

## 126. Stereoelectronic Properties of Tetrahedral Species Derived from Carbonyl Groups. *Ab initio* Study of Aminodihydroxymethane, $\text{CH}(\text{OH})_2\text{NH}_2$ , a Model Tetrahedral Intermediate in Amide Hydrolysis

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### Summary

An *ab initio* theoretical study of all fifteen fully staggered conformations of aminodihydroxymethane,  $\text{CH}(\text{OH})_2\text{NH}_2$  has been performed. Optimization of the C–O and C–N bond lengths, population analyses and orbital localisation reveal the presence of marked conformation dependent stereoelectronic effects which influence bond lengths and overlap populations. These effects may be parametrized as a function of number and nature of antiperiplanar (*app*) oriented electronic lone pairs (1p) and polar bonds. In a Y–C–X fragment an *app* orientation between a lone pair on Y and the C–X bond increases the length and weakens the C–X bond, shortens and strengthens the C–Y bond. Thus a C–X (X=O,N) bond of  $\text{CH}(\text{OH})_2\text{NH}_2$  is longest and weakest when: (i) it is *app* to two vicinal 1p's; (ii) the X 1p's are not *app* to a vicinal polar bond; (iii) the conformation of the molecule has as many axially oriented 1p's as possible. Results (i) and (ii) agree with a simple hyperconjugation picture involving interaction between an electronic 1p and an *app* oriented antibonding bond orbital  $\sigma^*(\text{C}-\text{X})$ . Bond properties, relative energies and effects on reactivity of the tetrahedral species are discussed, as well as their relations to experimental results on the cleavage of tetrahedral intermediates and to enzyme catalysis.

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Theoretical and experimental studies of reaction paths at carbonyl centres should provide general guidelines for the understanding of the various aspects of the reactivity of the carbonyl function and its derivatives (esters, amides, anhydrides, acetals *etc.*), which play a central role in chemistry and biochemistry.

Addition of a reagent to the carbonyl group, as occurs in the hydrolysis of esters and amides, leads to a tetrahedral intermediate which then decomposes to products or reverts to the starting materials. A theoretical investigation of tetrahedral intermediates provides means for detecting changes in electronic properties with structure and conformation and may be performed on any conformation of the species even those experimentally unavailable or difficult to produce.

Previous theoretical studies have demonstrated the presence of conformation dependent stereoelectronic effects which should markedly affect the properties and

reactivity of ketals, hemiacetals, esters [1] [2], amides [3], phosphate esters [4] carbanions [5] [6]. These effects in a Y-C-X fragment may be qualitatively described by a picture involving hyperconjugative interaction [1p,  $\sigma^*(\text{C-X})$ ] between a classical electronic lone pair (1p) on Y and a  $\sigma$  bond C-X in antiperiplanar (*app*) orientation to the 1p; as a result the C-X bond is lengthened and weakened and the C-Y bond is shortened and strengthened. Thus in a tetrahedral species CHXYZ (X, Y, Z = N, O) stereospecific weakening and lengthening of the C-X bond is strongest when i) C-X is *app* to two 1p's on Y and Z; ii) no X 1p is *app* to a polar C-Y or C-Z bond; iii) the CHXYZ species takes up a given overall conformation.

Interaction of a 1p with an *app*  $\sigma$  bond has been invoked for interpreting nuclear quadrupole coupling constants in chloromethylethers [7], in the perturbational treatment of the anomeric effects [8-10] and in various other cases (see for instance [11] [12]). It is also fundamentally of the same nature as the  $\sigma$ - $\sigma^*$  or 1p- $\sigma^*$  interactions present in the known classical *trans* orientation picture of elimination reactions [12]. Recent experimental studies have stressed the importance of conformation dependent stereoelectronic effects on the reactivity of tetrahedral intermediates for instance in the hydrolysis of esters and amides [13] [14]. Lone pair orientation has been proposed as the factor controlling decomposition of the intermediate: the products obtained under kinetic control arise from preferential cleavage of the C-O or C-N bond which is *app* to two 1p's of the geminal heteroatoms.

In the present report we describe *ab initio* computations of all fifteen fully staggered conformations of aminodihydroxymethane  $\text{CH}(\text{OH})_2\text{NH}_2$  which may be considered as a model of the *neutral* tetrahedral intermediate occurring in the hydrolysis of amides and imidates or in the aminolysis of esters or anhydrides. A qualitative picture of stereoelectronic effects (which might be termed epiphenomenological [15]) emerges from the computations, based on two conformation dependent effects: hyperconjugative (1p,  $\sigma^*$ ) interactions and electrostatic interactions. We shall limit our discussion to the data directly relevant to the question of stereoelectronic effects. To facilitate the description, the lone pairs will be considered as classical directional lobes (for a discussion and references to this point, see [5a] [10]).

A study of stereoelectronic effects in *charged* intermediates  $\text{CH}(\text{OH})_2\text{NH}_3^+$  and  $\text{CH}(\text{OH})(\text{O}^-)\text{NH}_2$  occurring in acid or based catalysed amide hydrolysis [16] [17] will be presented in a later publication.

**Method of Calculation.** - *Ab initio* LCAO-MO-SCF calculations were performed on the 15 different fully staggered conformations of  $\text{CH}(\text{OH})_2\text{NH}_2$  shown in the *Figure 1*. Three different basis sets of Gaussian functions have been used: two of double zeta type, respectively noted DZ (7s, 3p functions on C, O, N, and 4s functions on H, contracted into 3s, 2p, and 2s respectively [18]) and 4-31G [19], and a minimal 3G basis set [19]. The DZ basis set has been used in the preliminary report of this work [3]; the 3G and 4-31G results are also presented here in order to make homogeneous comparison between the neutral and the derived charged species possible.

