Reactivities of Acrylic and Methacrylic Acids in a Nucleophilic Addition Model of Their Biological Activity

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Abstract: The reactivities of derivatives of acrylic acid in nucleophilic Michael addition are evaluated from a study of the mechanism of addition of a nucleophile, F^-, to the activated double bond of acrylic acid (AA) and methacrylic acid (MAA). This reaction has been proposed to be the underlying mechanism for the toxicity of such compounds. The differences in the molecular properties of AA and MAA that account for the differences in their reactivity toward the nucleophile, as well as the differences in the structure and energy of the resulting carbanions, are calculated with ab initio methods of quantum chemistry using the split valence 6-31++G and 6-31G basis sets. The effects of correlation energy and of basis set superposition errors (BSSE) are evaluated for the main points on the potential energy curve, the transition state (TS) and the stable carbanion (SC). A difference of 3 kcal/mol in the stabilization energy of SC for AA compared to MAA is found with both basis sets used as well as after correction of BSSE. Electron correlation does not change this conclusion. Comparisons of calculated electron density distributions and molecular electrostatic potential maps for the two molecules, combined with the analysis of the energy terms calculated for the various stages of the interaction, reveal that the attacked carbon in the double bond of the two molecules carries a larger electron density in MAA than in AA. This charge density is directly responsible for the more negative electrostatic potential generated by MAA along the path of approach of the nucleophile and for the larger energy required to distort the MAA molecule upon close-contact interaction with the nucleophile. Thus, both the incipient, electrostatically controlled stage of the reaction with the nucleophile and the final stage of production of the carbanion are energetically preferred for AA compared to MAA. The good agreement between the results of these calculations and the experimental findings showing the lower toxicity of MAA derivatives as compared to AA derivatives underlines the discriminating powers of the molecular properties and adds support to the hypothesis that Michael addition in biological systems is a likely molecular mechanism for the toxicity of such compounds. Useful tools for predicting the biological activity of untested compounds in this series are thus obtainable on the basis of clear mechanistic hypotheses and discriminant molecular properties.

Acrylic acid (AA), methacrylic acid (MAA), and their esters constitute a class of chemicals that have diversified uses in industry and medicine. The resulting exposure to these chemicals has fostered an interest in their biological activities and toxic properties.[1-7] The chemicals have been found to be generally inactive in the *Salmonella typhimurium* mutation assay both with and without mammalian microsomal activation.[1,2] Recently, acrylates have been found to be active in the mouse lymphoma L5178Y mutagenesis assay system without microsomal activation,[4] whereas the methacrylates tested in the same assay were found to be inactive at two orders of magnitude higher concentrations.[4]

A quantitative difference in the biological activities of acrylates and methacrylates is suggested by the experimental data for the genotoxicity of chemicals in this class, but it is difficult to generalize about the untested congeners. Studies that define and quantitate the mechanisms of interaction between these chemicals and biomolecular systems will therefore be useful both as a paradigm for interpreting and generalizing existing bioassay data and as a tool for the design for critical bioassays that will make possible a discrimination between members of this class based on their potential toxicity. It has been proposed that chemicals containing a vinylic group next to an electron-withdrawing group, as is the case in the class of acrylate congeners, may add directly to biopolymers by the Michael addition.[8] Direct addition to DNA in vitro has been demonstrated for acrylonitrile[9] and acrylamide.[10] This paper reports a quantitative theoretical study of the mechanism of direct nucleophilic addition to acrylates and methacrylates as a probe of the relative ability of these compounds to undergo such a reaction.

Previous theoretical studies of the addition of nucleophiles to double bonds were secondary to the investigation of nucleophilic vinylic substitution. Such studies of the nucleophilic attack of a large number of nucleophiles on ethylene, cyanoethylene, and nitroethylene[11] led to the conclusion that the carbanion resulting from the addition is stabilized by electron-withdrawing groups. The carboxyl group in the acrylates should be expected to provide such stabilization. The explanation offered for the stability of the nearly planar carbanion on C_2 was given in terms of a hyperconjugation model that draws on the interaction between the lone pair of the anion on C_2 with the antibonding orbital that describes the bond between the nucleophile and C_1; the degree of hyperconjugation was expressed as the barrier to 90° rotation about the C_1–C_2 bond.[11]

In another study,[12] the energy of addition of a nucleophile to acetylene or ethylene was decomposed according to the Morokuma scheme.[13] The analysis revealed that the distortion around C_1,

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Table I. Calculated Energies (hartrees) of the Isolated Molecules of Acrylic Acid (AA), Methacrylic Acid (MAA), and the Carbanion Adducts of Their Interaction with Fluoride (F^-)

basis set	computational level	molecule				
		AA	MAA	F^-	AAF^-	$MAAF^-$
6-31G	HF	−265.532757	−304.556296	−99.350181	−364.947866	−403.967045
	MP2	−266.036575	−305.153350	−99.471693	−365.578381	−404.692431
	MP3	−266.039032	−305.163649	−99.469780	−365.575993	−404.692159
6-31++G	HF	−265.542440	−304.565913	−99.417376	−364.981918	−403.999511

caused by the addition of the nucleophile, brings about a decrease in exchange repulsion and an increase in the electrostatic, polarization, and charge-transfer contributions. These changes were considered as a "driving force" for bending, which lowers the energy of the unoccupied molecular orbital localized on the double bond and changes the localization of charge on C_1.[12] Lowering the energy of this unoccupied orbital increases the charge-transfer component, and the localization of charge density affects the electrostatic and polarization components.

