
	(H-eq)	*(H-ax)*
n (N4) → Ry*2 C3	1.35	1.59
n (N4) → Ry*2 C5	1.35	1.59
n (N4) → Ry*2 H13	1.21	1.22
n (N4) → σ* C3 - C2	1.34	10.16
n (N4) → σ* C3 - H11	1.71	1.66
n (N4) → σ* C3 - H12	11.38	3.52
n (N4) → σ* C5 - C6	1.34	10.15
n (N4) → σ* C5 - H14	1.71	1.66
n (N4) → σ* C5 - H15	11.37	3.52
Total n → σ* Δ Energies	28.8	28.7
Total Δ Energies	32.8	33.1

Nitrogen compounds are known to show a weak anomeric effect but the minimum energy conformation of 1-methyl-2-dimethylaminopiperidine is anti-anomeric. The second lowest conformer shows slightly increased $n \rightarrow \sigma^*$ C-N donation, but this is again insufficient to exert control over the molecular geometry. The total $n \rightarrow \sigma^*$ delocalization energies are slightly less for the *(ax,ax)* conformation

Table 7. Second Order Perturbation Analysis of Fock Matrix Energies in NBO Basis: (in Kcal/mol; threshold=1.00): 1-Methyl-2-dimethylaminopiperidin

NBO Interaction	6-311G** N-H Bond Conformers	
	(eq,eq)	*(ax,ax)*
n (N4) → Ry*3 C3	1.29	1.03
n (N4) → Ry*2 C5	1.10	2.01
n (N4) → Ry*2 C10	2.06	2.26
n (N4) → σ* C3 - C3	1.03	9.79
n (N4) → σ* C3 - N7	2.10	5.47
n (N4) → σ* C3 - H15	11.31	
n (N4) → σ* C5 - C6		10.09
n (N4) → σ* C5 - H16	2.18	1.30
n (N4) → σ* C5 - H17	11.25	4.18
n (N4) → σ* C10- H26	10.53	12.30
n (N4) → σ* C10- H27	1.89	2.41
n (N4) → σ* C10- H28	2.05	2.62
n (N7) → Ry*4 C3	1.55	1.57
n (N7) → Ry*2 C8	1.95	1.49
n (N7) → Ry*2 C9	1.93	1.71
n (N7) → σ* C2 - C3	10.82	
n (N7) → σ* C3 - N4	5.38	3.07
n (N7) → σ* C3 - H15	1.21	11.00
n (N7) → σ* C8 - H20	1.06	1.64
n (N7) → σ* C8 - H21	3.97	2.36
n (N7) → σ* C8 - H22	11.21	10.69
n (N7) → σ* C9 - H23	1.94	1.28
n (N7) → σ* C9 - H24	3.07	3.08
n (N7) → σ* C9 - H25	12.13	11.16
Total n → σ* Δ Energies	93.1	92.4
Total Δ Energies	103.0	102.5

VI. Steric Hindrance

The agreement between computed and experimental results in this study appears to be adequate to allow the use of computational methods to analyze the conformations of potentially anomeric systems. In diazane systems where the nitrogens are monosubstituted, computation of the magnitude of $n \rightarrow \sigma^*$ delocalization appears to be sufficiently accurate for identification of the dominant factor. In the more numerous and complex situations represented by diazanes with trisubstituted nitrogens some other factor controls the molecular geometry, but again appears to be computed with useful accuracy.

Clearly, the conformations of 1,3-diazanes with monosubstituted nitrogens differ from those of 1,3-diazanes with trisubstituted nitrogens. On this basis, the factor controlling the conformation of 1,3-diazanes with tertiary nitrogens is identified as a subtle form of steric hindrance, i.e., Coulomb repulsion of electron clouds. The steric interaction envisaged here will not be neatly identified by calculating overlap between rigid van der Waals spheres. Instead, the electron iso-density surface of these molecules is imagined to be comparable to a balloon partially filled with liquid; pressure at one point will cause swelling elsewhere. The energy of steric interactions will respond to subtle changes in electron density at crucial points, influenced by the position, electronegativity and symmetry of the atoms in the whole molecule.