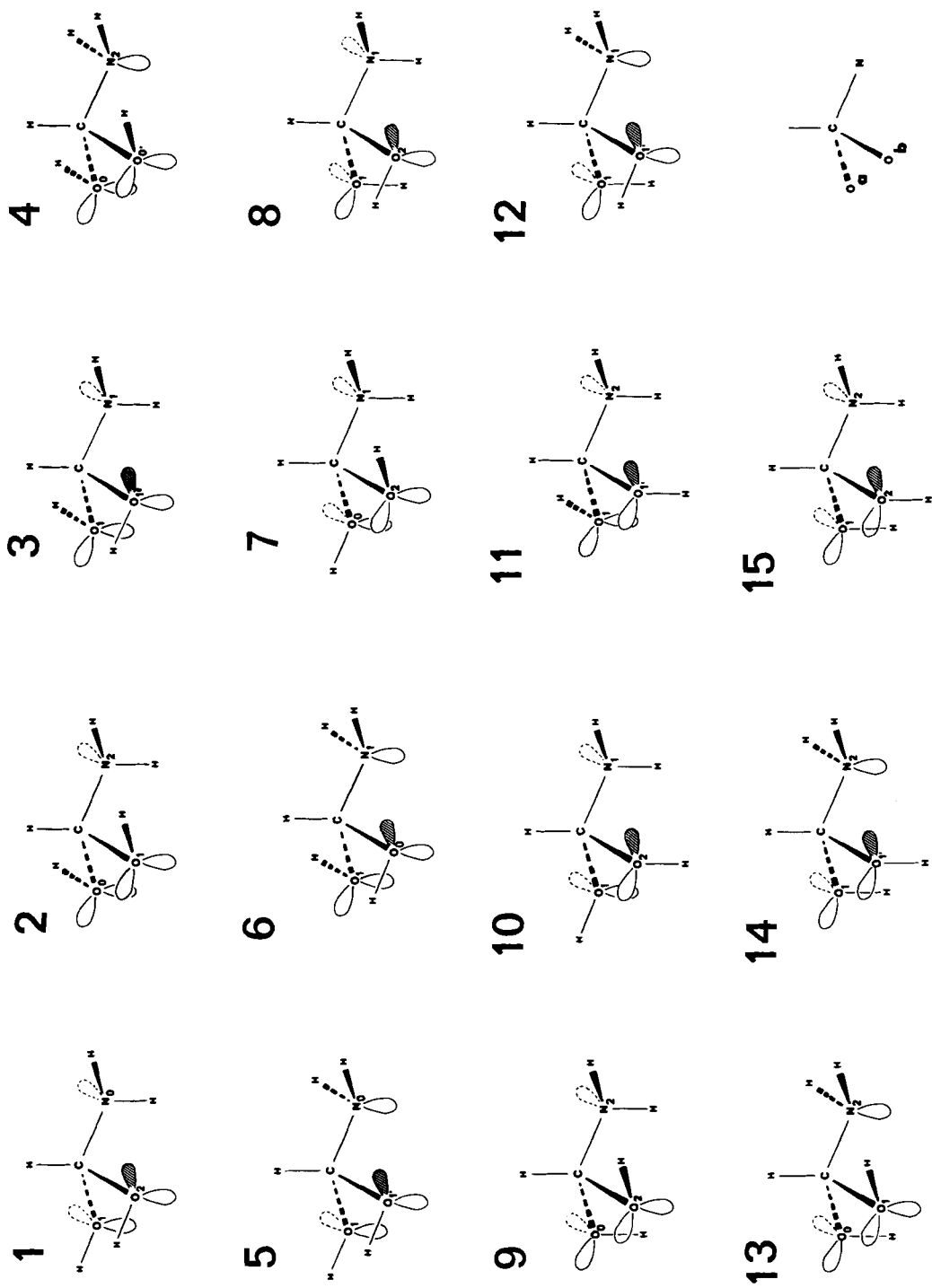


Fig. 1. The 15 gauche conformers of  $HC(OH)_2NH_2$ . The index on the heteroatom X of a C-X bond corresponds to the number of lp's app to that bond.

Table 1. Energy results (kcal/mol)

Species	Relative total energies <sup>a)</sup>					Relative nuclear repulsion <sup>b, d)</sup>	Relative electrostatic energy <sup>e, b)</sup>	
	DZ <sup>b)</sup>	DZ <sup>c)</sup>	4-31G <sup>b)</sup>	3G <sup>b)</sup>	3G <sup>c)</sup>		3G	4-31G
1	5.7	5.1	6.4	3.9	3.8	42.8	5.5	36.4
2	7.8	8.0	8.2	5.8	5.5	23.6	3.1	19.9
3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
4	17.5	17.5	17.7	11.1	10.4	-158.6	9.9	43.5
5	11.6	11.6	12.0	8.0	8.2	-156.5	7.6	37.8
6	11.1	11.2	11.1	7.2	7.0	-174.3	6.7	28.0
7	6.6	6.3	7.0	4.7	4.6	33.0	4.3	27.5
8	1.4	1.3	1.8	0.7	0.7	237.9	2.1	24.0
9	7.4	7.3	8.0	4.4	4.0	253.6	5.5	38.6
10	2.6	2.7	3.0	2.4	2.4	245.9	2.4	28.5
11	2.1	2.3	2.4	1.4	1.1	228.5	0.9	16.2
12	1.9	2.1	1.7	2.1	2.0	13.4	0.0	4.1
13	6.6	6.5	6.5	3.8	4.0	21.1	3.0	15.6
14	1.8	2.1	2.6	1.6	1.2	234.4	0.6	12.5
15	8.1	8.0	9.3	4.6	4.3	491.9	7.0	58.1

a) Energy difference between the listed species and 3; total energy of 3: -244.3888 (DZ<sup>b)</sup>), -244.3892 (DZ<sup>c)</sup>), -244.5790 (4-31G<sup>b)</sup>), -241.7075 (3G<sup>b)</sup>), -241.7077 a.u. (3G<sup>c)</sup>).

b) Results with standard bond lengths (C-O = 1.41 Å; C-N = 1.46 Å).

c) Results with optimized C-O and C-N bond lengths.

d) Nuclear repulsion energy difference between the listed species and 3;  $V_{NN} = 136.3739$  a.u. for 3.

e) The electrostatic interaction energy  $E_{es}$  is calculated from the Mulliken net atomic charges.