An investigation of the reactivity of substituted ethylene toward a nucleophilic attack was also carried out by Bach and Wolber,[14] who studied the addition of a hydride anion to variously substituted ethylenes. They also attributed the reactivity of the substituted ethylene in this reaction to the relative stability of the resulting carbanion. Their explanation[14] of the electronic factors that govern the addition of nucleophiles to a double bond is based on the interaction between the highest occupied molecular orbital (HOMO) of the nucleophile and the HOMO of the double bond. This interaction, in addition to being responsible for the observed barrier in the course of the addition, also raises the energy of the HOMO in the nucleophile such that its interaction with the lowest unoccupied molecular orbital (LUMO) of the double bond becomes much more favorable.

Yet another type of explanation for the barrier to nucleophilic addition to double bonds was offered by Cohen et al.,[15] based on a state correlation diagram between the reactants, i.e., the nucleophile and the double bond, and the products, i.e., the carbanion. These authors claimed that because the carbanion correlates with a charge-transfer state of the separated nucleophile–double bond system, and the nucleophile–double bond ground state correlates with an excited state of the carbanion, the avoided crossing between these two curves forms a barrier for the addition. However, the relative stability of the carbanion cannot be easily evaluated from such an approach.

In the work presented here we evaluate the mechanism of the addition of a nucleophile, a fluoride anion, to an activated double bond of acrylic or methacrylic acid, in terms of the molecular properties that are responsible for the reactivities of the acrylic acid (AA) and its C_2-methyl congener (MAA) and for the stabilization of the resulting carbanions. The purpose of this study is to evaluate the reaction of acrylates and methacrylates as potential agents that participate in Michael addition and to provide a quantitative comparison of the ability of various acrylic acid derivatives to follow this mechanism of action. Criteria for *differentiating* between the capacity of the various chemicals in this class to add directly to biomolecules by Michael addition are sought from such a comparison of the molecular properties and the relation of the properties to the mechanism of the reaction. The differences in the molecular properties that account for the differences in the reactivities of AA and MAA toward the attack by the nucleophile, as well as the differences in the resulting molecular structures and stabilization energies of the carbanions, are calculated explicitly in order to provide a basis for the evaluation of their relative ability to interact with biomolecules in the Michael-type additions. Such insight is expected to provide the parameters needed for a quantitative ranking of the biological effects of these compounds in studies relating molecular structure to activity.

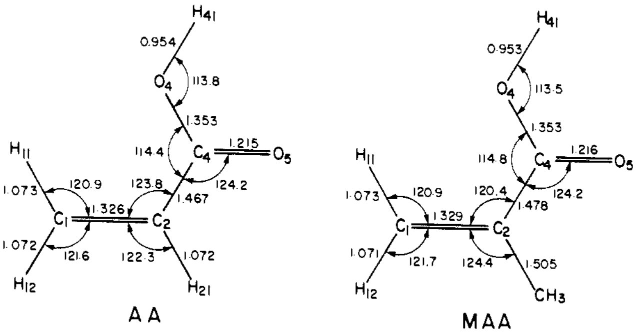

Figure 1. Energy-optimized structures of acrylic acid (AA) and methacrylic acid (MAA) calculated with the 6-31++G basis set.

Methods

All the calculations were performed with the GAUSSIAN 82 system of programs for ab initio calculations. The simulation of the nucleophilic attacks included optimization of stationary points and transition states, simulations of the approach of F^- to AA and MAA at the Hartree–Fock level (HF), and the evaluation of the correlation energies at the level of second-order (MP2) and third-order (MP3) perturbation in the Moller–Plesset scheme.[16] . The basis sets for these calculations were chosen as described below from those incorporated in the GAUSSIAN 82 package. Those include the split valence 6-31G[17] and 6-31++G basis sets,[17] the latter being the 6-31G basis set augmented with an sp shell of diffuse functions on the second-row atoms and a diffuse s function on hydrogens. Contributions from correlation energy were calculated only with the 6-31G basis set due to computational limitations.

The correction to the basis set superposition error (BSSE) was calculated with both basis sets for the complexes of both the acrylic and the methacrylic acid by the method of Boys and Bernardi,[18] in which the separated molecules of the complex (e.g., AA and F^-) were each calculated in the entire complement of basis functions describing the complex, as described before.[19] Because the molecules containing the double bond become distorted in the course of complex formation, the separated molecules had to be calculated in their distorted geometry in the complex. Consequently, in addition to the correction value for BSSE, these calculations also afforded a value of the distortion energy for AA and MAA to their conformation in the carbanion adduct. The change in nonbonded repulsion energy upon distortion was evaluated with the MM2 molecular mechanics method.[26]

The molecular electrostatic potentials (MEP) were calculated with the GAUSSIAN 82 program from the wave functions of the various species and were plotted as isoenergy contours, as described before (e.g., see ref 20). In order to avoid spurious results in the calculation of charge density differences, the corresponding structural parameters in acrylic and methacrylic acid were averaged before the calculation of the electron densities and their difference maps. This was justified by our finding that these structural parameters were only slightly different for the two molecules (see Results and Discussion). The energy of the averaged structures differed from the optimized structures only by 0.1 kcal/mol

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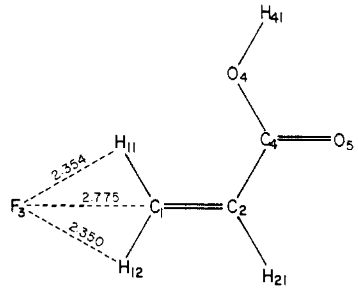
Scheme I



for AA and by 0.2 kcal/mol for MAA. The charge densities were obtained from the wave functions of the averaged molecules, and the charge density differences were obtained by subtracting the density of AA from that of MAA and then multiplying the difference by a factor of 1000.

