$$\textbf{3a} \rightleftharpoons \textbf{3b} \rightleftharpoons \quad \rightleftharpoons \tag{6}$$

tributed to the difficulty of protonating the weakly basic, hindered dimethylamino group of $T_1{}^+$, so that base-catalyzed proton removal from the hydroxylammonium group of $T_1{}^+$ is the lowest energy, observed reaction pathway. The two phenyl groups interfere with the approach of an acid to the dimethylamino nitrogen atom and are likely to lower the pK_a of this group even below the estimated value of 1.8 by providing an unfavorable nonpolar environment to the protonated species in T^{2+}, so that protonation of the dimethylamino group occurs only after the deprotonation of $T_1{}^+$ to give the more basic T^0.

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Stereoelectronic Control in Acid and Base Catalysis of Amide Hydrolysis. A Theoretical Study

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Abstract: The intrinsic stereoelectronic properties of the protonated, $CH(OH)_2NH_3{}^+$, and deprotonated, $CH(OH)(NH_2)O^-$, model species for acid- and base-catalyzed decomposition of the tetrahedral intermediate in amide hydrolysis have been computed: nitrogen protonation leads to selective weakening of the C–N bond; hydroxyl deprotonation causes unselective weakening of both C–N and C–OH bonds; both effects are subject to strong conformational dependence. The conformational dependence of these effects is of the same magnitude as the effect of protonation itself. With respect to the neutral species, *acid catalysis* enhances both the reactivity and C–N/C–O selectivity of the C–N cleavage; on the other hand, *base catalysis* facilitates the cleavage of both the C–N and C–OH bonds but not the selectivity. Furthermore, the effects are larger for acid catalysis than for base catalysis. A limited study of the influence of binding to metal ions and of hydration has been performed. Coordination of Mg^{2+} to the nitrogen site of $CH_2(OH)NH_2$ leads to effects similar to protonation. Hydration of $CH_2(OH)NH_3{}^+$ by a water molecule slightly decreases the magnitude of the stereoelectronic effects. The results are discussed with respect to experimental results on amide hydrolysis and enzyme-catalyzed reactions. They also give information about the *stereochemistry of proton-transfer* reactions.

Amide hydrolysis, a reaction of fundamental importance in chemistry and biology, proceeds via a tetrahedral intermediate whose properties have been shown by previous experimental[1] and theoretical[2,3] work to be subject to control by

conformation-dependent stereoelectronic effects.

The theoretical results for *neutral* aminodihydroxymethane, $CH(OH)_2NH_2$ (**1–15**)(T^0), show that bond lengthening and weakening occur in those conformations where the bond under
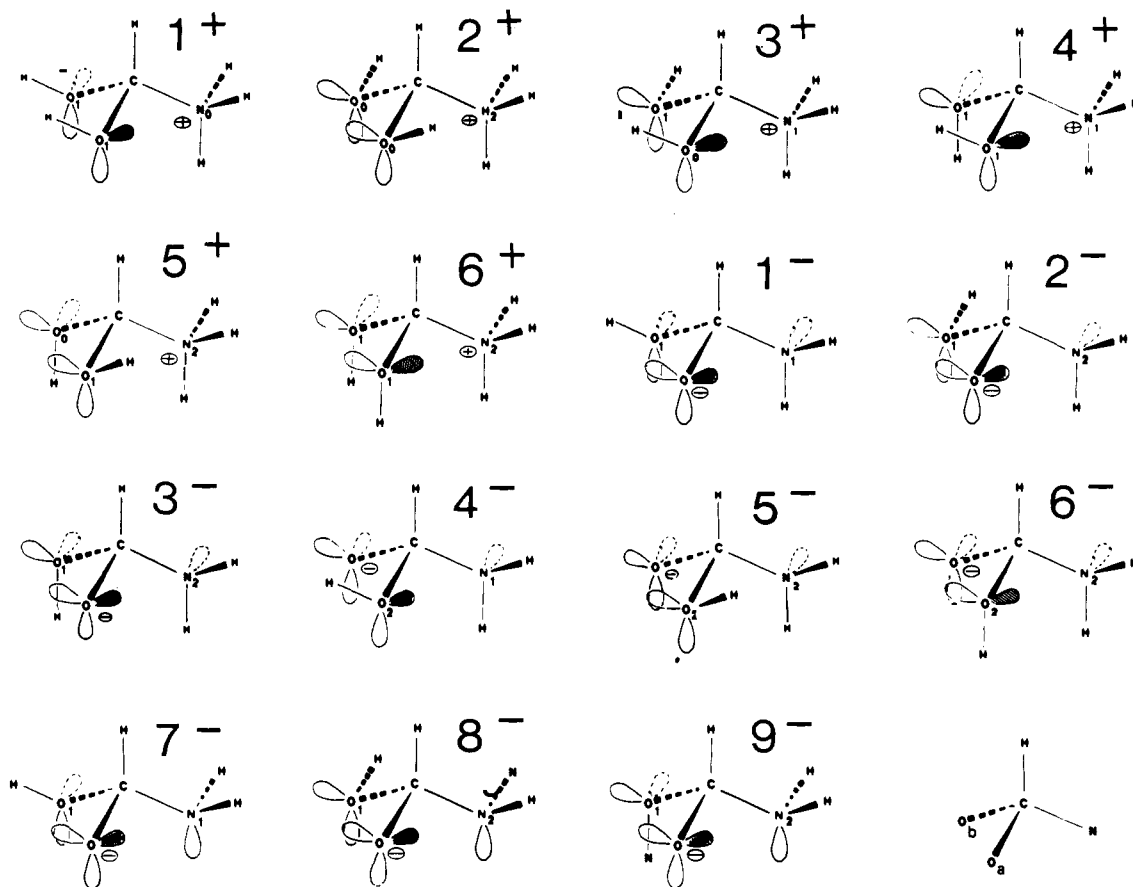
Figure 1. The six T⁺ and the nine T⁻ conformers. The index on the heteroatom X of a C–X bond corresponds to the number of lp's app to that bond.

consideration is in antiperiplanar (app) orientation to electronic "lone pairs" (lp's) (represented in their classical, sp³-hybridized form). In particular, the weakest C–N bonds of $CH(OH_2)NH_2$ are found in the conformations where C–N is in app orientation with respect to two oxygen lp directions and where the nitrogen lp itself is not app to a C–O (but to the C–H) bond. It was also suggested[2,3] that the reactivity and selectivity of C–N vs. C–O cleavage in enzymatic amide hydrolysis might incorporate a significant contribution from such effects: especially, an enzyme might make use of its substrate binding energy to twist the tetrahedral intermediate into the conformation which would not be the most stable (in the free state) but display the weakest C–N bond.

A further factor of great importance remained to be studied: the effect of acid or base catalysis on the properties of these intermediates, since most amide hydrolysis reactions usually occur under such catalytic conditions. Depending on the pH conditions, neutral, N-protonated, OH-deprotonated, or zwitterionic intermediates may occur.[4] Such species are intermediates of several important acyl transfer, or related, reactions.