 Table 2. C-O and C-N bond properties. (DZ basis set)<sup>a)</sup>

Species	Bond length (Å)			Total overlap population				Overlap population in the 1p <sup>s</sup> <sup>b)</sup>			
	C-N	C-O <sub>a</sub>	C-O <sub>b</sub>	C-N	C-O <sub>a</sub>	C-O <sub>b</sub>	C-H	C-N	C-O <sub>a</sub>	C-O <sub>b</sub>	C-H
1	1.430	1.427	1.447	0.490	0.387	0.313	0.833	0.025	-0.036	-0.073	-0.024
2	1.461	1.404	1.425	0.368	0.427	0.363	0.833	-0.092	-0.020	-0.049	-0.026
3	1.440	1.415	1.417	0.430	0.371	0.372	0.836	-0.033	-0.060	-0.006	-0.024
4	1.485	1.406	1.406	0.314	0.393	0.393	0.838	-0.137	-0.040	-0.040	-0.038
5	1.438	1.424	1.424	0.443	0.359	0.359	0.842	-0.032	-0.046	-0.046	-0.034
6	1.461	1.424	1.403	0.382	0.340	0.411	0.841	-0.068	-0.079	-0.006	-0.035
7	1.446	1.403	1.440	0.433	0.442	0.302	0.832	-0.041	+0.008	-0.092	-0.025
8	1.446	1.420	1.436	0.473	0.404	0.327	0.818	-0.048	-0.053	-0.055	-0.009
9	1.473	1.400	1.440	0.406	0.458	0.316	0.814	-0.093	-0.012	-0.085	-0.010
10	1.453	1.417	1.435	0.479	0.403	0.342	0.818	-0.026	-0.022	-0.080	-0.006
11	1.466	1.420	1.414	0.407	0.386	0.400	0.817	-0.088	-0.043	-0.035	-0.008
12	1.454	1.408	1.417	0.429	0.385	0.384	0.829	-0.066	-0.043	-0.034	-0.016
13	1.478	1.391	1.426	0.354	0.436	0.365	0.824	-0.181	-0.004	-0.059	-0.018
14	1.462	1.411	1.411	0.382	0.408	0.408	0.810	-0.119	-0.046	-0.046	-0.001
15	1.473	1.417	1.440	0.431	0.417	0.352	0.797	-0.096	-0.058	-0.085	+0.006

a) The C-O<sub>a</sub> and C-O<sub>b</sub> bonds are defined in Figure 1.

b) Sum over the five localized heteroatom lone pairs (Boys criteria).

Table 3. C-O, C-N and C-H bond properties (3G and 4-31G basis sets)<sup>a)</sup>

Species	Bond lengths (Å) <sup>b)</sup>			Overlap populations <sup>d)</sup>								Dipole moments (Debye)	
	C-N	C-O <sub>b</sub>	C-O <sub>a</sub>	C-N <sub>b)</sub>	C-O <sub>b</sub> <sub>b)</sub>	C-O <sub>a</sub> <sub>b)</sub>	C-H <sub>b)</sub>	C-N <sub>c)</sub>	C-O <sub>b</sub> <sub>c)</sub>	C-O <sub>a</sub> <sub>c)</sub>	C-H <sub>c)</sub>	b	c
1	1.464	1.437	1.426	0.336	0.265	0.271	0.369	0.264	0.133	0.164	0.425	2.40	3.37
2	1.491			0.321	0.271	0.275	0.369	0.225	0.158	0.180	0.425	2.33	3.69
3	1.477	1.421	1.423	0.328	0.270	0.268	0.369	0.250	0.162	0.153	0.427	1.09	1.87
4	1.499	1.418	1.418	0.317	0.276	0.276	0.364	0.192	0.161	0.161	0.434	3.93	5.73
5	1.472	1.428	1.428	0.331	0.272	0.272	0.363	0.229	0.147	0.147	0.435	3.29	4.63
6	1.486			0.325	0.276	0.269	0.363	0.214	0.170	0.137	0.435	3.31	4.73
7	1.480			0.330	0.263	0.276	0.369	0.245	0.128	0.188	0.425	2.42	3.47
8	1.476	1.433	1.421	0.329	0.264	0.274	0.374	0.258	0.133	0.178	0.419	1.53	1.85
9	1.494	1.436	1.408	0.323	0.264	0.280	0.379	0.231	0.128	0.202	0.418	2.56	3.69
10	1.478			0.331	0.269	0.271	0.374	0.252	0.154	0.163	0.419	1.45	1.73
11	1.491			0.322	0.276	0.268	0.375	0.230	0.183	0.153	0.419	1.34	2.17
12	1.482			0.323	0.271	0.274	0.370	0.233	0.153	0.168	0.431	1.31	1.81
13	1.497			0.316	0.269	0.280	0.370	0.200	0.143	0.191	0.431	2.44	
14	1.493	1.420	1.420	0.314	0.275	0.275	0.376	0.200	0.172	0.172	0.424	1.38	2.28
15	1.492	1.434	1.421	0.323	0.270	0.276	0.379	0.230	0.151	0.175	0.410	2.57	3.54
16	1.503	1.428	1.428	0.320	0.274	0.274	0.378						
17	1.500	1.430	1.424	0.318	0.273	0.275	0.379						

<sup>a)</sup> The C-O<sub>a</sub> and C-O<sub>b</sub> bonds are defined in Figure 1. <sup>b)</sup> 3G basis set. <sup>c)</sup> 4-31G basis set. <sup>d)</sup> These values correspond to standard bond length C-N = 1.46 Å, C-O = 1.41 Å.

All C-O and C-N bond lengths have been optimized with the DZ basis set, and also in some cases with the 3G basis set (C-H = 1.09; O-H = 0.97; N-H = 1.015 Å). All angles were taken as tetrahedral; this is a good assumption for the <HCN and <HCO angles for which a 3G optimization leads to 109.7° in **7** (see also [20]). All dihedral angles were taken as fully staggered conformations; they may in several cases not correspond to the energetically optimal angles but have been fixed in order to force *app* orientations. Some additional computations have been performed on intermediate conformations (see below). The relative energies of the species **1-15** are reported in *Table 1*. *Tables 2* and *3* summarize the optimized bond lengths and the *Mulliken* population analyses<sup>1)</sup>.

**The C-N, C-O and C-H bond properties.** - Although the optimized C-N and C-O bond lengths (BL's) and overlap populations (OP's) are basis set dependent (the 3G BL's are about 0.02 Å greater than the DZ values), the data obtained with the three basis sets show striking orientation dependent properties: the changes in the C-N and C-O BL's cover respectively over 0.05 and 0.04 Å (DZ), 0.035 and 0.030 Å (3G), corresponding to OP variations of respectively 0.17 and 0.15e<sup>-</sup> (DZ), 0.02 and 0.02e<sup>-</sup> (3G), 0.07 and 0.07e<sup>-</sup> (4-31G).