Results and Discussion

Structures of AA and MAA. Calculations of the structures of AA, of MAA, and of their stable carbanion adducts with F⁻ were carried out with full geometry optimization both with the 6-31G and with the 6-31++G basis sets (Table I). The structures obtained with the 6-31++G basis set are shown in Figure 1. Optimizations of these molecules with the smaller 6-31G basis set yields structures that are virtually identical with those obtained from the optimization with the larger basis set. This is best illustrated by the results of a calculation of the structures optimized with the 6-31++G basis set and of those optimized with the 6-31G basis set with a common basis set, e.g., 6-31G: the difference in the calculated energies does not exceed 0.01 kcal/mol. While this work was in progress another optimized structure of AA was published.[27] The structures obtained from optimizations with the basis sets used here and the 3-21G basis set used in ref 27 are nearly identical.

The structural parameters shown in Figure 1 are in good agreement with experimental values determined by electron diffraction,[21] with the exception of the C_4–O_4 bond length, for which the experimental value is given as 1.43 ± 0.03 Å whereas the calculated value is 1.353 Å. However, the experimental results for the dimer show the C_4–O_4 distance as 1.36 Å,[21] reducing the significance of the single minor discrepancy between the results from theory and experiment.

The structures calculated for AA and MAA are remarkably similar to each other, an observation also made in the experimental study.[21] The only change produced in the structure of MAA by the presence of the methyl group seems to be in the bond angles around C_2 and in the C_2–C_4 bond length. This can be attributed to a steric effect that tends to increase the C_1–C_2–CH_3 angle by 2° and to reduce the C_1–C_2–C_4 angle by 3.4°. The C_2–C_4 bond length is longer in MAA by 0.011 Å, which is probably due to the same effect. The differences in other bond lengths do not exceed 0.003 Å.

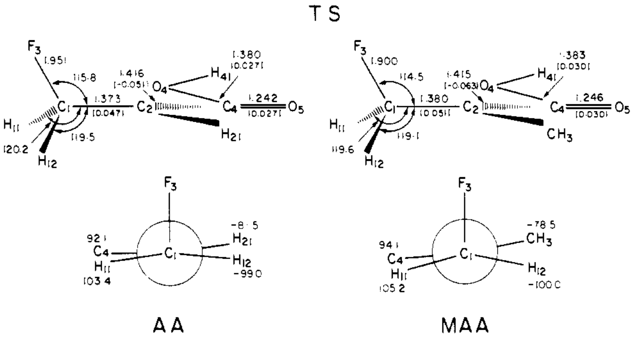


Figure 2. Structural parameters of the transition state (TS) of acrylic acid (AA) and methacrylic acid (MAA) interacting with F⁻. Bond lengths are given in angstroms and bond angles in degrees. Changes from values in the ground state (Figure 1) are given in parentheses. Numbers in the Newman projections of the TS of AA and MAA are torsional angles measured with respect to the $F_3C_1C_2$ plane.

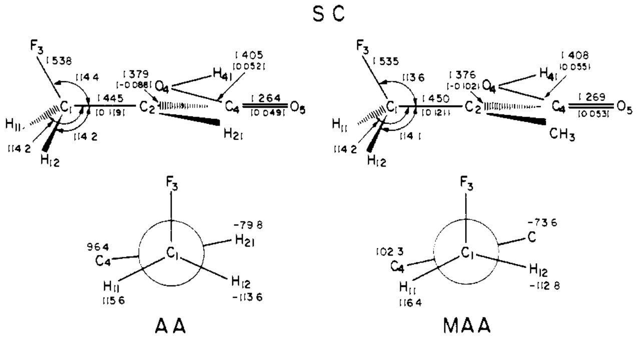


Figure 3. Structural parameters for the stable carbanion formed from the interaction of AA and MAA with F⁻. See legend to Figure 2 for details.

Addition of Fluoride Anion to the Activated Double Bond in AA and MAA. The course of the nucleophilic addition of a fluoride anion to the double bond of acrylic and methacrylic acid is characterized by three distinct stages. Upon the approach of C_1 at an incident angle of 115° with the C_1–C_2 bond, perpendicular to the $H_{12}C_1C_2$ plane, the energy decreases monotonically until the F–C_1 distance reaches the value of 2.485 Å. At this distance the potential energy curve of the approach of fluoride reaches a shallow minimum, M1, with an energy of −10.95 kcal/mol relative to the separated molecules. On the complete potential surface for the interaction, M1 is not a local minimum with respect to a full optimization of the structures of AA and MAA interacting with F⁻. A complete optimization yields the planar structure shown in Scheme I, in which the fluoride is closest not to C_1 but to the hydrogens on this atom, with which it forms a bifurcated hydrogen bond in the $H_{11}C_1H_{12}$ plane. The energy of this hydrogen-bonded complex is −14.81 kcal/mol relative to the separated molecules. In this complex the AA is practically undistorted compared to the isolated molecule. The complex represents a dead-end product which is inconsequential to the nucleophilic attack of the fluoride ion on the double bond.

