

15- and 16-membered rings, these are presumed to be the lowest energy conformations.

We find a minimum in strain energy for the 14-membered ring. The greater strain energies of the 12- and 16-membered rings parallel the observed resistance of these rings toward coordination in a planar fashion.^{6,19}

For a given size of macrocyclic ligand of this class, the idealized metal–nitrogen distance calculated by this method represents the hole size for which the strain energy in the ligand is at a minimum. A metal ion having this ideal M–N distance would chelate with minimum strain of the macrocyclic ligand. A larger or smaller metal ion would require readjustment of the M–N distance and an attendant increase in the strain energy of the ligand. The ideal metal–nitrogen bond distances calculated according to this scheme are given in Table III. Most transition metal–nitrogen linkages

Table III. Ideal Metal–Nitrogen Bond Lengths and Planarity of the Macrocyclic Ligands

Ring size	Average ideal bond length (Å)	Average deviation from the ideal N ₄ plane (Å)
[12]	1.83	0.41
[13]	1.92	0.12
[14]	2.07	0.00
[15]	2.22	0.14
[16]	2.38	0.00

fall within the 1.8–2.4 Å range spanned by the idealized values given in Table III, but the most distinctive feature of this data is the regular increase in ideal M–N distance as the number of ring members increases. This amounts to some 0.1–0.15 Å increase in M–N distance for each ring member added. Immediate significance is found in the fact that the metal ions for which we have experimental data (Co(III) and Ni(II)) differ in their M–N distances by just the amount calculated for best fits in rings that differ by one member. That is, the Co–N distance in Co(en)₃³⁺ is 2.00 Å, while the range of Co–N distances for many Co(III) complexes is 1.94–2.03 Å.²⁰ The larger high spin Ni(II) ion has a Ni–N distance of 2.12 Å in Ni(en)₃²⁺,²¹ and the difference of 0.1–0.15 Å between the Co(III)–N and Ni(II)–N distances is general. Thus our calculational model predicts that if the 14-membered ring provides the best fit for Co(III), the 15-membered ring will fit high spin Ni(II) best. It is apparent that the data of Table III can be used to make predictions in many other cases. The close correspondence between prediction and observation for the metal ions we have studied establishes the conformational strain energy as the source of the effects we have described.

A very important aspect of these results is the irrefutable demonstration that mechanical constraint, of molecular origin, on the metal–donor distance can have a profound effect on the strength of the metal–donor interaction. Thus, the rings that are smaller than those that fit best exert abnormally high *Dq* values for the given donor atoms because the distribution of strain energy over the whole complex results in shortening

(19) E. K. Barefield and D. H. Busch, *Inorg. Chem.*, **10**, 1216 (1971).

(20) Y. Saito, "Spectroscopy and Structure of Metal Chelate Compounds," K. Nakamoto and P. J. McCarthy, Ed., Wiley, New York, N. Y., 1968.

(21) L. N. Swink and M. Atoji, *Acta Crystallogr.*, **13**, 639 (1960).

the metal–donor distance. Similarly oversized rings result in markedly low ligand field strengths. In consequence, we caution against the easy assumption that the properties of a given metal–donor linkage are insensitive to the detailed structure of the ligand. It is possible that such mechanical effects may be used in natural systems to alter metal–donor interactions under appropriate conditions, e.g., by changes in the tertiary structure of a protein. An effect of mechanical pressure on ligand field strength has been found in spectroscopic studies on samples under very high pressure.²²

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(22) H. G. Drickamer, *Comments Solid State Phys.*, **3**, 53 (1970).

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Stereoelectronic Properties and Reactivity of the Tetrahedral Intermediate in Amide Hydrolysis. Nonempirical Study of Aminodihydroxymethane and Relation to Enzyme Catalysis

Sir:

We wish to report that an *ab initio* quantum chemical study of aminodihydroxymethane provides theoretical evidence for the operation of marked stereoelectronic effects on the properties of this species. Taking CH(OH)₂NH₂ as a model of the tetrahedral intermediate in amide hydrolysis, the results give insight into the conformational requirements for optimal reactivity and selectivity in this chemically and biologically most important reaction.

Recent experimental results led to the proposal that the selective cleavage of tetrahedral intermediates in ester and amide hydrolysis is controlled by trans-anti-periplanar (app) oriented electronic lone pairs.^{1,2} It has also been considered that orientational effects may play an important role in the catalytic configurations of biochemical reactions.^{3–6}

Our previous theoretical work on the hydroxymethanes^{7a} led to a coherent picture of the electronic and structural properties of these model tetrahedral species and of the resulting reactivity patterns in oxygen exchange, ester hydrolysis, and transesterification reactions.