We report here an ab initio theoretical study of the six gauche conformations of the protonated species $CH(OH)_2$-NH_3^+ ($\mathbf{1^+}$-$\mathbf{6^+}$) as well as of the nine gauche deprotonated forms $CH(OH)(NH_2)O^-$ ($\mathbf{1^-}$-$\mathbf{9^-}$). These species (Figure 1) are models for the tetrahedral intermediates which form under conditions of acid or base catalysis, and will be noted T⁺ and T⁻, respectively. Two O-protonated conformers, $\mathbf{7^+}$ and $\mathbf{8^+}$, and some other nongauche structures obtained by rotation around the C–OH bond in $\mathbf{1^+}$, $\mathbf{1^-}$, and $\mathbf{4^-}$, have also been considered (see next and Figures 5 and 6). Finally, a limited study of catalysis by binding to metal ions and of hydration has been performed on $CH_2(OH)NH_2$ coordinated to Mg^{2+} by the amine group and on $CH_2(OH)NH_3^+\cdot H_2O$ (Figures 3 and 4). The 15 neutral T⁰ species (**1–15**) are described in ref 2.

Method of Calculation. Results

The computation was performed with the same standard basis set of the GAUSSIAN 70 program as for the neutral species.[5] All C–N and C–O bond lengths (BLs) have been optimized at the 3G level (N–H = 1.015, O–H = 0.97, C–H = 1.09 Å). The conformations are ideally staggered with all bond angles tetrahedral; this may in several cases not correspond to the energetically optimal angles, especially in the protonated species where the carbon site should exhibit some carbocation character. In order to check if the tetrahedral model at carbon is not too crude, we have optimized at the 3G level the angles α in $\mathbf{2^+}$ (assuming $\alpha = \angle NCH = \angle NCO$) and in $\mathbf{8^+}$ (assuming $\alpha = \angle OCH = \angle OCO = \angle OCN$) along with the C–O and C–N bond lengths; the resulting structures, which will be referred to as $\mathbf{2^+}_{opt}$ and $\mathbf{8^+}_{opt}$, have α angles of 105.2 and 104.6°, respectively, not far indeed from the tetrahedral value. A complete geometry optimization of $CH(OH)$-$(NH_2)O^-$ performed by Alagona et al.[6] shows also that "the deviation from tetrahydrality of the carbon atom is quite limited in spite of the asymmetry of the substituents at the carbon atom". It must also be noted that the C–O and C–N BLs depend on the pyramidalization at carbon,[7] so that our BLs optimized with tetrahedral angles differ somewhat from the values obtained with optimized angles (see Tables II and III). The conformations studied here may not be the most stable ones, but they have been fixed so as to give the best app orientation between sp³ lone pairs and bonds. For calculations performed with the 4-31G basis set, we have taken the 3G optimized BLs and C–OH = 1.41 Å for all T⁺ species, and C–N = 1.55, C–O⁻ = 1.35, C–OH = 1.46 Å for all T⁻ species (these lengths correspond to about the mean 3G optimized values). In $CH_2(OH)(NH_2)Mg^{2+}$ (Figure 3) a $N\cdots Mg^{2+}$ distance of 1.90 Å has been assumed.[8] For the hydrated $CH_2(OH)NH_3^+$ molecule (Figure 4), we have taken $N\cdots OH_2$

Table I. Energy Results (kcal/mol)

species	rel total energies[a] c	d	ΔV_{NN}[b]	compare with neutral species[f]	protonation energies[e] c	c	c	d	d	d	ΔE_{es}[g] c	d
1⁺	2.3	0.1	509.4	**1, 5**	261	266		222	227		0.0	0.0
2⁺	5.5	13.4	−809.0	**2, 4**	260	265		210	214		18.2	35.5
3⁺	1.3	3.1	−244.7	**3, 6, 7**	259	266	263	212	223	219	6.3	5.0
4⁺	0.0	0.0	0.0	**8, 10, 12**	261	262	262	217	219	217	3.3	0.2
5⁺	1.6	8.1	−634.0	**9, 11, 13**	262	259	262	215	211	214	15.3	25.6
6⁺	3.2	10.6	−363.0	**14, 15**	259	261		207	214		17.7	42.0
7⁺	28.7	39.9	51.5	**2, 7**	237	236		184	182		15.3	43.5
8⁺	24.9	38.7	−363.9	**1, 7**	239	240		183	184		33.1	100.6
1⁻	3.4	1.2	−208.2	**1, 7, 10**	514	513	515	390	390	394	0.0	0.0
2⁻	0.0	1.3	−207.4	**2, 3, 11**	509	514	513	389	397	395	5.6	10.1
3⁻	0.9	0.0	0.0	**8, 9, 15**	515	511	511	394	388	386	1.5	10.9
4⁻	1.3	0.4	−197.2	**1, 3, 8**	512	516	515	390	396	394	4.5	14.8
5⁻	0.6	5.1	−166.7	**2, 7, 9**	509	510	511	393	394	393	12.0	47.2
6⁻	0.1	0.1	18.4	**10, 11, 15**	512	513	510	393	393	387	5.9	29.5
7⁻	5.3	5.6	−382.1	**5, 6, 12**	511	513	518	389	390	400	6.0	18.1
8⁻	3.5	9.4	−359.0	**4, 6, 13**	507	511	514	387	394	399	13.4	46.7
9⁻	1.1	0.0	−196.2	**12, 13, 14**	513	511	514	394	389	393	4.4	7.7

[a] Energy difference between the listed species and the most stable species of the series. For **4⁺**, $E_T = -242.1215$ (3G). $E_T = -244.9220$ au (4-31G). For **2⁻**, $E_T = -240.8888$ au (3G). For **3⁻**, $E_T = -243.9489$ au (4-31G). [b] Relative nuclear repulsion energy: $V_{NN} = 143.7048$ au for **4⁺**; $V_{NN} = 125.3347$ au for **3⁻** (standard geometry). [c] 3G basis set. [d] 4-31G basis set. [e] Correspond to the protonation energies of the neutral species listed in column 5 respectively for **1⁺–8⁺** and to the protonation of the species listed in column 1 to give those listed in column 5 respectively for **1⁻–9⁻**. [f] Neutral species of ref 2 with which the charged species are compared. [g] Relative electrostatic interaction energy calculated from the Mulliken atomic net charges on the atoms. The electrostatic energies for **1⁺** are −0.1484 (3G) and −0.8438 au (4-31G); for **1⁻**, they are −0.0640 (3G) and −0.6052 au (4-31G).