Further approach of the fluoride ion to C_1 along the angle of incidence of 115° raises the energy of the complex until it reaches a transition state (TS) at a distance F–C_1 of 1.951 Å. Along this path of approach, this state has the characteristic of a real transition state, with a single negative eigenvalue in the matrix of force constants; the major contribution to the corresponding eigenvector comes from the F–C_1 internal coordinate. The energy of this state is −10.14 kcal/mol relative to the separated molecules and 0.81 kcal/mol above M1. The distortion of the acrylic acid in the TS is of the anti form; i.e., the ligands on the attacked carbon C_1 move away from the nucleophile, whereas the ligands on C_2 move toward the nucleophile. This is in agreement with the general trend observed by others.[12,14,15] The extent of the distortion is best described by the Newman projection shown in Figure 2, which identifies the main changes in the bond angles and bond lengths compared to the undistorted optimized structure. The distortion represents a tilt to the $H_{11}C_1H_{12}$ plane by 18.7° downward and a tilt of the $C_4C_2H_{21}$ plane by 5.2° upward with respect to the fluoride that approaches the molecule from above. This distortion is accompanied by alternating changes in the bond lengths: the C_1–C_2 bond length increases by 0.047 Å, the C_2–C_4 bond shrinks by 0.051 Å, and the C_4–O_4 and C_4–O_5 bonds are lengthened again by 0.027 Å each. Other structural parameters remain virtually the same.

From this transition state the complex moves down the potential energy surface to produce a stable carbanion (SC) which is the product of the addition of fluoride to the double bond. Its energy is −13.87 kcal/mol relative to the separated molecules. The structure of the SC is shown in Figure 3 together with the Newman projection that also depicts the main dihedral angles in the molecule. As in TS, an alternating distortion of bond lengths is observed, but larger in magnitude. The distortion at C_1 is also

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Table II. Basis Set Dependence of Stabilization Energies (kcal/mol) of the Stable Carbanion Product of an Attack by F^- on Acrylic Acid (AA) and Methacrylic Acid (MAA)

molecule	computational level	basis set 6-31G	basis set 6-31++G
AAF$^-$	HF	−40.74	−13.87
	MP2	−44.00	
	MP3	−42.16	
MAAF$^-$	HF	−38.01	−10.18
	MP2	−42.29	
	MP3	−36.85	

Table III. Energy Components (in kcal/mol) for the Calculation of Corrections to the Basis Set Superposition Error (BSSE) in the Stabilization of the Carbanion Adduct of Acrylic Acid (AA) and Methacrylic Acid (MAA) with Fluoride (F^-)

	molecule			
	AAF$^-$		MAAF$^-$	
energy component	6-31G	6-31++G	6-31G	6-31++G
distortion energy ($DIST_{AA}$)	32.22	31.82	35.46	35.04
E_{int}	−55.99	−43.82	−55.74	−43.32
$BSSE_{dist}$	−15.59	−0.69	−16.35	−0.74
$BSSE_F$	−15.59	−0.69	−16.35	−0.74
cor stabilization energy (E_s)	−23.77	−12.00	−20.28	−8.28

bigger as the $H_{11}C_1H_{12}$ plane is tilted 43.0° downward, but the distortion at C_2 remains practically the same: 3.8° upward.

The course of the addition of the fluoride anion to MAA is very similar to the process described for AA; i.e., the system passes through a transition state (TS) and ends with the stable carbanion (SC). The distortions in the TS and SC of the complex with MAA are also very similar to those with AA: in the TS the $H_{11}C_1H_{12}$ plane is tilted 21.1° downward and the $C_4C_2C_6$ plane is tilted 6.0° upward (Figure 2); in the SC these angles become 42.9° and 3.9°, respectively (Figure 3). *The only significant difference between the potential energy curves for AA and MAA is in the relative energies of the TS and SC complexes.* The transition state of the F^- addition to methacrylic acid is −7.00 kcal/mol relative to the separated molecules, compared to an energy of −10.15 kcal/mol for the acrylic acid; the stable carbanion is −10.18 kcal/mol for MAA compared to −13.87 kcal/mol for the AA (Table II). Thus, the additional methyl on C_2 of the double bond in MAA causes a reduction in the stabilization of TS and SC of the reaction with F^- by about 3 kcal/mol compared to the separated molecules. This result is consistent with both the lower stability of carbanions formed from methacrylic acid and a slower rate of nucleophilic addition to methacrylates compared to acrylates.[22]

Basis Set Effects, Correlation Energies, and the Basis Set Superposition Error. Calculations of anionic structures, such as the ones formed in the simulated addition of fluoride to the double bond, require a basis set augmented with diffuse functions to properly account for the weakly bound electron and the diffuse charge distribution. Even for medium-size molecules presented here such calculations become very expensive due to the large number of basis functions. Consequently, attempts to simulate such reactions for molecular structures larger than AA and MAA will be prohibited by the computational limitations. It is therefore desirable to examine the performance of smaller basis sets in replicating the results obtained here with the extended basis sets. One of the main features of the difference observed between the stabilization energies calculated for the interaction of AA and MAA with F^- is the nearly constant value of 3 kcal/mol that is consonant with the experimentally observed differences in the reactivities of these molecules. We examined the dependence of this nearly constant difference on the basis set used in the calculations. For comparison we chose the split valence 6-31G basis set because it only lacks the diffuse function of the 6-31++G basis set.