Calculations (same method as in ref 7; see footnote 2 in ref 7b) were performed on the 15 different, fully

(1) P. Deslongchamps, P. Atlani, D. Fréhel, and A. Malaval, *Can. J. Chem.*, **50**, 3405 (1972).

(2) P. Deslongchamps, C. Lebreux and R. Taillefer, *Can. J. Chem.*, **51**, 1665 (1973).

(3) W. J. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

(4) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971.

(5) R. Henderson and J. H. Wang, *Ann. Rev. Biophys. Bioeng.*, **1**, 1 (1972).

(6) D. R. Storm and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **94**, 5815 (1972); A. Dafforn and D. E. Koshland, Jr. *Biochem. Biophys. Res. Commun.*, **52**, 779 (1973) and references therein.

(7) (a) J. M. Lehn, G. Wipff, and H. B. Bürgi, *Helv. Chim. Acta*, **57**, 493 (1974); (b) H. B. Bürgi, J. M. Lehn, and G. Wipff, *J. Amer. Chem. Soc.*, **96**, 1956 (1974).

staggered, conformations of $\text{CH}(\text{OH})_2\text{NH}_2$. All C-N and C-O bond lengths were optimized (C-H, 1.090; 0.97; N-H, 1.015 Å). All bond angles were taken as tetrahedral. We summarize the general conclusions about stereoelectronic effects on C-N and C-O bond lengths and overlap populations (OP's) in different conformations of $\text{CH}(\text{OH})_2\text{NH}_2$, relating length and OP of a given bond to its relative strength and ease of cleavage.⁸ Results for five selected conformations 1-5 are listed in Table I. Striking orientation-dependent

Table I. Computed Stereoelectronic Effects on Bond Overlap Population and Bond Length in Five Selected Conformations of $\text{CH}(\text{OH})_2\text{NH}_2$

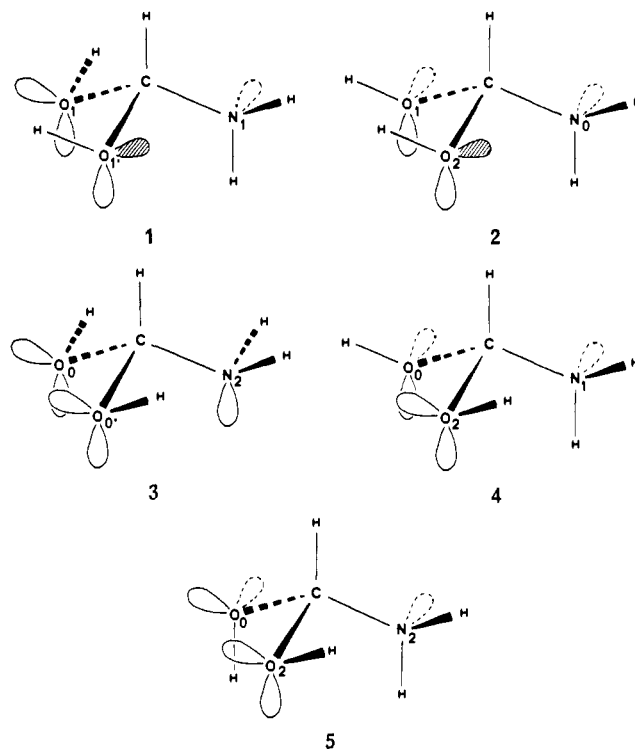
Species (relative energy, kcal/mol)	Bond	App lone pairs ^a	App bonds ^b	Overlap population ^c total (LP)	Optimized bond length (Å)
1 (0.0) ^d	C-N	O ₁	C-O ₁ '	0.430 (-0.033)	1.440
	C-O ₁	O ₁ '	C-N	0.371 (-0.060)	1.415
	C-O ₁ '	N	C-O ₁	0.372 (-0.006)	1.417
2 (5.1)	C-N		C-O ₂	0.490 (+0.025)	1.430
	C-O ₁	O ₂	C-O ₂	0.387 (-0.036)	1.427
	C-O ₂	O ₁ , N	C-O ₁	0.313 (-0.073)	1.447
3 (17.5)	C-N	O ₀ , O ₀ '		0.314 (-0.137)	1.485
	C-O		C-N	0.393 (-0.040)	1.406
4 (6.3)	C-N	O ₂	C-O ₂	0.433 (-0.041)	1.446
	C-O		C-O ₂	0.442 (+0.008)	1.403
	C-O ₂	O ₀ , N	C-N	0.302 (-0.092)	1.440
5 (7.4)	C-N	O ₀ , O ₂	C-O ₂	0.406 (-0.093)	1.473
	C-O ₀		C-O ₂ , C-N	0.458 (-0.012)	1.400
	C-O ₂	O ₀ , N	C-N	0.316 (-0.085)	1.440

^a Lone pairs on heteroatom X app to the bond considered.