We shall analyse these results by comparing two by two the conformers which differ by a lone pair or bond orientation in the same type of conformation; this type may be characterized by the number of axial and equatorial oxygen and nitrogen lp's, depending on whether they are respectively parallel or not

<sup>1)</sup> More detailed results may be obtained on request.

to the C-H bond. We have plotted in *Figure 2a* the DZ optimized BL's versus the OP of the corresponding unoptimized C-O and C-N bonds. In the absence of ionic bonding, the OP's may be used as indicators of bond length and bond energy [21], especially in a closely related set of structures. One can recognize three groups of bonds according to the number of *app* lp's; the weakest bonds have two *app* lp's; the strongest have no *app* lp. Nevertheless, there are important deviations from linearity between BL's and OP's which indicate that (i) the BL's depend not only on electronic but also on nuclear factors<sup>2)</sup> and (ii) other electronic effects than the interaction of the polar C-N or C-O bond with *app* lp's need to be considered (see below).

The following orientation dependent trends are observed:

1) When an electronic lp (on oxygen or nitrogen) is *app* to a polar bond (C-N or C-O), the length of this bond is increased (*ca.* +0.02 Å, DZ; +0.015 Å, 3G) and its OP is decreased (*ca.* -0.06 e<sup>-</sup>, DZ; -0.005 e<sup>-</sup>, 3G; -0.02 e<sup>-</sup>, 4-31G<sup>3)</sup>).

2) When the nitrogen lp is *app* to a C-O bond, the C-N BL decreases (*ca.* -0.015 Å, DZ; -0.007 Å, 3G) and its OP increases (*ca.* +0.005 e<sup>-</sup>, DZ; +0.007 e<sup>-</sup>, 3G; +0.03 e<sup>-</sup>, 4-31G<sup>4)</sup>) despite the higher nuclear repulsion energy in those forms where a N-H bond is axial (see *Table 1*).

Similarly, a slight C-O bond shortening (less than -0.01 Å, DZ) and OP increase (*ca.* +0.02 e<sup>-</sup> or less, DZ) occurs when an oxygen lp is *app* to the other C-O bond rather than to the C-N bond<sup>5)</sup> (This is not apparent with the 3G basis set).

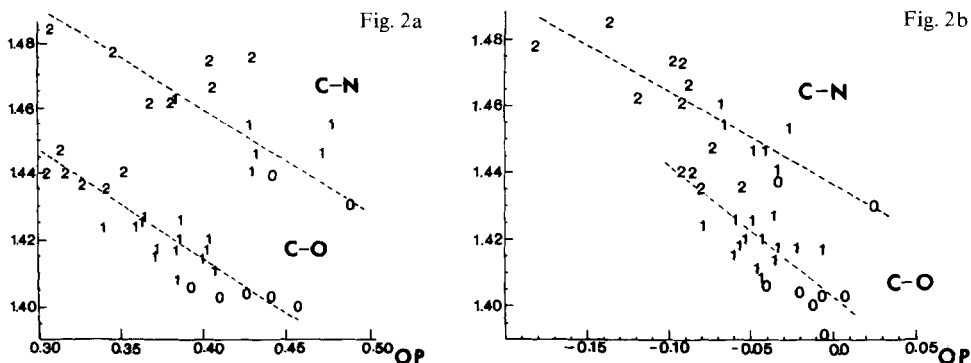


Fig. 2. Optimized C-N (upper part) and C-O (lower part) bond lengths in species 1-15 versus the corresponding overlap populations in the forms with standart bond lengths (C-O=1.41 Å, C-N=1.46 Å; DZ basis set).

Fig. 2a. Total OP's. Fig. 2b. OP's in the five localized lp orbitals.

The figures 0, 1, 2 represent the points corresponding to C-O or C-N bonds which are *app* to respectively 0, 1 and 2 lone pairs as pictured in structures 1-15.

- 2) For example, the OP of the CO<sub>0</sub> bond in **9** (0.458 e<sup>-</sup>) being much greater than in **4** (0.393 e<sup>-</sup>), a marked strengthening of this bond is expected in **9**. It does not occur because it would increase the nuclear repulsion energy ( $\Delta V_{NN} = 412$  kcal/mol for **4-9**! See *Table 1*).
- 3) Compare the C-N bonds in **1, 2, 3, 7**; in **4, 5, 6**; in **8** to **11**; the two C-O bonds in **1, 2, 9, 15**; the C-O<sub>a</sub> bond in **1, 2, 7**; the C-O<sub>b</sub> bond in **1, 3**.
- 4) Compare the C-N bonds in **1-5, 2-4, 3-6, 6-7, 10-12, 11-13, 14-15**.
- 5) Compare the C-O<sub>b</sub> bond in **2-3, 6-4, 8-9, 12-13**.

3) The above increments found for the OP's define *additivity rules* which yield in all cases the correct pattern of contributions to OP(C-N) and OP(C-O)<sup>6</sup>; for example with the DZ basis set, we obtain:

$$\text{OP}(\text{CN}) = -0.06 n_1 + 0.05 n_2 + \text{OP}_0(\text{CN})$$

$$\text{OP}(\text{CO}) = -0.07 n'_1 - 0.05 n'_2 + 0.02 n'_3 + \text{OP}_0(\text{CO})$$

where  $n_1$  = number of oxygen lp's *app* to CN,  $n'_1$  = number of nitrogen lp's *app* to CO,  $n'_2$  = number of oxygen lp's *app* to CO;  $n_2 = 1$  or  $0$ ,  $n'_3 = 1$  or  $0$  respectively if the N or the O lp is *app* to another polar bond, or not.