Table II. Protonated Species **1⁺–8⁺**. Bond Properties

	compare to[a]	C–N bond BL, Å[b]	OP[c]	OP[d]	ΔBL[e]	ΔOP[c,e]	ΔOP[d,e]	C–Oₐ bond BL, Å[b]	OP[c]	OP[d]	ΔBL	ΔOP[c,e]	ΔOP[d,e]	C–O_b bond BL, Å[b]	OP[c]	OP[d]	ΔBL[e]	ΔOP[c,e]	ΔOP[d,e]
1⁺	1, 5	1.509	0.274	0.076	0.041	−0.060	−0.170	1.421	0.269	0.187	−0.007	−0.002	0.031	1.421	0.269	0.187	−0.007	0.001	0.046
2⁺	2, 4	1.598	0.214	0.011	0.103	−0.104	−0.197	1.397	0.279	0.205	−0.021	0.003	0.035	1.397	0.279	0.205	−0.021	0.004	0.045
3⁺	3, 6, 7	1.558	0.244	0.048	0.077	−0.084	−0.188	1.403	0.274	0.213	−0.018	0.003	0.054	1.410	0.272	0.177	−0.013	0.003	0.024
4⁺	8, 10, 12	1.556	0.246	0.061	0.077	−0.082	−0.187	1.413	0.270	0.191	−0.008	−0.003	0.021	1.407	0.273	0.201	−0.026	0.004	0.054
5⁺	9, 11, 13	1.600	0.214	0.022	0.106	−0.106	−0.198	1.405	0.273	0.180	−0.003	−0.003	−0.005	1.389	0.284	0.227	−0.047	0.104	0.076
6⁺	14, 15	1.598	0.215	0.026	0.106	−0.104	−0.189	1.405	0.279	0.199	−0.015	0.003	0.025	1.405	0.279	0.199	−0.015	0.004	0.025
7⁺	2, 7	1.471	0.327	0.264	−0.014	0.002	0.029	1.484	0.228	0.001	0.060	−0.047	−0.183	1.418	0.266	0.175	−0.010	−0.005	0.032
8⁺	1, 7	1.435	0.356	0.279	−0.037	0.023	0.025	1.391	0.288	0.199	−0.035	0.014	0.023	1.577	0.161	−0.075	0.140	−0.101	−0.205
2⁺_opt		1.641						1.388						1.388					
8⁺_opt		1.417						1.377						1.646					

[a] Neutral aminodihydroxymethane $CH(OH)_2NH_2$ described in ref 2, with which the species listed in column 1 are compared. [b] Optimized 3G values. [c] 3G basis set. [d] 4-31G basis set. [e] Mean difference between the value corresponding to the bond of the species listed in column 1 and the neutral species listed in column 2.

Table III. Deprotonated Species **1⁻–9⁻**. Bond Properties

	compare to[a]	C–N bond BL, Å[b]	OP[c]	OP[d]	ΔBL[e]	ΔOP[c,e]	ΔOP[d,e]	C–Oₐ bond BL, Å[b]	OP[c]	OP[d]	ΔBL	ΔOP[c,e]	ΔOP[e,d]	C–O_b bond BL, Å[b]	OP[c]	OP[d]	ΔBL[e]	ΔOP[c,e]	ΔOP[d,e]
1⁻	1, 7, 10	1.540	0.271	0.168	0.066	−0.061	−0.085	1.352	0.294	0.374	−0.085	0.028	0.236	1.480	0.231	0.084	0.054	−0.042	−0.088
2⁻	2, 3, 11	1.556	0.258	0.145	0.070	−0.066	−0.090	1.350	0.294	0.377	−0.071	0.022	0.209	1.458	0.231	0.071	0.035	−0.039	−0.091
3⁻	8, 9, 15	1.562	0.256	0.148	0.073	−0.069	−0.092	1.351	0.295	0.371	−0.083	0.029	0.234	1.460	0.234	0.096	0.043	−0.043	−0.089
4⁻	1, 3, 8	1.527	0.277	0.172	0.055	−0.054	−0.085	1.492	0.225	0.065	0.062	−0.041	−0.078	1.342	0.291	0.368	−0.081	0.020	0.203
5⁻	2, 7, 9	1.547	0.264	0.148	0.058	−0.061	−0.086	1.469	0.226	0.060	0.033	−0.040	−0.078	1.329	0.292	0.366	−0.079	0.015	0.176
6⁻	10, 11, 15	1.550	0.261	0.149	0.063	−0.064	−0.088	1.485	0.229	0.082	0.051	−0.043	−0.081	1.337	0.293	0.365	−0.084	0.021	0.201
7⁻	5, 6, 12	1.536	0.272	0.151	0.056	−0.054	−0.074	1.345	0.293	0.363	−0.083	0.019	0.201	1.480	0.232	0.079	0.052	−0.039	−0.067
8⁻	4, 6, 13	1.556	0.258	0.128	0.062	−0.061	−0.074	1.330	0.294	0.362	−0.088	0.017	0.188	1.473	0.232	0.065	0.055	−0.039	−0.082
9⁻	12, 13, 14	1.556	0.255	0.128	0.066	−0.063	−0.083	1.353	0.294	0.365	−0.067	0.022	0.209	1.459	0.235	0.095	0.039	−0.041	−0.082
10⁻[f]		1.580						1.314						1.500					

[a] Neutral aminodihydroxymethanes $CH(OH)_2NH_2$ described in ref 2, with which the species listed in column 1 are compared. [b] Optimized 3G values. [c] 3G basis set. [d] 4-31G basis set. [e] Mean difference corresponding to the bond of the species listed in column 1 and the neutral species listed in column 2. [f] Corresponds to Alagona's optimized geometry.[6]

= 2.89 Å and O···OH₂ = 2.70 Å.[9]

The energetic results, the optimized BLs, and some population analysis data for various T⁺ and T⁻ species are reported in Tables I–III.[10] These results will be analyzed along the following lines: (i) the effect of protonation or deprotonation on the properties of the C–N and C–O bonds; (ii) the conformation-dependent stereoelectronic effects in species of a given type (as in the case of the neutral species,[2] the changes in BLs and overlap populations (OPs) between different conformations will be decomposed into several contributions); (iii) the relative magnitude of stereoelectronic effects in protonated, neutral, and deprotonated species.

The results pertaining to both (i) and (iii) show clear differences between the effect of the acid- and base-catalyzed cleavage of the tetrahedral intermediate: these differences concern both the dependence of reactivity and selectivity on type of catalysis (related to (i)) and the *conformational selectivity* (related to (iii)).

Bond Properties in the N-Protonated Species 1⁺–6⁺. Protonation of the amino group of the various conformers of $CH(OH)_2NH_2$ to form the corresponding $CH(OH)_2NH_3^+$ species produces characteristic changes in the properties of the C–O, C–N, and C–H bonds.

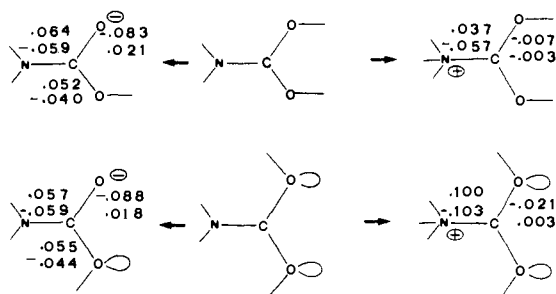(1) Protonation leads to a marked and *selective lengthening*

Figure 2. Changes in bond length (Å, first line) and in overlap populations (e, second line) resulting from the N-protonation (right) and from the deprotonation (left) of two neutral conformers of $CH(OH)_2NH_2$.
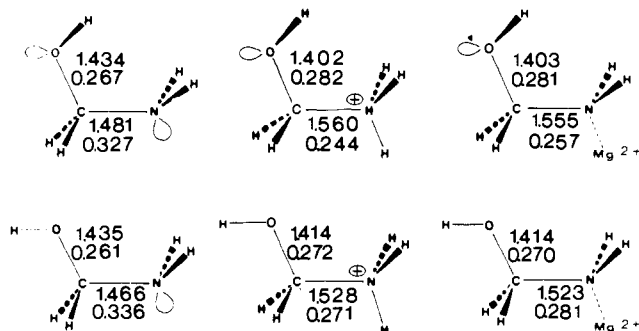

Figure 3. Optimized bond length (Å) and overlap populations of the C–O and C–N bonds in two conformers of $CH_2(OH)NH_2$: neutral (left), N-protonated (middle), and complexed by Mg^{2+} (right).

and weakening of the C–N bond, whereas the C–O bonds are slightly shortened (Table II) and strengthened.