^b Polar bonds app to the lone pair(s) belonging to the heteroatom of the bond considered. ^c Total bond OP's and contributions from the localized lone pairs (LP) in the unoptimized species. ^d Total energy = -244.3892 au.

trends are observed. (1) When an electronic lone pair (on oxygen or nitrogen) is app to a polar bond (C-N or C-O), the length of the bond is increased (*ca.* +0.02 Å) and its OP is decreased (*ca.* -0.06 electron). (2) When the nitrogen lone pair is app to a C-O bond, the C-N bond length decreases (*ca.* -0.015 Å) and its OP increases (*ca.* +0.05 electron). Similarly, a slight C-O bond shortening (less than -0.01 Å) and OP increase (*ca.* +0.02 electron or less) occurs when an oxygen lone pair is app to the other C-O bond; very small effects in the same directions seem present when the O lone pair is app to the C-N bond. (3) Effects (1) and (2) lead to the following conclusion; the longest and weakest C-X bond is that which has highest number of app lone pairs (*i.e.*, two) and no X lone pair app to an adjacent polar bond. The above increments define *additivity rules* which yield in all cases the correct patterns of lone pair contributions to OP (C-N) and OP (C-O). (4) The N-H and O-H bonds may be classified as axial (a) or equatorial (e) depending on whether they are respectively parallel or not to be the C-H axis (see 1-5). The a or e rotameric form also influences the C-N and C-O bond lengths and OP's. An e X-H orientation corre-

(8) One may reasonably assume that the effects acting on the intermediate also operate in the transition state. It is not possible at present to assess quantitatively how a change in bond length and OP affects activation energy and reaction rate of the different pathways. However, the available experimental data^{1,2} indicate that such orientational effects are able to impose a preferred cleavage pathway with typically over 90% selectivity.



sponds to a weakening effect on the C-X bonds compared to the a orientation. These conformational effects may also be parametrized. They add to the lone pair effects in the determination of bond properties. In more complex species they may be affected by replacement of hydrogens by substituents. (5) Simultaneous operation of the effects mentioned above leads to a complex pattern of bond properties in the 15 possible conformations of $\text{CH}(\text{OH})_2\text{NH}_2$. The changes in C-N and C-O bond lengths cover respectively about 0.05 and 0.04 Å. The C-N bond is strongest in 2 and weakest in 3, which is the least stable form. The weakest C-O bonds are C-O₂ in 4, 2, and 5. The weakest C-N and C-O bonds all have two app lone pairs (see also ref 2). The most stable form, 1, has comparatively unreactive bonds. (6) The main part of the observed effects is due to the N lone pair and to the p type O lone pairs. After localization of the MO's, the localized lone pairs all give negative contributions to the C-O and C-N OP's except for C-N in form 2 where only a stabilizing interaction is present. (7) As in the case of the hydroxymethanes^{7a} the bond weakening and strengthening effects are in agreement with a simple perturbation scheme;⁹⁻¹² interaction of a lone pair on Y with the antibonding $\sigma(\text{C-X}^*)$ MO in a X-C-Y fragment should lengthen C-X and decrease its OP and shorten C-Y and increase its OP. (8) The above conformational effects on bond OP's are observed with standard, unoptimized, bond lengths as well as with optimized lengths, thus the OP's from a single calculation provide the correct pattern of bond properties. (9) The theoretical patterns of bond properties agree with the available experimental data on

(9) E. A. C. Lucken, *J. Chem. Soc.*, 2954 (1959); P. Linscheid and E. A. C. Lucken, *Chem. Commun.*, 425 (1970).

(10) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, 4, 35 (1969).

(11) L. Radom, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, 94, 2371 (1972).

(12) S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Amer. Chem. Soc.*, 95, 3806 (1973), and references therein.

bond lengths¹³ and reactivity.^{1,2} (10) The optimal paths and conformations deduced from computations may be of particular interest in the study of enzyme reactions.

In a nonenzymatic hydrolysis reaction the most stable tetrahedral species is expected to form preferentially. However this thermodynamically preferred conformer may not be (and, in the present $\text{CH}(\text{OH})_2\text{NH}_2$ case, is not) the kinetically most labile one.

In enzymatic hydrolysis the arrangement of the catalytic groups in the active site may be such as to impose upon the tetrahedral intermediate optimal stereoelectronic effects for fast and specific reaction. By making use of the enzyme-substrate binding forces, the active site may lock the tetrahedral intermediate in the conformation (3 in the present case, or perhaps one of the most closely related other forms) which is *not* the most stable one of the free species but which leads to *easiest* and most *selective* cleavage of the C–N bond in the case of amide hydrolysis. Such conformational locking can occur both in the substrate cleavage step and in the deacylation of the acyl enzyme. Conversely, from an independent knowledge of the optimal conformer it is possible to make inferences about the required geometry of the active site. A special class of nonproductive substrates would be those which bind and undergo reaction with the catalytic groups but lead to a tetrahedral species which favors C–O cleavage over C–N cleavage (as in 2, 4, or 5), thus reverting to the starting material.