As expected, the calculated stabilization energies are strongly dependent on the presence of the diffuse functions in the basis set. However, results in Table II clearly indicate that the calculated difference between AA and MAA remains the same: −13.87 vs −10.18 kcal/mol calculated at the Hartree–Fock level (HF) for the stabilization of the carbanion with the diffuse basis set, and −40.74 vs −38.01 kcal/mol calculated with the 6-31G basis sets. These values are similar to those calculated for acrolein with a 4-31G basis set.[28] Examination of the effect of the diffuse function on the individual energies of the interacting molecules and of the complex listed in Table I identifies the main source for this basis set dependence as the change in the energy of the fluoride ion. The addition of the diffuse shell on the fluoride lowered its energy by 42.2 kcal/mol (Table I); AA and MAA are affected equally by a small difference, amounting only to 6.0 kcal/mol (Table I). The effect on the SC is larger but again nearly equal for the two acrylates: 21.4 kcal/mol for AAF$^-$ and 20.4 kcal/mol for MAAF$^-$ (Table I). This 1 kcal/mol difference is responsible for the somewhat smaller difference in the stabilization energies (Table II) calculated at the HF level with the 6-31G basis set (2.73 kcal/mol) compared to the results from the calculation with the 6-31++G basis set (3.7 kcal/mol).

The effect of electron correlation was evaluated by the Moller–Plesset perturbation method[16] up to third order in energy (MP3). Such calculations are prohibitively expensive with the 6-31++G basis set due to the magnitude of the "ghost" basis[19] required. The correlation energy contributions for the isolated molecules and the complexes were thus evaluated only with the 6-31G basis set (Table I). The MP2 corrections are of the same sign as the energy values obtained at the HF level, but for F^- and its complexes with AA and MAA, the MP3 correction is of opposite sign, albeit smaller in absolute value. Nevertheless, inspection of results in Table II reveals that the correlation effects do not change the preference in stabilization energy of the AAF$^-$ carbanion over the MAAF$^-$; the difference in stabilization energies is 5.31 kcal/mol at the MP3 level.

Calculations of intermolecular interactions are subject to the well-known basis set superposition error (BSSE).[18] We have investigated the effect of the BSSE on the calculated interaction energies with both basis sets discussed above, i.e., 6-31++G and 6-31G. Because the interaction of fluoride with AA and MAA causes a distortion of their structure, the usual procedure we followed[19] by calculating the BSSE from the difference between the energy of the complex and that of the separated molecules calculated in the "ghost" basis set of entire complex is not directly applicable here.

The BSSE for distorted molecules can be calculated by first decomposing the total energy of the complex of fluoride with AA (E_{AAF}) into the energy of AA in the complex ($E_{AA}{}^c$), the energy of fluoride in the complex ($E_F{}^c$), and the interaction energy between them (E_{int}). The energy of the fluoride in the complex, $E_F{}^c$, is the energy of fluoride in its own basis set (E_F) plus the BSSE due to the extended basis set of the complex ($BSSE_F$) (see Table III).

The energy of AA in the complex ($E_{AA}{}^c$) is that of the distorted molecules and includes the distortion energy ($DIST_{AA}$) as well as the BSSE of the distorted molecule. The corrected stabilization energy (E_s), defined as the difference between the energy of the complex and the energies of the separated molecules corrected

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for the BSSE, is easily seen to be given by

$$E_s = \mathrm{DIST}_{AA} + E_{int}$$

The results from calculations of corrected stabilization energies for the stable carbanion (SC) of AA and MAA calculated with two different basis sets are given in Table III.

The source of the large difference in the stabilization energies computed with the 6-31G and the 6-31++G basis sets is evident from the comparison of the results of the BSSE correction for the molecules calculated with two different basis sets (Table III). The major difference appears in the BSSE for the fluoride anion, which is 15.59 kcal/mol if the computation is done with the 6-31G basis set but is very small, 0.69 kcal/mol, when the computation is with 6-31++G. This finding is in agreement with our conclusion reached above that the 6-31G basis set is grossly deficient in describing the diffuse electrons of the fluoride so that the greater apparent stabilization energy at the 6-31G level can be attributed to the artificial increase in the energy of F^-. In the complex formed by the addition of F^- to AA or MAA, the basis functions on these molecules provide the fluoride with a certain compensation for the deficient 6-31G basis set through the basis set superposition effect. However, this compensation is not as effective as the set of diffuse functions in 6-31++G, as seen from the fact that the basis set superposition correction (BSSE_F) is only about 15–16 kcal/mol while the difference in the calculated energy of F^- with the two basis sets (Table I) is as large as 42.2 kcal/mol. Consequently, the corrected stabilization energy calculated with the 6-31G basis set is still higher than with the 6-31++G basis set by about 12–13 kcal/mol.