(2) These changes in C–N BLs show strong *stereoelectronic conformation dependence;* the forms where C–N is app to two lp's (like 5^+, 6^+) have a very long and very weak C–N bond.[11] Comparing the protonated species with the unprotonated ones shows that the lengthening and weakening of the C–N bond resulting from the N-protonation are enhanced from 0.04 Å, -0.06 e^- to 0.10 Å, -0.10 e^- when the number of O lp's app to C–N increases from zero to two (Table II). On the other hand, comparing the different protonated species with each other indicates than an app O lp lengthens and weakens the C–N bond by $+0.05$ Å and -0.03 e, respectively; these changes are about three times larger in the N-protonated species than in the unprotonated ones.[2] Thus, *protonation leads to a marked amplification of the stereoelectronic effects on C–N bond properties.*

(3) The C–O bond properties are also conformation dependent: in an O–C–O' fragment, the C–O bond is shortest when it is not app to a lp on O'[13] and when an O lp is app to C–N$^+$ rather than to C–O'.[14] These conformational changes in C–O BLs and OPs are of the same order of magnitude as in the corresponding neutral species,[2] and about five times smaller than the conformational changes in C–N$^+$ BLs and OPs. Similar trends are observed in the $CH(OH)_2^+$ cation itself.[12,15]

(4) As a consequence of effects (1), (2), and (3) (see also Table II and Figure 2) *the C–N bond in the N-protonated species should be cleaved more easily and more selectively than in the unprotonated ones.* Thus acid catalysis of the decomposition of the $CH(OH)_2NH_2$ species by protonation of the amine function (i) facilitates markedly the cleavage of the C–N bond; (ii) increases the C–N/C–O selectivity; (iii) increases the conformational dependence of ease and selectivity of cleavage.

One can look at the computed T^+ structures as points on the reaction path leading to the decomposition into the NH_3 and $CH(OH)_2^+$ products: the C–N distance becomes large and the
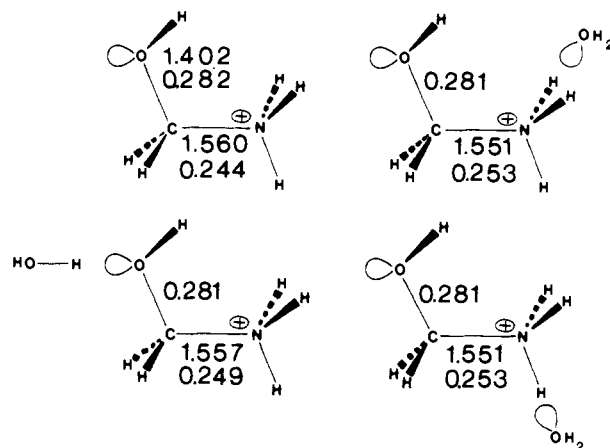

Figure 4. C–O overlap populations, C–N optimized bond lengths, and overlap populations in three hydrated forms of $CH_2(OH)NH_3^+$. The "unsolvated" molecule (top left) is shown as a reference.

C–OH distance decreases to the C–OH distance in the cation (1.328 Å if a tetrahedral geometry is imposed at carbon, and 1.303 Å in the planar carbocation derived from 2^+ (3G optimized values)).

(5) The stereoelectronic effects mentioned in (2) can be represented by a *perturbation interaction* between an O' lp and the app σ^*_{C-N} or σ^*_{C-O} antibonding orbitals; this strengthens the C–O' bond and weakens the C–N$^+$ or C–O bonds. Since the relative energies are $\sigma_{C-N^+} \ll \sigma_{C-O} < \sigma_{C-N}$ and $\sigma^*_{C-N^+} < \sigma^*_{C-O} < \sigma^*_{C-N}$, the largest effect comes from the $|O$ lp, $\sigma^*_{CN^+}|$ interaction, which weakens the C–N$^+$ bond in the protonated species much more than the C–N bond in the unprotonated species.

(6) This scheme may be extended to *other heteroatoms* in an X–C–Y fragment (X, Y = O, N, S, P, etc.) where a similar stabilization of the σ_{C-X} and σ^*_{C-X} bond orbitals should be achieved by protonation of the heteroatom X. As a result of the enhanced interaction between the σ^*_{C-X} orbital and the Y app lp, stereoelectronic effects on C–X and C–Y bond properties should be increased: the C–X bond should lengthen and the C–Y bond should shorten more than in the neutral or isolated molecule.

(7) An important variant is *that coordination to a metal cation,* $M^{n+} \cdots X-C-Y$, may cause effects similar to those due to protonation. Indeed, using $CH_2(OH)NH_2$ as model, coordination of Mg^{2+} to the amino group in the direction of the nitrogen lone pair is found to induce conformation-dependent C–N lengthening and C–O shortening of a magnitude similar to the effects of N-protonation (Figure 3). Thus, *metal ion catalysis* by $N \cdots M^{n+}$ coordination (M = Mg^{2+}, Zn^{2+}, etc.) should facilitate C–N cleavage and increase C–N/C–O selectivity as compared to the uncomplexed species. In addition, whereas metal-ion catalysis (as in metalloenzymes) is usually considered to result from coordination to the starting amide, it is seen that it may also act on the tetrahedral intermediate.

(8) Finally, the *effect of solvation* may influence the magnitude of the stereoelectronic effects. In order to gain some insight into this factor, a limited study was performed by letting a single water molecule interact with the $CH_2(OH)NH_3^+$ ion. The results are summarized in Figure 4. It is seen that solvation of the $-NH_3^+$ group slightly decreases the C–N bond length; a similar, but even weaker, C–N shortening results from solvation of O lp app to the C–N bond. Thus, solvation is expected to decrease the magnitude of the stereoelectronic effects but not their nature and conformation dependence. Solvation should also affect relative energies of different conformations (see below); this factor has not been studied.

Bond Properties in the Deprotonated Species 1^-–9^-. (1)

Deprotonation of an OH group in $CH(NH_2)(OH)_2$ lengthens and weakens the C–N bond, but on the average less than what is observed on N-protonation. Furthermore, contrary to what occurs on N-protonation, this lengthening is *not specific* to the C–N bond; indeed, the C–OH bond is also lengthened ($\Delta BL \simeq 0.05$ Å) and weakened by deprotonation of the other OH group.

(2) This bond lengthening and weakening shows some stereoelectronic conformational dependence.[16] The C–N bond is weaker when it is app to an O lp of OH, rather than to the O–H bond,[17] and when the N lp is app to C–O⁻ rather than to C–OH;[18] these conformational changes in C–N BLs and OPs of the T⁻ species are similar to those observed in the neutral species,[2] and therefore about three times weaker than in T⁺ species (see above).