4) The constants  $\text{OP}_0(\text{CN})$  and  $\text{OP}_0(\text{CO})$  depend on the conformation:  $\text{OP}_0(\text{CN}) = 0.44$  (for **1** to **7**),  $0.48$  (for **8-13**),  $0.50$  (for **14** to **15**);  $\text{OP}_0(\text{CO})$  varies from  $0.39$  (for **4**, **5**, **6**) to  $0.45$  (for **15**). These variations in  $\text{OP}_0$  are grossly comparable to the increment of a single lp; they represent the contributions of all conformational effects which remain after having parametrized and subtracted those attributed to the relative orientation of lp's and C-X bonds. These results clearly indicate that an axial orientation of the X lp (X-H bond equatorial) corresponds to a weakening effect of the C-X bond compared to an equatorial orientation of this lp (X-H bond axial)<sup>7</sup>.

5) As a consequence, the C-X bond ( $X = \text{O}, \text{N}$ ) is longest and weakest when (i) it is *app* to two vicinal lp's, (ii) the X lp is not *app* to an adjacent polar C-Y bond, and (iii) the molecule adopts a conformation where there are as many axial lp's as possible.

6) The OP of the C-H bond is also conformation dependent<sup>8</sup>, but contrary to the C-N and C-O case, the different basis sets give opposite trends: the C-H OP increases with the number of *app* lp's with both DZ and 4-31G basis sets, but decreases with the 3G basis set (Table 2 and 3). Consequently, it is not possible to use C-H OP's as a measure of C-H bond properties.

7) The orientational effects 1) and 2) are in accord with a *qualitative picture* derived from simple perturbation theory: the interaction between the antibonding  $\sigma^*_{\text{C-X}}$  orbital and a vicinal *app* Y lp should lengthen and weaken the C-X bond, and shorten and strengthen the C-Y bond<sup>9</sup>. Since the relative orbital energies are expected to follow the sequence  $\sigma(\text{CH}) < \text{O lp} < \text{N lp}$ ,  $\sigma^*_{\text{CO}} < \sigma^*_{\text{CN}} < \sigma^*_{\text{CH}}$ , the strongest interaction occurs between the N lp, which is the HOMO of all species **1-15**<sup>10</sup>, and the *app*  $\sigma^*_{\text{CO}}$  bond. Also the oxygen lp interacts more efficiently with the *app*  $\sigma^*_{\text{CO}}$  than with  $\sigma^*_{\text{CN}}$ .

<sup>6</sup>) Since the BL's depend not only on electronic but also on steric factors, it is more difficult to parametrize the lp orientational effects on BL's.

<sup>7</sup>) The increase in C-X bond OP which is observed when a lp goes from an axial to an equatorial position corresponds to a bond shortening only if the nuclear repulsion energy change is not too great (compare C-N in **2** and **9**, **3** and **8**, **4**, **13** and **14**).

<sup>8</sup>) The C-H force constants [22] and C-H reactivity in ozonolysis reactions [23] depend markedly on lp heteroatom orientation.

<sup>9</sup>) In simpler systems, the p type oxygen lp is at higher energy than the  $\sigma$  type oxygen lp [10]. In the species **1-15**, the splitting of the oxygen lp orbitals (MO's N<sup>o</sup> 13 to 16) goes from 1.6 eV (in **6**) to 5.1 eV (in **10**) but, as in  $\text{H}_2\text{C}(\text{OH})_2$  [24], the  $\sigma$  and p type oxygen lp's show much complex mixing<sup>1</sup>. For this reason we use the localized  $\text{sp}^3$  lp's in order to simplify the present analysis.

<sup>10</sup>) The nitrogen charge in the HOMO of species **1-15** is greater than 1.5e (DZ).

The fact that the main part of the effect observed on C-N and C-O bond properties is due to the nitrogen and oxygen 1p's can be shown from the five *localized* lone pair orbitals (DZ basis set; *Boys* criteria [25]): the corresponding C-N and C-O OP's (Table 2) show the same trends as the total OP's (see also plot of Figure 2b); they are always negative, except for C-N in form 7 where the two stabilizing interactions (N 1p,  $\sigma^*_{CO}$ ) and (O 1p,  $\sigma^*_{CN}$ ) are present. Similar results can also be obtained from the five canonical highest occupied MO's of 1-15, which are essentially the nonbonding lone pair orbitals<sup>1)</sup>.

The 'conformational effect' defined by the OP<sub>0</sub> values in 4) contains a contribution from a 4 electron destabilizing interaction between a heteroatom X 1p orbital and the *bonding*  $\sigma_{CH}$  orbital, which weakens the C-X bond more with X=O than with N. The way in which this interaction influences the C-H bond itself leads to inconsistencies due to the weakness of the effect; the total C-H OP's (Table 2) show opposite trends when different basis sets are used<sup>1)</sup>.

Changes in C-O bond lengths with orientation may be found in crystal structures of tetrahedral species like CH<sub>2</sub>(OR)<sub>2</sub> [26]. A striking example involving N and O atoms is found in an *app* oriented N-C-OCO fragment in the structure of the alkaloid haplophytine; the C-O bond (1.53 Å) is significantly longer than the corresponding bonds in  $\gamma$ -lactones (1.45-1.47 Å), while the N-C bond (1.42 Å) is unusually short (average 1.47 Å) [27].

**Relative energies of the 15 *gauche* conformers.** - The relative total energies  $\Delta E_T$  (Table 1) show also marked conformation dependence, but are rather insensitive to BL optimization. They follow the same trend with the three basis sets; the DZ and 4-31G basis sets give very close values, higher than the 3G values. Since we have restricted ourselves to *gauche* rotamers, the greatest energy difference, found here between 3 and 4 (about 17 kcal/mol, DZ and 4-31G; 11 kcal/mol, 3G)<sup>12)</sup> might still be higher if other forms were considered. The energy difference between these intermediates and the corresponding transition states could then also show important conformation dependent changes.

There is no correlation between the relative total energies and the relative bond length variations due to the lone pair orientations. The most stable conformer 3 has rather short C-O and C-N bonds, and the least stable 4 has the weakest C-N bond; on the other hand, strong C-O and C-N bonds are found in conformers of relatively high energy, like 5 and 6. Although the interaction of anomeric type shown above is stabilizing, it does not *alone* govern the changes in total energy, which result also from interactions between other MO's as well as from electrostatic contributions: internuclear repulsions (Table 1), dipole-dipole bond interactions, *etc.* Indeed the most stable conformer 3 possesses the greatest number of internal hydrogen bonds, whereas the least stable 4 has no hydrogen bond, but possesses the greatest number of parallel lone pairs; in terms of the 'gauche effect'

<sup>1)</sup> Nevertheless the total electron population on H of the C-H bond increases with the number of *app* 1p's with the three basis sets<sup>1)</sup>.