Another difference between the two basis sets is also noteworthy and becomes evident from the calculation of the corrected stabilization energy (E_s) as the sum of the distortion energy (DIST) and the interaction energy (E_{int}). Since the distortion energy is found to be essentially basis set independent (Table III), the interaction energy reflects the difference between the two basis sets. Since E_{int} represents an interaction between the F^- anion and a polarized molecule in a "prepared" geometry, the major component in this term should be electrostatic. The difference between the E_{int} values calculated with the two basis sets should therefore reflect a different charge distribution of the fluoride interacting with the distorted double bond. This conclusion is consonant with the arguments presented above for the shortcomings of the 6-31G basis set being mainly in the representation of F^-, not of the acrylates.

Results in Table III also provide an explanation for the difference in the stabilization energies of the stable carbanions AAF^- and $MAAF^-$ with respect to the separated molecules. Comparison of the basis set superposition corrections for the two compounds reveals that within one basis set, the BSSE is the same for both the acids and for the fluoride in the two compounds. Furthermore, the interaction energy, E_{int}, calculated within one basis set is nearly the same for the two compounds. Consequently, *the difference between the stabilization energies is only reflected in the difference of the distortion energies for the acrylic and the methacrylic acid.* It is tempting to attribute this difference to the trivial proposition that because methacrylic acid becomes more crowded in the distorted state, the difference in the distortion energies simply reflects a steric effect; this is found to be untrue: First, the nuclear repulsion energy, which should be the main contributor to the steric repulsion, is smaller in the distorted form than in the undistorted form of the molecules due primarily to the changes in bond lengths upon distortion (see Figure 3). Second, the nuclear repulsion energy in the distorted MAA is smaller by 387.1 kcal/mol than in the distorted AA, but the distortion energy is larger for MAA than for AA (Table III). Lastly, the nonbonded repulsion energy calculated according to the empirical formulation in the molecular mechanics program MM2[26] shows that the repulsion is reduced upon distortion of the molecules. The reduction in AA is by 0.2 kcal/mol and in MAA it is lower by 0.3 kcal/mol. Examination of the structural changes that accompany the distortion process suggest that the crowding around C_1 due to the distortion is compensated by bond stretching, so that all the parameters that describe steric repulsion are smaller in the distorted state. Thus, we must conclude that the difference in the distortion energy is due to an electronic effect that stems from the different charge distributions in the two molecules.

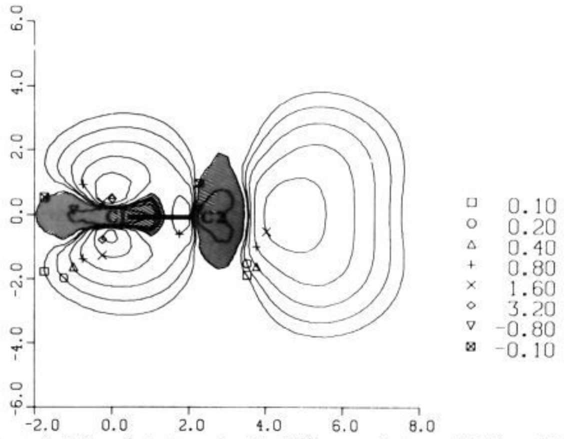

Figure 4. Map of electron density differences between MAA and AA calculated in a plane containing the C_1–C_2 double bond and perpendicular to the $H_{11}C_1H_{12}$ plane. Electron density values were calculated from the wave functions of the molecules obtained with the 6-31++G basis set, and their differences was obtained by subtracting the density of AA from that of MAA. Values are in e/Å^3 × 1000. Shaded area highlights regions where the values are negative; i.e., the density in AA is greater than in MAA.

It is important to note that the analysis shows the difference in the stabilization energies of AA and MAA to depend *only on the properties of the isolated molecules* and not on the interaction terms. For this reason it becomes possible to search for reactivity criteria based on the properties of the isolated molecules that will faithfully describe the differences in their susceptibility to nucleophilic attack and the different stabilization energy of the products.

Reactivity Properties of the Isolated Molecules. The interaction of fluoride with acrylic and methacrylic acid can be decomposed into the distortion energy required to bring the molecules into the geometry of the SC and the interaction energy (E_{int}) between the distorted molecules and fluoride. The analysis of these components for the two compounds indicated that E_{int} is practically identical for AA and MAA (Table III) and thus that the difference in the interaction energy stems from the different distortion energies, DIST, required for acrylic and methacrylic acid (Table III). This difference should be reflected in the electronic properties of the two molecules: The net charge on the terminal CH_2 group of AA, calculated from a Mulliken population analysis, is positive (+0.0307) whereas in MAA it is negative (−0.0724), consistent with AA being more reactive than MAA with respect to a nucleophilic attack directed at the C_1 terminal. The difference in charge distribution in the plane perpendicular to the double bond in the two molecules is compared from the charge density difference plot shown in Figure 4. The charge density in the π region of MAA is shown to be greater than in AA. Since the approach of the fluoride is from above the molecule and its initial repulsive interaction is with the π density, a higher density on MAA is consistent with a lower reactivity of this molecule compared to AA.