Similarly, a weakening of the C–OH and of the C–O⁻ bonds[19] is observed when they are in app orientation to the N lp rather than to a N–H bond; also the C–OH bond is weaker when the OH lp is app to C–O⁻ rather than to C–N.[20] As for the C–N bond, these conformational changes in C–OH BLs and OPs are of the same order of magnitude as in the neutral species.

(3) As a result of (1) and (2), both C–N and C–OH bonds should be cleaved in the deprotonated $CH(OH)(O^-)NH_2$ species, *more easily*, but *not more selectively*, than in the neutral species. Indeed, in no conformation is there simultaneously a short C–N bond and a weak C–O bond or vice versa.

(4) The above results fit also a qualitative perturbation picture between a σ^*_{C-X} bond and the Y app lp in the X–C–Y fragment (X, Y = O, N) with the relative order of energies $\sigma_{C-O^-} \simeq$ O lp < N lp $\ll$ O⁻ lp and $\sigma^*_{C-OH} < \sigma^*_{C-N} < \sigma^*_{C-O^-}$. The C–O and C–N bonds, being always app to one of the O⁻ lp's, will be weakened simultaneously on deprotonation of an O–H bond; since the $|O^- \text{ lp}, \sigma^*_{C-X}|$ interaction is greater than the $|O \text{ lp}, \sigma^*_{C-X}|$ interaction, the C–X bond is more lengthened and weakened by an app O⁻ lp ($\Delta BL \simeq 0.06$ Å) than by an OH lp ($\Delta BL \simeq 0.015$ Å) and the C–O⁻ bond is more shortened that the C–OH bond. This may account for the effects described in (1). In addition to the two electron interactions, the four electron $|Y \text{ lp}, \sigma_{C-O^-}|$ destabilizing interaction, which is greater than the $|Y \text{ lp}, \sigma_{C-O}|$ interaction, can also account for the C–Y bond weakening in the conformations where the Y lp is app to C–O⁻ rather than to the other polar C–X bond.[21]

Bond Properties in Nongauche Rotamers of T⁺ and T⁻. The above conclusions concerning the T⁺ and T⁻ conformers also hold when nongauche structures, obtained by the rotation of a C–OH bond in 1⁺, 1⁻, and 4⁻, respectively, are considered (3G calculations). The changes in C–N and C–O OPs reported in Figures 5, 6a, and 6b, respectively, show clear differences between protonated and deprotonated species. In the T⁺ rotamers the changes in OP_{CN} are in opposite phase to those in OP_{CO}: the strongest C–OH bonds correspond to the weakest C–N bond (at $\phi \simeq 150°$), whereas the weakest C–OH bonds correspond to a stronger C–N bond (at $\phi = 60$ and 240°). This is not the case in the T⁻ rotamers, where there is no conformation having simultaneously a strong C–OH bond and a weak C–N bond (or vice versa). Furthermore, an increase in selectivity can be obtained by smaller conformational changes in the protonated than in the deprotonated species. Thus, again the conformation selectivity should be much more pronounced in acid than in base catalysis.

Bond Properties of the O-Protonated Species 7⁺ and 8⁺. Table II shows that the bond properties of the two O-protonated conformers 7⁺ and 8⁺ are similar to those observed in the N-protonated species and in the protonated dihydroxymethanes:[22] the C–O⁺ bond lengthens on protonation by about 0.1 Å and weakens ($\Delta OP \simeq -0.07$ e, 3G; -0.2 e, 4-31G), whereas
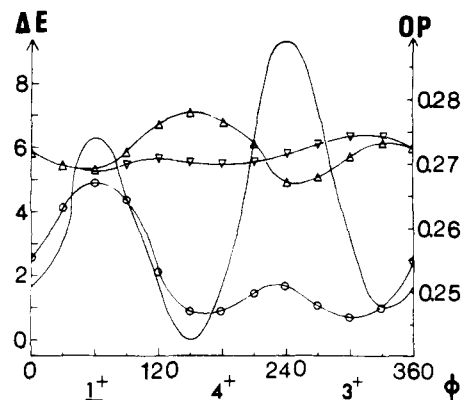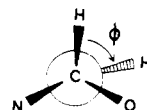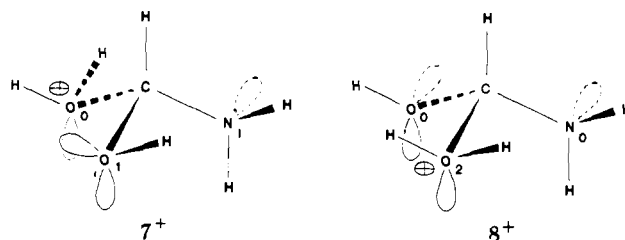
Figure 5. Rotation of a C–OH bond in the N-protonated $CH(OH)_2NH_3^+$ species derived from 1⁺, 4⁺, 3⁺ (C–N + 1.55, C–OH = 1.41 Å). Plot of the relative energies (full curve) and of the OP's of the C–N bond (○), of the rotating C–OH bond (△), and of the other C–OH bond (▽) vs. the dihedral angle ϕ = HCOH.

the C–N and C–OH bonds are shortened by about 0.02 Å. These changes also depend markedly on the conformation: in

7⁺   8⁺

8⁺, where the C–O⁺ bond is in app orientation to two lp's, it is much longer ($\Delta BL \simeq 0.1$ Å) and weaker ($\Delta OP \simeq -0.05$ e, 3G; -0.07 e, 4-31G) than in 7⁺, where it is app to two bonds. As in the N-protonation case, these conformational changes are of the same magnitude as the mean changes resulting from the protonation itself. The other C–X bonds (X = N, O) show smaller conformation-dependent variations: the C–X bond is about 0.03 Å shorter when the X lp is app to the C–O⁺ bond rather than to the other C–Y bond (Y = O, N, respectively). These results, which can be interpreted by the perturbation scheme described above, suggest that the C–O⁺ bond cleavage in an O-protonated tetrahedral species should be easier and more selective than in the unprotonated one.