VII. Conclusion

The anomeric effect was analyzed using the NBO method, and concepts of steric hindrance. The effect of $n \rightarrow \sigma^*$ donation to C-N antibonds appears to control the conformation of diazane systems in which nitrogens are monosubstituted. The computed and experimental results show that specific $n \rightarrow \sigma^*$ donation to C-N antibonds is irrelevant to the conformations of 1,3-diazane systems in which the nitrogens are trisubstituted. Lone pair electron repulsion would normally operate in the same sense as $n \rightarrow \sigma^*$ donation, but extensive delocalization of the lone pairs in the σ orbitals appears to diminish this effect to insignificant levels. In the methyl substituted molecules, a generalized and subtle type of steric hindrance seems to be dominant over $n \rightarrow \sigma^*$ electron donation in determining conformational preference.

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FOOTNOTES

1) E. Juarista and G. Cuervas, *Tetrahedron*, 1992, **48**, 5019.
2) A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer Verlag, Berlin, 1983.
3) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 1969, **4**, 39.
4) (a) V. G. S. Box, *Heterocycles*, 1990, **31**, 1157.
(b) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Am. Chem. Soc.*, 1968, **90**, 90.
5) T. J. Edwards, *Chem. Ind.*, (London), **1955**, 1102.
6) M. L. Sinnot, *Adv. Phys. Org. Chem.*, 1988, **24**, 113.
7) Gaussian92, Revisions C and D: M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, 1992.
8) 6-31G basis: W. J. Hehre, R. Ditchfield, and J. A. Pople, *J. Chem. Phys.*, 1972, **56**, 2257.
9) (a) 6-31G* basis: P. C. Hariharan, and J. A. Pople, *Theor. Chim. Acta.*, 1973, **28**, 213.
(b) M. S. Gordon, *Chem. Phys. Lett.*, 1980, **76**, 163.
10) MP2: P. Moller and M. S. Plesset, *Physical Review*, 1934, **46**, 618.
11) (a) 6-311G basis: R. Krishnan, J. S. Binkley, R. Seeger, and J. A. Pople, *J. Chem. Phys.*, 1980, **72**, 650. (b) multiple polarization functions: M. J. Frisch, J. A. Pople, and J. S. Binkley, *J. Chem. Phys.*, 1984, **80**, 3265.
12) (a) A. E. Reed, R. B. Weinstock, and F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 735.
(b) J. P. Foster and F. Weinhold, *J. Am. Chem. Soc.*,1980, **102** 7211.
(c) A. E. Reed and F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 1736.
(d) L. A. Curtiss, D. J. Pochatko, A. E. Reed, L. A. Curtiss, and F. Weinhold, *J. Chem. Phys.*, 1985, **82**, 2679. (e) A. E. Reed, L. A. Curtiss, and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899. (f) J. E. Carpenter and F. Weinhold, *J. Molec. Struct. (Theochem)*, 1988, **169**, 41.
(g) F. Weinhold and J. E. Carpenter, *The Structure of Small Molecules and Ions*, Plenum Press, New York, 1988, 227.
13) T. K. Brunck and F. Weinhold, *J. Am. Chem. Soc.*, 1979, **101**, 1700.
14) The Gaussian92 version of the NBO analysis is: NBO v. 3.1; E. D. Glendening, A. E. Reed, J. E. Carpenter, and F. Weinhold,1992. This is added to link 607.
15) (a) R. Faust, E. D. Glendening, A. Streitwieser, and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1992, **114**, 8263. (b) J. E. Carpenter, M. P. McGrath, and W. J. Hehre, *J. Am. Chem. Soc.*, 1990, **111**, 6154. (c) R. A. Moss, B. Wilk, K. Krogh-Jespersen, J. T. Blair, and J. D Westbrook, *J. Am. Chem. Soc.*, 1989, **111**, 250. (d) J. T. Blair, J. C. Weisshaar, J. E. Carpenter, and F. Weinhold, *J. Chem. Phys.*, 1987, **87**, 392.
16) (a) A. E. Reed and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1987, **109**, 7362.
(b) A. E. Reed and P. v. R. Schleyer, *Inorg. Chem.*, 1988, **27**, 4821.
17) H. Senderowitz, P. Aped, and B. Fuchs, *Tetrahedron*, 1992, **48**, 1131.
18) K. B. Wiberg and M. A. Murcko *J. Am. Chem. Soc.*, 1989, **111**, 4821.
19) H. Van der Does, F. C. Mijlhof, and G. H. Reres, *J. Molec. Struct.*, 1981, **74**, 153.
20) I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *Acc. Chem. Res.*, 1975, **8**, 300.
21) T. A. Crabb and A. R. Katritzky, *Adv. Heter. Chem.*, 1984, **36**, 123, and references therein.
22) A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J. Chem. Soc., Perkin Trans.II*, 1979, 143.

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