<sup>12)</sup> An energy difference of 11.0 kcal/mol has been calculated for different conformations of HC(OH)<sub>3</sub> [20].



[28], this is an unfavorable situation. A simple electrostatic picture also yields the correct energy trends: the relative energies calculated from the interaction between the *Mulliken* atomic net charges parallel closely the relative total energies, especially with the 3G basis set (the 4-31G values are overestimated as a result of exaggerated charges separation with this basis set). In fact if one just considers the number of parallel 1p, 1p arrangements, the species 1-15 may be grouped in four sets: the relative energies of the species having 1, 2, 3 and 4 such arrangements are respectively 0 (for 3) - 2.6, 5.7-8.1, 11.1-11.6 and 17.5 (for 4) kcal/mol (DZ basis set).

The importance of the nuclear term in the  $\Delta E_T$ 's (*Table 1*) indicates that substitution of H atoms by alkyl groups to give hemioorthoamides could modify seriously the relative energies<sup>13</sup>. The above energy differences correspond to intrinsic properties of the bare species; they should be reduced or may even be reversed by environmental effects in solution or in enzyme catalysis: since the least stable conformers have the greatest dipole moments (*Table 3*), they should be more stabilized by solvation or polar neighbouring groups than the most stable conformers.

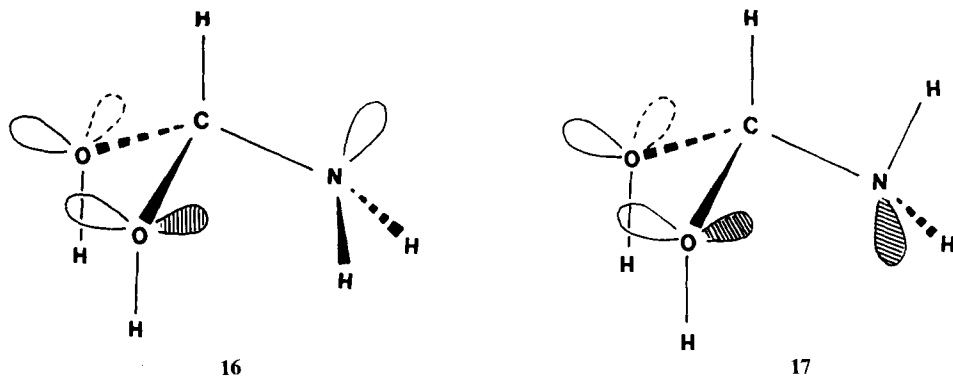
**Bond properties of the tetrahedral species and reactivity.** - The orientational effects found for the tetrahedral intermediate should also operate in the transition state for its formation and decomposition. As a result they are expected to influence the reactivity and selectivity of the processes. This should be the case in gas phase reactions and has been observed in solution [13] [14]. It is clear that solvation and acid-base catalysis effects must play an important role. The theoretical studies (and/or gas phase experimental results) provide information about the *intrinsic* properties of the reacting species; as a consequence, the difference with the energetics in solution provides a powerful approach to the study of solvent effects, proton transfers *etc.*

Simultaneous operation of the effects mentioned above leads to a complex pattern of bond properties in the 15 gauche conformations of  $\text{HC}(\text{OH})_2\text{NH}_2$ , where three classes of conformers can be distinguished: (i) the conformers 3, 5, 6, 12 have both strong C-O and C-N bonds with not more than one *app* 1p; such species should be the least reactive; (ii) species of the second class have two rather strong bonds and one weak bond; this bond is C-N in 2, 4, 11, 13, 14 and C-O in 1, 7, 8, 10; selective cleavage of this bond is expected; (iii) species of the third class have one short C-O bond and both a weak C-N and a weak C-O bond (9, 15); in this case, the bond cleavage should be less selective.

In the above classification, only the gauche conformers have been considered because the heteroatom 1p's have the best orientation for interaction with *app* vicinal bonds. Eclipsed conformations where a 1p is *syn* with respect to a vicinal bond have also been considered; the stereoelectronic effects are weaker and the steric effects are greater than in the gauche conformations, as exemplified on the

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<sup>13</sup>) Such a substitution should not modify significantly the 1p effects on C-N and C-O bond properties. As a check, we have found that the optimization of the C-O BL in  $\text{H}_2\text{C}(\text{OH})_2$  and  $\text{H}_2\text{C}(\text{OCH}_3)_2$  in the same conformation, where only one C-O bond has an *app* 1p, gives the same BL's and OP's differences in the two molecules (respectively 0.027 Å and 0.010e<sup>-</sup>, 3G basis set).



conformers **16** and **17** derived from **14** and **15** respectively. The C–O and C–N bonds are longer in **16** than in **14** by 0.008 Å and 0.010 Å respectively due to the increased nuclear repulsion in the eclipsed form ( $\Delta V_{\text{NN}}=402$  kcal/mol). In **17**, the C–O bond which is *syn* parallel to the nitrogen lp is weaker and longer ( $\Delta\text{OP}=0.002e$ ,  $\Delta\text{BL}=0.006$  Å) than the other C–O bond, but this difference is weaker than in **15** ( $\Delta\text{OP}=0.006e$ ,  $\Delta\text{BL}=0.013$  Å); the C–N bond strengthening due to the (N lp,  $\sigma^*_{\text{CO}}$ ) interaction is also weaker in **17** than in **15** (Table 3); thus a *syn* parallel lp has weaker effects than an *app* lp (see also [29]).