Further support for the inference from the density difference map is provided by the molecular electrostatic potentials (MEP) calculated for these molecules. The MEP in the plane perpendicular to the double bond of AA is shown in Figure 5a and for MAA in Figure 5b. The potential in this plane exhibits a local negative minimum above the double bond; the values of the potential become increasingly positive in the direction of C_1, suggesting that at long range the approach of a nucleophile will be directed by electrostatic forces toward C_1. A comparison of the MEP of MAA to that of AA (Figure 5b vs Figure 5a) indicates the expected difference in the electrostatic steering. In MAA the minimum in the MEP has a lower value and the negative contours

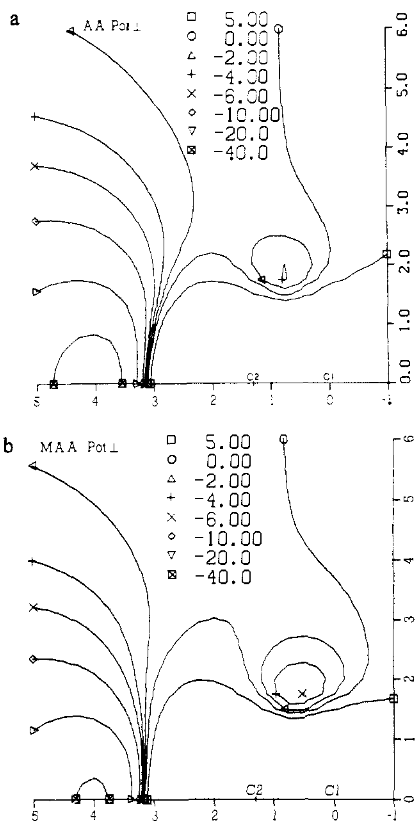

Figure 5. Molecular electrostatic potential maps in the same plane as defined in Figure 4. Electrostatic potentials were calculated from the wave functions of (a) acrylic acid (AA) and (b) methacrylic acid (MAA) obtained with the 6-31++G basis set. Values are in kcal/mol.

are extended much farther toward C_1 than in AA, thus predicting a larger repulsive component for the approach of a nucleophile toward MAA than toward AA. This difference in the reactivity towards a nucleophile approaching C_1 is further illustrated by the comparison of MEP maps computed for the two compounds in a plane parallel to the double bond plane at 2 Å above the molecule (Figure 6a for AA and Figure 6b for MAA). The MEP for AA shows a much more extended positive area near C_1 than the MEP for MAA; at this distance the electrostatic potential above C_1 of MAA has a value of −3 kcal/mol while above C_1 of AA the value is 0.0. These comparisons of the electrostatic properties of the isolated molecule indicate that a nucleophilic attack on C_1 of MAA will be more difficult than on C_1 of AA.

The difference in the electrostatic properties revealed by the MEP maps relate to the differences in the charge distributions of MAA and AA discussed above: An increased charge density on C_1 in MAA compared to AA is responsible for the more negative electrostatic potential and the electrostatic reactivity criteria related to it; this same increased charge density is also responsible for the larger distortion energy required for the preparation of the complex of F^- with MAA compared to the complex with AA. In the process of distortion, C_1 undergoes a rehybridization from an sp^2 to an sp^3 type of localization. This rehybridization will reduce the delocalization of the charge on C_1 into the carboxyl group. Because the charge density on C_1 of MAA is higher than on C_1 of AA, the rehybridization and the consequent distortion require more energy for MAA than for AA. *The reactivity of MAA toward the nucleophilic attack is reduced in comparison to that of AA both by its lower electrostatic susceptibility and by its higher demands of distortion energy to prepare the molecule for its conformation in the stable carbanion.*

Concluding Remarks

The present studies of the mechanism of nucleophilic addition to the activated double bonds in acrylic acid derivatives indicate that the addition of fluoride anion is governed by two main effects: One is the interaction of the anion with the double bond, which includes electrostatic attraction, mutual polarization, and charge transfer. The other is the induced distortion in the structure of the attacked double bond. The opposing contributions to the energy of the system from these two effects determine the relative stability of the carbanion that is formed in the course of the nucleophilic addition. The relative stability of the carbanion should correlate with the reactivity of the double bond with respect to nucleophilic addition, in agreement with the experimental observations of anionic addition to double bonds.[23] Thus, in studies of nucleophilic addition to olefins, Bernasconi et al.[24] observed that at high pH values in the range of 11–12 the rate-determing step was the nucleophilic attack by a hydroxide anion on a substituted double bond. These authors interpreted the dependence as evidence that the carbanion is a steady-state intermediate in the reaction. The same assumption can be made for the reaction studied here in which the fluoride anion adds to the double bond to produce the stable carbanion that constitutes an intermediate ready for the rapid protonation which completes the addition reaction. The choice of F^- to model the nucleophilic interaction of a variety of active biomolecules with the activated double bond of the acrylate congeners was intended to minimize the dependence of the conclusions on the nature of the nucleophile. Since the active centers in biomolecules that are likely to interact with the acrylates can be expected to have higher polarizabilities than F^- and to be affected by steric crowding, the path of attack and the energetic contributions from the nucleophile may vary. However, the discriminant factors dependent on the molecular structures and properties of the substituted acrylates, which constitute our major interest, should remain close to those revealed by this study.