The present and previous^{7a} conclusions apply to neutral tetrahedral intermediates. Similar stereoelectronic effects should operate in the charged derivatives occurring in acid or base catalyzed reactions and in other species containing geminal heteroatoms (derived from imines, urea, etc.).

Theoretical studies which help uncover the requirements for optimal reactivity and/or specificity should have impact both on the understanding of enzyme catalysis and on the design of synthetic molecular catalysts.

(13) H. B. Bürgi, J. D. Dunitz, and E. Shefter, in preparation; H. B. Bürgi, private communication.

(14) E. R. A. 265 du C. N. R. S.

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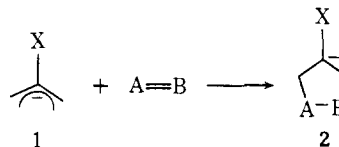
Cycloadditions of Allyl Anions. I. A Regiospecific and Stereospecific Pentannelation Reaction

Sir:

In recent years, the synthetic challenges posed by the much heralded prostaglandins have stimulated a flurry of activity in new syntheses for functionalized cyclopentanes. Despite many very elegant approaches to the aforementioned molecules,¹ there is still noticeably lacking a direct method for the construction of five-

(1) For recent reviews on Prostaglandin syntheses, see U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products," Vol. I, J. ApSimon, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 81–142; N. M. Weinshenker and N. H. Anderson in "The Prostaglandins," Vol. I, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973, pp 5–82.

membered rings which would rival the generality and stereospecificity of the Diels–Alder reaction. The timely formulation and predictions of the Woodward–Hoffmann rules² have clearly delineated the possibility for concerted cycloadditions of allyl anions with unsaturated systems to produce cyclopentyl anions. To date, the symmetry allowed concerted process of the type $\pi 2_s + \pi 4_s$ has not been clearly demonstrated for allyl anions.³ We have been involved in the preparation and utilization of allyl anion synthons of the general type 1, with the objective of cycloadding these four-electron systems to unsaturated molecules (A=B).



Our approach to the synthesis of cyclopentanoids requires that our allyl anion synthons meet the following criteria: (1) that the allyl anion can be rapidly generated under irreversible conditions, (2) that the stability of the allyl anion is not so great as to diminish the nucleophilicity of the carbanion, and (3) that an electron-withdrawing X moiety be cross-conjugated with the allyl system in order to stabilize the resulting cyclopentyl anion. While these requirements are not inherent for a concerted $\pi 2_s + \pi 4_s$ process, we did not expect them to perturb the "concertedness" of the cycloaddition, and in fact we anticipated that they would provide maximum driving force for the cycloadditions. A final point of definition in the design of our allyl synthons needs some elaboration. Substituents at the extremities of the allyl anion must be arranged in such a manner as to prevent formation of an allyl anion which is conjugated with the X group. This objective may be met if an anion directing moiety resides at one end of the allyl system.

In this communication we wish to report on one example of the above approach which promises to be the prototype for a general regiospecific and *stereospecific pentannelation*⁴ process. The present system contains a cyclic ketone function as the electron-withdrawing X group, while the allyl anion is derived from a vinyl sulfide. Over a decade ago, Ireland and Marshall⁵ introduced the exo-thiobutylmethylene moiety as a protecting group for the α position of cyclic ketones. Synthetically, this allowed for specific substitution at the other α positions. We have revived this functionality and transformed it from a protecting group to an activating group. Instead of *n*-butylthiol, we have used *p*-chlorobenzenethiol to form the exo-methylene sulfide for the following reasons: (1) to enhance the crystallinity of the products, (2) to facilitate allyl anion formation and stabilize the resulting anion, and (3) to ensure the unidirectional deprotonation of the vinyl sulfide.

(2) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(3) Kauffmann has stereoselectively trapped the 1,3-diphenyl-2-azaallyl anion (T. Kauffman, *Angew. Chem., Int. Ed., Engl.*, **11**, 290 (1972)) and has reported one instance of the cycloaddition of 2-phenyl allyl anion to stilbene (*Angew. Chem.*, **84**, 292 (1972)). For a summary of allyl anion formations from cyclopropyl anion openings, see W. T. Ford and M. Newcomb, *J. Amer. Chem. Soc.*, **95**, 6277 (1973); R. Huisgen and P. Eberhard, *ibid.*, **94**, 1346 (1972).

(4) The term pentannelation is defined as the annulation of a five-membered ring to another ring of any size in one synthetic operation.

(5) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).