Relative Energies. The discussion of the relative energies (ΔE_T) of these species suffers some limitations related mainly to the geometry constraints and to the basis-set effects. The angular constraints imposed in order to fit app orientations can be viewed as deformations of the most stable conformer corresponding to a point on the reaction path for the formation or decomposition of the tetrahedral intermediate. Comparison of the ΔE_T's calculated here supposes that this deviation is of the same order of magnitude for all T⁺ or T⁻ species. Although the tetrahedral structures do not differ much from the optimized ones, their energy is higher by an amount equal to or greater than the relative ΔE_T's reported in Table I: 2.6 (3G) and 2.8 (4-31G) kcal/mol for 2⁺ compared to 2⁺opt, 3.8 kcal/mol (3G) for 8⁺ compared to 8⁺opt, and 18.9 (3G) and 5.8 (4-31G) kcal/mol for 6⁻ compared to the optimized structure of Alagona et al.[6] However, the ΔE_T values should give at least trends in relative energies, which correlate also with the relative energies of the decomposition products.[23] Although the 4-31G basis set gives in general more reliable energies than the 3G basis set, there can be furthermore some
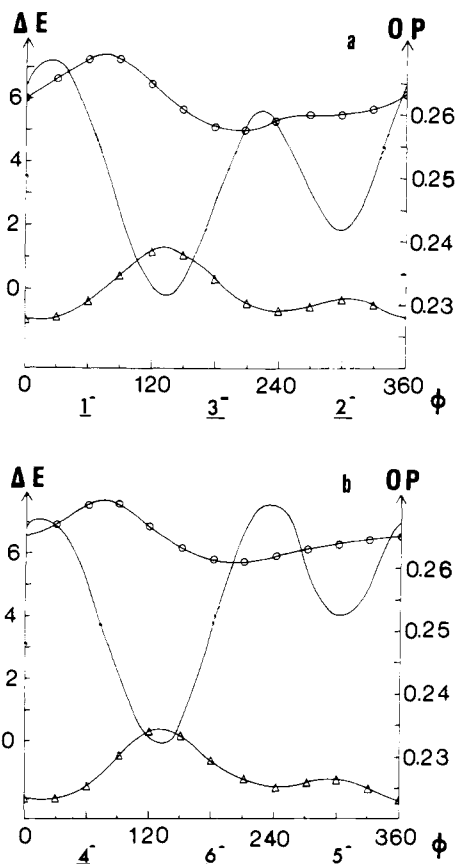
Figure 6. Rotation of a C–OH bond in the deprotonated CH(OH)NH₂O⁻ species derived from **1⁻**, **3⁻**, and **2⁻** (a) and from **4⁻**, **6⁻**, and **5⁻** (b), respectively (C–N = 1.55, C–O⁻ = 1.35, C–OH = 1.41 Å). Plot of the relative energies (solid curve), of the OP's of the C–N bond (O), and of the rotating C–OH bond (△) vs. the dihedral angle ϕ = HCOH.

basis-set effects on the 4-31G ΔE_T's since the BLs used for the 4-31G calculations derive from partially optimized 3G geometries. Nevertheless, Table I shows that both basis sets give the same trends in relative energies, especially for the N-protonated structures: **4⁺** is the most stable and **2⁺** and **6⁺** are the least stable of the T⁺ species. Similar trends have been observed in solution: indeed, the unstable conformer **6⁺** and the stable conformer **2⁺** correspond respectively to a pyranosyl ring bearing an axial and equatorial protonated substituent ("reverse anomeric effect" [24]). Among the T⁻ species, **2⁻**, **3⁻**, **4⁻**, **6⁻**, and **9⁻** are of comparable energy, lower than the energy of **7⁻** and **8⁻**. Both basis sets also indicate that the N-protonation is preferred to the O-protonation by about 25 (3G) and 39 kcal/mol (4-31G): this difference is of the same order of magnitude as the gas-phase protonation energy difference between alcohols and amines[25] (about 40 kcal/mol between Me₂NH and MeOH), and about twice the difference obtained in aqueous solution for an *N*-dimethylaminodihydroxymethane (12.6 kcal/mol[26]). The analysis of the electronic and nuclear contributions to the total energy shows that the internuclear repulsion energy V_{NN} is greater in the most stable conformers (Table I): the ΔE_T's are then dominated by the electronic component.

As in the neutral species, there is no correlation between the relative total energies and the relative BL variations related to the lp orientations for species of one given type: indeed, the least stable conformer **2⁺** of the T⁺ species has the weakest C–N bond, whereas the more stable **1⁺** and **3⁺** conformers have a stronger one: the C–OH and C–N BLs of the least stable species **8⁻** are not among the longest of the T⁻ species. Although the interaction of the anomeric type described above is stabilizing, it does not govern *alone* the *total* energies, which

contain terms like the interaction between other MOs or electrostatic charge–charge or dipole–dipole interactions. Indeed, the most stable **4⁺** species also has the greatest number of internal hydrogen bonds and no parallel lp dipoles, while **2⁺**, which is at higher energy, has no internal hydrogen bond and two parallel oxygen lp's; similar correlations are found to a lesser extent in the T⁻ conformers. Since the calculated Mulliken atomic charges are conformation dependent[27] the corresponding relative electrostatic interaction energies ΔE_{es} between these charges change also with conformation. Table I shows that they follow qualitatively the same trends as the ΔE_T's in one series. This simple electrostatic picture also favors the N- vs. the O-protonation. These results apply to the "bare species": in condensed phase, environmental effects and solvation energies should also be conformation dependent and affect (probably reduce) the relative energies.

Protonation Energies. Stereochemistry of Proton Transfer. Another aspect concerns *the conformation dependence of the protonation energies*. Since a given T⁺ species may derive from T⁰ conformers of different energy (see Table I), the corresponding pK_a's should differ from one conformer to another. Thus, **3⁺** results from the N-protonation of the neutral species **3**, **6**, or **7** of ref 2, with protonation energies of respectively 259, 266, and 263 (3G) or 212, 223, and 219 kcal/mol (4-31G): this leads to a difference of about 5 pK units between the conjugated bases **3** and **6**. Conversely, a given T⁻ species can be formed from different neutral conformers: for example, **7⁻** is conjugated with either the **4**, **6**, or **13** rotamers of relative energies 0, 4, and 7 (3G) and 0, 7, and 12 kcal/mol (4-31G), respectively. These changes in protonation energies can still be enhanced if other intermediate nongauche structures are considered (Figures 5 and 6). Most energy extrema do not correspond to gauche structures: the minima are found in the conformers allowing internal hydrogen bond type interactions (for example, at ϕ = 150° in Figure 5, 120° in Figure 6: see also the T⁻ optimized structure of Alagona et al.[6]): the eclipsed conformations where such interactions are not present are disfavored (for example, at $\phi \simeq$ 240° in Figure 5, 0° in Figure 6). The range in protonation energies corresponding to those structures should then be greater than that obtained from gauche structures only. Although there is no general picture for the changes in protonation energies, it seems more difficult to remove a proton when it is hydrogen bonded as in **12** than when it participates in a repulsion between two parallel O–H dipoles as in **5**, to give conjugated base **7⁻**. In terms of perturbation, the proton abstraction is also facilitated when the newly formed sp³ lp is app to a low-lying empty orbital (σ^*_{CO} < σ_{CN}^* < σ^*_{CH}: compare the OH deprotonation of **4**, **6**, and **13** to give **8⁻**).[28] For the T⁺–T⁰ couples, one observes that the N-protonation is easier when the N lp is app to C–H (this removes the possible $|\sigma_{C-H}, N\ lp|$ repulsion) than when it is app to C–O (one loses a favorable $|N\ lp, \sigma^*_{C-O}|$ interaction).

It is thus clear that there are preferred, conformation-dependent pathways for protonation and deprotonation of the CH(OH)₂NH₂ species, i.e., there is a defined *stereochemistry of proton transfer subject to stereoelectronic effects*. Such factors may be of much importance in proton transfer relay systems of enzymes as well as for the design of artificial molecular catalysts: the correct positioning of the catalytic groups which donate or accept protons to and from the bound substrate must thus take into account transfer pathways of defined stereochemistry.