We may now discuss which of the conformers studied here may play a role in the basic hydrolysis of imidate salts investigated experimentally [13] [14]. According to the microreversibility principle, the C–OH bond formed most easily by addition of the hydroxide ion on imidate salts should also be cleaved most easily; it should thus be weak, being *app* to two lp's and having only one of its own lp's *app* to one of the other two polar bonds. Conformers of the first class should then not be formed directly. Since it is not possible to have simultaneously two weak C–O bonds, but at most one weak C–O bond and one weak C–N bond, the only conformers which would decompose without conformational change are **9** and **15**. They correspond respectively to the **38A** and **42** species of reference [13] which indeed lead specifically to C–N bond cleavage under kinetic control<sup>14</sup>). Species of the second class with only a weak C–O bond (**1**, **7**, **8**, **10**) should not decompose immediately to the products since cleavage of that C–OH bond gives back the starting material; they must first convert by rotation around the C–O or C–N bonds into conformations where the initially formed bond is shortened and another bond (C–O or C–N) is weakened. Starting with conformation **10**, where C–O<sub>2</sub> is the newly formed bond, (*cf.* structure **52** of reference [13]), rotation around the C–N bond leads to **8** (*cf.* **53** in [13]), where the C–N bond is strengthened and the weakened C–O bond ( $\Delta\text{BL}=0.019$  Å, DZ basis set) is cleaved; rotation around the C–O<sub>1</sub> bond in **10** leads to **11** (*cf.* **54** in [13]), where the weakened

<sup>14</sup>) This implies the energy barrier for conformational changes in **9** and **15** is higher than the energy barrier for their breakdown [13]. **9** and **15** are relatively high energy species which could be nearer to the transition state than the other conformers; furthermore the orientation of the oxygen lp's is expected to stabilize the transition state for C–N cleavage.

C-N bond ( $BL = 0.013 \text{ \AA}$ , DZ basis set) is cleaved [13]. Since this implies that the rotation of the C-O and C-N bonds in **10** must be more facile than its breakdown to the products, we have investigated the energy profile for the conversion of **10** to **8** and of **10** to **11** (3G basis set) and found low energy barriers of respectively 0.9 and 1.2 kcal/mol. The interconversion of these rotamers should indeed be very fast<sup>15</sup>). Species of the second class can also convert into unreactive species of the first class (for example **10** to **12**). The critical point for such processes is the lifetime of the reactive species and the energy barriers for interconversion.

Finally, one should also note that if two forms react *via* the *same* transition state (TS), the reaction should be slower for the more stable form, which may be that stabilized by 'anomeric' type interactions. For instance, consider forms **1** (or **5**) and **14**; C-N cleavage *via* a common TS should be faster for **1** than for **14** (since **1** is less stable than **14**; *Table 1*) although **14** presents stronger (O lp)- $\sigma$  (C-N) stereoelectronic interactions and has a longer C-N bond. If however the reaction of the two forms proceeds to a common intermediate like  $^+\text{CH}(\text{OH})_2$ , *via* two different transition states TS-**1** and TS-**14**, stabilization by the stereoelectronic effects is expected to be larger in TS-**14** than in TS-**1**; **14** should react faster than **1** if TS-**14** is stabilized more with respect to TS-**1** than **14** with respect to **1**. This appears quite likely, especially in apolar media (or gas phase) where no solvation occurs. On the other hand, form **4** which has both the favorable *app* (O lp)-(C-N) orientations of **14** as well as higher energy than **14** should be especially labile. It is clear that the observation or non-observation of stereoelectronic effects on reactivity is not a simple matter and depends on reaction path and environmental effects. Thus, a recent study of the relative rates of hydrolysis of conformationally locked acetals did not show evidence for stereoelectronic control [30].

The role of stereoelectronic effects is of particular interest in the *hydrolysis of amides*, which is one of the most important chemical and biological reactions. In a non enzymatic reaction, the most stable tetrahedral intermediate may form preferentially when there are no conformational constraints. However, this thermodynamically preferred conformer may not be (and in the present case of  $\text{HC}(\text{OH})_2\text{NH}_2$  is not) the 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 substrat binding forces, the active site may lock the tetrahedral intermediate in a conformation which is *not* the most stable one of the free species (for example **4**, or **2**, **11**, **13**, **14**) but which leads to *easiest* and *most selective* cleavage of C-N bond. Such conformational locking can occur both in the substrate cleavage step and in the deacylation of the acyl enzyme. Specific interconversion of tetrahedral species can also be considered in the enzyme; they may be brought about not only by internal rotation or nitrogen inversion but also by proton transfer whose direction may be subject to the stereoelectronic effects. A special class of non productive substrates would be those which bind and undergo

<sup>15</sup>) The different conformers could also interconvert by nitrogen inversion, but this process has a higher barrier than rotation; flattening of the nitrogen site in species **7**, **10**, **11** raises the energy by about 8 kcal/mol (calculations with the DZ basis set + a d polarization function on nitrogen).

reaction with the catalytic groups but lead to tetrahedral species of the second class with only one weak C–O bond, thus reverting to starting material. Substrates yielding species of the first class (*via* some kind of carbonyl activation for instance) could be inhibitors. Another case of unreactive substrates may be found when steric hindrance prevents the favorable lp orientations [31]. A detailed theoretical study of all species may be of use in conjunction with crystallographic data on the disposition of catalytic groups in enzyme hydrolytic reactions for elucidating the intimate mechanism of the enzymatic reaction.

**Conclusion.** – The present results apply to *neutral* tetrahedral species. Similar stereoelectronic effects are found [32] in the charged derivatives occurring in acid or base catalysed reactions of carbonyl or imine functions (formation, hydrolysis, aminolysis of oximes, imines, esters, amides, amidines, ureas, carbamates, *etc.*) [33]. Studies of such species have bearing on the effect of the NH<sub>2</sub> groups basicities which differ in the various conformations and have been shown to determine the cleavage of the tetrahedral intermediate in the aminolysis of amidines [34]. The formation of these charged species involves proton transfer processes whose stereochemistry may also be subject to stereoelectronic effects since different conformations are involved depending on the direction of formation or cleavage of an X–H bond (X=O,N). Stereoelectronic effects are general phenomena also found in tetrahedral species at centers other than carbon (for instance phosphorus [4]) and in other species than tetrahedral ones (for instance bipyramidal species [4]). They may be expected to operate at larger distances, for instance in 1,3-elimination and fragmentation reactions (see for example [35]). Finally, in a broad area of inorganic chemistry, stereoelectronic effects could affect the polar coordination bonds of transition metal complexes and therefore influence their geometries and reactivities (for instance ligand exchange processes and redox potentials).