Discussion

The present results compared with those obtained for neutral aminodihydroxymethanes[2] show clear differences between the *intrinsic* bond properties of the isolated, unsolvated N-protonated, neutral, and deprotonated species. These changes in bond properties should correspond to different reactivities

inasmuch as the rate-limiting step involves bond formation or bond breaking in the tetrahedral intermediates (TI) and the transition state (TS) properties are close to the TI properties. With these two restrictions in mind, one may assume that a long C–O or C–N bond of the TI should be weak and cleaved more easily than a shorter bond.[33] If the nature and conformation of the TI are known, the above results yield trends in *intrinsic reactivities;* a comparison with the products obtained in solution or in a polar environment can then provide information about solvation or environmental effects, specific proton transfer, changes in the rate-limiting step, substituent effects, etc.

The changes in bond properties indicate that (i) *acid-catalyzed* breakdown of tetrahedral O–C–N species should lead to preferential C–N cleavage with *higher reactivity* and *higher conformational selectivity* than in the absence of catalyst; (ii) base *catalysis* facilitates both C–N and C–OH cleavage, with an increase in reactivity but not in conformational selectivity for C–N cleavage with respect to the neutral species. Since the conformation-dependent changes in bond lengths are greater in the protonated species and smaller in the deprotonated species than in the neutral species, the stereoelectronic effects on the leaving group should be amplified under conditions of acid catalysis but not with base catalysis. (iii) Combining conclusions (i) and (ii), the selectivity in base catalysis should be increased by an electrophilic group located specifically near the heteroatom X of the leaving group as may be the case in multifunctional intramolecular or enzymatic catalysis or in solution (specific solvation, hydrogen bonds between X and the solvent, etc.). (iv) The present data on T^+ and T^- species together with the previous results on T^0 [2] show that the conformational selectivity for bond breaking increases in the order $T^- < T^0 < T^+$. (v) The stereoelectronic effects operate not only on the C–X bond which will be cleaved but also on the other C–Y bonds which can acquire more or less double-bond character. This effect increases in the order $T^+ < T^0 < T^-$.

One may wonder if aminodihydroxymethanes are good models for the more complex tetrahedral species formed in the hydrolysis of amides, imidates, aminolysis of esters, etc. For instance, the energetics of hydrolysis reactions,[26] the amine basicity,[34] and the partitioning of C–N/C–O cleavage in related species[35] depend on the substituents on the heteroatoms. Substituents also affect the solvation of the species, as well as the energy barrier for the interconversion of different rotamers. All these factors must be considered in addition to the orientation effects in order to account for the mode of formation and/or cleavage of the tetrahedral species.

As far as stereoelectronic effects are concerned, the changes in C–X and C–Y bond properties resulting from the substitution of H atom on X by an R group should be qualitatively represented by the $|X$ lp, $\sigma^*_{C-Y}|$ and/or the $|Y$ lp, $\sigma^*_{C-X}|$ interaction between the X and Y lp's and the app C–Y and C–X polar bonds, respectively. If R destabilizes the X lp and σ^*_{C-X} orbitals, the C–X bond should shorten and the C–Y bond should lengthen by the above interactions more than with R = H; opposite effects should be observed when R is electron withdrawing with respect to H. Previous calculations showed that replacing H by CH_3 has only a small influence on stereoelectronic effects.[36]

Antiperiplanar two-electron lp–empty orbital interaction is of course a very general phenomenon which in its simplest stereochemical expression has been known for a long time, as in the preferred trans orientation in elimination reaction, participation and assistance effects, conjugation, etc. More recently, it has also been proposed to be an important factor in the asymmetric nucleophilic addition reactions on the carbonyl group.[41] The observation or nonobservation of specific bond cleavage and of stereoelectronic effects in various solutions depends on the ionic state of the TS as well as on its

structure and conformation in the medium. Evidence for the absence[37] or presence[38] of stereoelectronic control in a hydrolysis reaction depends on the knowledge of these parameters. Conversely, from the products of the reaction and the structure of the reactants, it is possible to infer the structure of the tetrahedral intermediates. The extensive experimental results obtained by Deslongchamps[1,39] and other groups[40] on the operation of stereoelectronic effects in the cleavage of tetrahedral intermediates agree with the present theoretical results.

The effects discussed above should also operate in the enzyme-catalyzed hydrolysis of amides;[42] the high selectivity and reaction rate may result from specific proton transfers between the enzyme and the substrate[43] leading to ionic species held in a given conformation. Two factors may contribute to enzymatic activation: (i) since the protonation energies are conformation dependent, the specific protonation or deprotonation of the substrate may yield a TI of higher energy than the species which would form in solution but which exhibits a higher reactivity; (ii) the TI may be locked by the enzyme in a conformation where the lp orbitals are properly oriented to expel quickly a specific group (lowering of the TS energy). These two factors may operate simultaneously, particularly in acid-catalysis conditions, where the most labile C–N bonds are found here in conformers of high energy. In addition, the presence of charged groups in the active site of the enzyme, interacting with the substrate, may amplify the stereoelectronic effects for selective bond cleavage or formation.

References and Notes

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(10) More detailed results can be obtained on request.
(11) One may wonder whether such C–N or C–O distances (about 1.6 Å) found in some N- and O-protonated or deprotonated species still correspond to a "bond", and if complete geometry relaxation would not lead to bond dissociation. More complete optimization of 2^+ and 8^+ (see above) and of the deprotonates species[6] shows that this is not the case. Furthermore, using the 3G optimized geometry of the $CH(OH)_2^+$ cation derived from 8^+,[12] stabilization energies of 43.3 and 5.7 kcal/mol are found for 6^+ and 8^+, respectively, which indicates at least some binding character between the fragments; the deprotonated species 3^- is also more stable (92.2 kcal/mol, 3G basis set; 26.4 kcal/mol, 4-31G basis set) than the separated $OH^- + HCONH_2$ fragments.[6] The bonding character is also shown by the clearly positive 3G OPs (Tables II and III). However, the 4-31G OPs are only weakly positive, or even negative (Tables II and III), so that the question of the electronic state to which the 4-31G SCF calculation has converged can be raised. A detailed comparison between the 3G and 4-31G MOs of the initial guess and along the SCF iterations indicates no significant change in electronic structure. We think that the weak 4-31G OPs are rather an artifact of this basis set which exaggerates charge separation. This can also result in part from the use of 3G instead of 4-31G optimized structures for 4-31G calculations. Nevertheless, the conformational changes in OPs observed with the two basis sets follow the same trends from one species to another.
(12) Del Bene, J. *J. Am. Chem. Soc.* **1978,** *100,* 1673.
(13) Compare the $C-O_b$ bonds in 2^+ and 3^+, 4^+ and 5^+, 5^+ and 6^+. $\Delta BL \simeq$ 0.015 Å, $\Delta OP \simeq -0.006$ (3G), -0.025 e (4-31G).
(14) This is found at the 3G level only. Compare the $C-O_a$ bonds in 2^+ and 3^+, 4^+ and 5^+, and the $C-O_b$ bonds in 1^+ and 3^+, 1^+ and 4^+; $\Delta BL \simeq -0.010$ Å, $\Delta OP \simeq 0.004$ e per app lp.
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(16) Although the two π-type lone pairs on O^- are at nearly the same energy and higher than the σ-type lp, we shall consider three sp^3 localized lp's on O^- for the sake of simplicity and ease of geometrical reference.
(17) Compare 1^- and 2^-, 4^- and 5^-, 7^- and 8^-; $\Delta BL \simeq 0.019$ Å, $\Delta OP \simeq -0.013$ (3G), -0.023 e (4-31G).
(18) Compare 1^- and 4^-, 2^- and 5^-, 3^- and 6^-; $\Delta BL \simeq 0.011$ Å, $\Delta OP \simeq -0.006$ e (3G). No significant changes in OPs are found at the 4-31G level.
(19) Compare the C–OH and the $C-O^-$ bonds in 1^- and 4^-, 2^- and 5^-, 3^- and