#### REFERENCES

- [1] J. M. Lehn, G. Wipff & H. B. Bürgi, *Helv.* 57, 493 (1974).
- [2] H. B. Bürgi, J. D. Dunitz, J. M. Lehn & G. Wipff, *Tetrahedron* 30, 1563 (1974).
- [3] J. M. Lehn & G. Wipff, *J. Amer. chem. Soc.* 96, 4048 (1974).
- [4] a) J. M. Lehn & G. Wipff, *J. chem. Soc. Chem. Commun.* 1975, 800; b) D. G. Gorenstein & D. Kar, B. Luxon & R. Momii, *J. Amer. chem. Soc.* 98, 1668 (1976); D. G. Gorenstein & D. Kar, *J. Amer. chem. Soc.* 99, 672 (1977); c) D. M. Hayes, P. A. Kollman & S. Rothenberg, *J. Amer. chem. Soc.* 99, 2150 (1977).
- [5] a) J. M. Lehn & G. Wipff, *J. Amer. chem. Soc.* 98, 7498 (1976); b) see also F. Bernardi, I. G. Csizmadia, A. Mangini, H. B. Schlegel, M. H. Whangbo & S. Wolfe, *J. Amer. chem. Soc.* 97, 2209 (1975).
- [6] J. M. Lehn & G. Wipff, *Helv.* 60, 1239 (1977).
- [7] E. A. C. Lucken, *J. chem. Soc.* 1959, 2954; P. Linscheid & E. A. C. Lucken, *Chem. Commun.* 1970, 425.
- [8] C. Romers, C. Altona, H. R. Buys & E. Havinga, *Topics Stereochemistry* 4, 39 (1969).
- [9] G. A. Jeffrey, J. A. Pople & L. Radom, *Carbohydr. Res.* 25, 117 (1972).

- [10] S. David, O. Eisenstein, W.J. Hehre, L. Salem & R. Hoffmann, *J. Amer. chem. Soc.* **95**, 3806 (1973) and references cited therein; O. Eisenstein, N.T. Anh, Y. Jean, A. Devaquet, J. Cantacuzène & L. Salem, *Tetrahedron* **30**, 1717 (1974).
- [11] G. Baddeley, *Tetrahedron Letters* **1973**, 1645; I. Tvaroska & T. Bleha, *Tetrahedron Letters* **1975**, 249; R.C. Bingham, *J. Amer. chem. Soc.* **97**, 6743 (1975); J. Augé & S. David, *Nouv. J. Chim.* **1**, 57 (1977).
- [12] N.D. Epiotis, W.R. Cherry, S. Shaik, R.L. Yates, F. Bernardi, 'Topics in Current Chemistry', *Fortschritte der chemischen Forschung* n° 70, Springer-Verlag Berlin, Heidelberg, New York 1977; G. Klopman, 'Chemical Reactivity and Reaction Paths', Wiley Interscience 1974.
- [13] P. Deslongchamps, *Pure appl. Chemistry* **43**, 351 (1975).
- [14] P. Deslongchamps, *Tetrahedron* **31**, 2463 (1976); P. Deslongchamps, U.O. Cheriyen, A. Guida, R.J. Taillefer, *Nouv. J. de Chim.* **1**, 235 (1977) and references cited therein; P. Deslongchamps, C. Lebreux & R. Taillefer, *Canad. J. Chemistry* **51**, 1665 (1973).
- [15] J.M. Lehn, *Topics Current Chemistry* **15**, 311 (1970).
- [16] A.C. Hopkinson & I.G. Csizmadia, *Theoret. chim. Acta* **31**, 83 (1973).
- [17] G. Alagona, E. Scrocco & J. Tomasi, *J. Amer. chem. Soc.* **97**, 6976 (1975).
- [18] B. Roos & P. Siegbahn, *Theoret. chim. Acta* **17**, 209 (1970); S. Huzinaga, *J. chem. Physics* **42**, 1293 (1962).
- [19] W.J. Hehre, W.A. Lathan, R. Ditchfield, M.D. Newton & J.A. Pople, Q.C.P.E. n° 236, University of Indiana, Bloomington, Indiana. We thank Professor W.J. Hehre for a copy of this program.
- [20] W.A. Lathan, L. Radom, W.J. Hehre, J.A. Pople, *J. Amer. chem. Soc.* **95**, 699 (1973).
- [21] P.O.D. Offenhardt, 'Atomic and Molecular Orbital Theory', McGraw Hill, New York, N.Y. 1970; G. Leroy, P. Martin & D. Peeters, *J. chim. phys.* **71**, 319 (1974).
- [22] S. Wolfe, H.B. Schlegel, M.H. Whangbo & F. Bernardi, *Canad. J. Chemistry* **52**, 3787 (1974) and references cited therein; L.J. Bellamy & D.W. Mayo, *J. phys. Chemistry* **80**, 1217 (1976).
- [23] P. Deslongchamps, C. Moreau, D. Fréhel & P. Atlani, *Canad. J. Chemistry* **50**, 3402 (1972).
- [24] G. Wipff, Thèse de Doctorat d'Etat, Strasbourg 1974.
- [25] S.F. Boys, *Rev. mod. Physics* **32**, 300 (1960).
- [26] H.B. Bürgi, J.D. Dunitz & E. Shefter, *Acta crystallogr.* **B30**, 1517 (1974).
- [27] P.T. Cheng, S.C. Nyburg, F.N. MacLachlan & P. Yates, *Canad. J. Chemistry* **54**, 726 (1976).
- [28] S. Wolfe, *Accounts chem. Res.* **5**, 102 (1972).
- [29] N.D. Epiotis, R.L. Yates, J.R. Larson, C.R. Kirmaier & F. Bernardi, *J. Amer. chem. Soc.* **99**, 8379 (1977).
- [30] S. Chandrasekhar & A.J. Kirby, *J. chem. Soc. Chem. Commun.* **1978**, 171.
- [31] S.A. Bizzozero & O. Zweifel, *FEBS Letters* **59**, 105 (1975).
- [32] J.M. Lehn & G. Wipff, to be published.
- [33] W.P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw Hill, New York, N.Y. 1969.
- [34] B.A. Burdick, P.A. Benkovic & S.J. Benkovic, *J. Amer. chem. Soc.* **99**, 5716 (1977).
- [35] C.A. Grob, *Angew. Chem.* **81**, 543 (1969).