6⁻; ΔBL $\simeq$ 0.015 Å, ΔOP $\simeq$ −0.005 (3G), −0.015 e (4-31G) for C–OH; ΔBL $\simeq$ 0.015 Å for C–O⁻ (the changes in OP$_{C-O^-}$ are in the opposite direction).

(20) Compare the C–OH bond in 1⁻ and 2⁻, 4⁻ and 5⁻, 7⁻ and 8⁻; ΔBL $\simeq$ 0.014 Å. This is not apparent from the ΔOPs.

(21) Compare, for example, the C–N bond in 1⁻ and 4⁻, 2⁻ and 5⁻, 3⁻ and 6⁻; compare the C–OH bond in 1⁻ and 2⁻, 4⁻ and 5⁻, 7⁻ and 8⁻.

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(23) For example, a least motion decomposition of the least stable 2⁺ species into NH₃ + CH(OH)₂⁺ gives the least stable form of the protonated formic acid (trans,trans), while the more stable conformers 3⁺ and 4⁺ can lead to the most stable (cis,trans) protonated conformer ($\Delta E \simeq$ 7.6 kcal/mol[15]); similar results hold with 7⁺ compared to 8⁺ which correlate respectively with the cis and trans protonated formamide.[12]

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(27) This can result in part from the anomeric type |X lp, σ^*_{C-Y}| interaction which shifts charge from the X atom to the Y group. Indeed, in the T⁺ conformers with respectively 0, 1, and 2 oxygen lp's app to the C–N bond, the electronic charge on the NH₃ group increases respectively by about 0.04 e (3G and 4-31G) per app lp. In the T⁻ conformers, about 0.04 e (3G and 4-31G) is dispersed from the O⁻ atom to the hydrogen atoms of the O–H or N–H app bonds (compare, for example, 1⁻ and 5⁻).

(28) Similar stereoelectronic control of α-proton abstraction from iminium ions[29] or from ketones[30] has been recently reported: the most acid CH bond is such that the charge of the incipient carbanion can interact with the vicinal π^* orbital; delocalization of the negative charge into empty orbitals has also been shown to be an important factor in the stereoselective formation of α-oxa, α-thia, and α-seleno carbanions.[31,32]

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Unusual Kinetic Behavior in the Self-Reactions of Acyl Methyl Nitroxides[1a]

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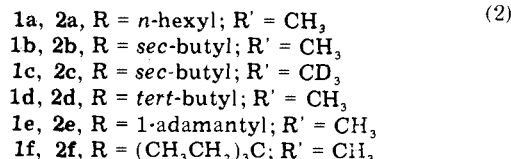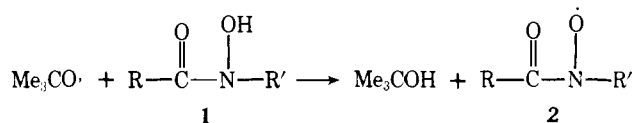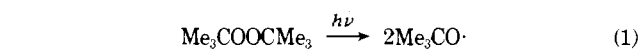
Abstract: The self-reactions of a series of acyl methyl nitroxides have been studied in solution. These reactions proceed by β-disproportionation, for which the measured rate contants lie in the range 10^1–10^3 M⁻¹ s⁻¹ at 298 K. Arrhenius parameters derived from the kinetic data are unusual, having low A factors (ca. 10^4 M⁻¹ s⁻¹) and low activation energies (ca. 1–4 kcal/mol); such values indicate that the reactions do not proceed by a simple mechanism. These results are interpreted in terms of a strong dipole-dipole induced orientation within the caged radical pair which disfavors the disproportionation reaction.

Acyl nitroxides are persistent radicals which have been studied spectroscopically[2] for some years. It has recently been shown that some acyl *tert*-alkyl nitroxides may be isolated as pure materials,[7] and that such radicals have a potential synthetic role as mild oxidizing agents,[8] converting monohydric phenols to quinones and allylic alcohols to aldehydes. Thus, vitamin A alcohol can be oxidized to retinal by *tert*-butyl undecanoyl nitroxide in ca. 90% yield.[8b]

There are also strong indications that acyl nitroxides play a significant role in biological environments.[9] For example, it has been suggested that acyl aryl nitroxides are the active reagents formed in the metabolic transformation of certain carcinogenic amines.[10] This proposal has recently given cause for concern[11] since hydroxamic acids are used widely in chemotherapy and are easily oxidized to the corresponding acyl nitroxides.

As part of our general investigations of fundamental chemistry in this area we have now undertaken a kinetic study of the self-reactions of acyl methyl nitroxides, **2a–f**, in an attempt to understand the reasons for their persistence. The radicals were generated from the corresponding hydroxamic acids (**1a–f**) using *tert*-butoxy radicals which were produced by UV photolysis of di-*tert*-butyl peroxide.

Our results show that compounds **2** decay by a compara-

$$Me_3COOCMe_3 \xrightarrow{h\nu} 2Me_3CO\cdot \qquad (1)$$

$$Me_3CO\cdot + R-\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{N}-R' \longrightarrow Me_3COH + R-\overset{\overset{O}{\|}}{C}-\overset{\overset{\cdot O}{|}}{N}-R' \qquad (2)$$

$$\underset{1}{\qquad} \qquad \qquad \underset{2}{\qquad}$$

1a, 2a, R = *n*-hexyl; R' = CH₃
1b, 2b, R = *sec*-butyl; R' = CH₃
1c, 2c, R = *sec*-butyl; R' = CD₃
1d, 2d, R = *tert*-butyl; R' = CH₃
1e, 2e, R = 1-adamantyl; R' = CH₃
1f, 2f, R = (CH₃CH₂)₃C; R' = CH₃

tively slow bimolecular disproportionation to yield **1** and the corresponding nitrone **3**, e.g.

$$2R-\overset{\overset{O}{\|}}{C}-\overset{\overset{\cdot O}{|}}{N}-CH_3 \longrightarrow R-\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{N}-CH_3$$

$$\underset{2}{\qquad} \qquad \qquad \underset{1}{\qquad}$$

$$+ R-\overset{\overset{O}{\|}}{C}-\overset{\overset{\bar{O}}{|}}{N}{=}\!\!=\!\!\overset{+}{C}H_2 \qquad (3)$$

$$\underset{3}{\qquad}$$