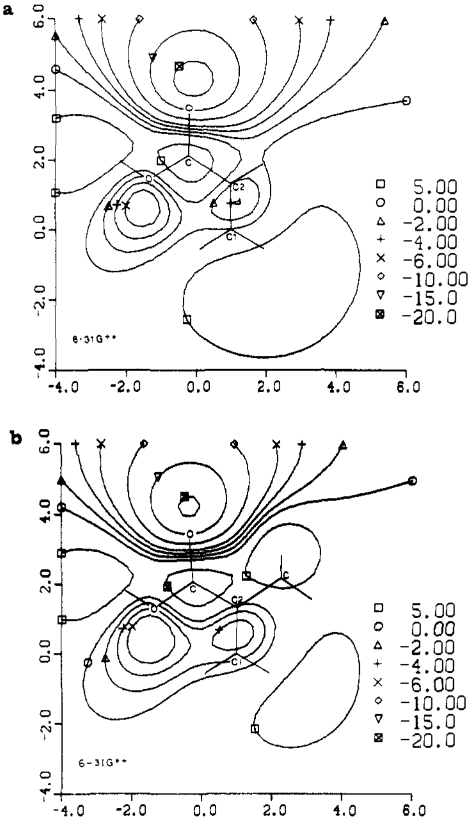

Figure 6. Molecular electrostatic potential maps in a plane parallel to $H_{11}C_1H_{12}$ and positioned 2 Å above the molecule of (a) acrylic acid (AA) and (b) methacrylic acid (MAA). The potential was calculated from the wave functions obtained with the 6-31++G basis set. Values are in kcal/mol.

The comparison of the relative stabilities of the stable carbanions of acrylic and methacrylic acid obtained here indicates that the carbanion of acrylic acid is at least 3 kcal/mol more stable than that of methacrylic acid. Analysis of the components of this stabilization energy suggested that the intrinsic properties of the isolated molecules should provide discriminant parameters for the reactivities of these compounds in a nucleophilic addition reaction.

Indeed, the attacked carbon (C_1) carries a larger electron density in methacrylic acid than in acrylic acid, and this difference is directly responsible for the more negative electrostatic potential generated by MAA along the path of approach of the nucleophile. The difference in charge distribution is thus responsible for different recognition properties at relatively long distances from these molecules. This difference in electron density distribution is also responsible for the difference in the energies required to distort the two molecules upon close-contact interaction with the nucleophile. The distortion of the C_1 carbon with the higher charge density in MAA requires more energy than that in AA. This difference in energy is mainly responsible for the difference in stabilization energies of the stable carbanions produced when the molecules interact with the nucleophile F^-.

The discriminating properties discussed above for the acrylic and methacrylic acids can thus become the basis for structure–reactivity correlations in substituted double bonds with respect to a nucleophilic addition. Furthermore, this type of discriminant reactivity criterion can be correlated with experimental measurements of toxicity.[25] The observed correlation, indicating lower reactivity of MAA derivatives as compared to AA derivatives in nucleophilic addition as well as in the bioassays, supports the hypothesis that Michael addition is a likely molecular mechanism for the biological activity of activated double bonds and reaffirms the discriminating power of the molecular properties. Such discriminant reactivity criteria that are anchored in the properties of the molecules and are based on clear mechanistic hypotheses should provide useful tools for predicting the ability of untested compounds in this series to exhibit similar biological activities.

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Molecular and Macromolecular Nonlinear Optical Materials. Probing Architecture/Electronic Structure/Frequency Doubling Relationships via an SCF–LCAO MECI π Electron Formalism

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Abstract: This contribution explores the use of perturbation theory and the computationally efficient PPP π electron model Hamiltonian to relate quadratic molecular optical nonlinearities to architecture and electronic structure. A detailed study of aniline, nitrobenzene, and *p*-nitroaniline, using all monoexcited configurations, yields β (hyperpolarizability) tensors in good agreement with all-valence-electron CNDO calculations. Moreover, PPP-derived vector (observable) components for frequency doubling ($\beta_{\mathrm{vec}}(-2\omega;\omega,\omega)$) are in excellent agreement with experiment over a wide frequency range. For a series of para-disubstituted benzenes, there is a linear relationship between calculated β_{vec} values and Hammett σ parameter differences for the substituents. For a series of α,ω-$N(CH_3)_2,NO_2$-disubstituted trans polyenes, there is a linear relationship over a broad frequency range between calculated ln β_{vec} and the number of double bonds between the substituents. Multiple $N(CH_3)_2,NO_2$ substitution at the polyene ends has little additional effect on β_{vec} beyond that of single substitution. Examination of a simple two-level perturbation model reveals that this insensitivity of β_{vec} to multiple donor/acceptor substitution reflects the corresponding insensitivity of the dipole moment as well as of the energy and oscillator strength of the first optical transition. The utility of the PPP model Hamiltonian in designing new, elaborate nonlinear chromophores is illustrated by an examination of several hypothetical molecules of sequentially varied substitution.

Substances which exhibit highly nonlinear optical (NLO) responses are currently of great scientific and technological interest.[1] While such materials have traditionally been inorganic in nature (e.g., $LiNbO_3$, KH_2PO_4, $KTiOPO_4$, etc.), recent results suggest that organic conjugated π-electron molecular and polymeric NLO materials offer great promise.[2] The attraction vis-à-vis more conventional materials lies in the inherent tunability of organic molecular structures, greatly enhanced NLO responses over a wide frequency range, ultrafast response times, the possibility of better processing/film-forming characteristics, lower dielectric constants, and the possibility of higher laser damage thresholds.[2]

The fundamental relationship describing the change in molecular dipole moment (polarization) upon interaction with an oscillating external electric field can be expressed in a power series (eq 1).[1,2] Here P_i is the polarization induced along the ith

$$P_i = \sum_j \alpha_{ij}E_j + \sum_{jk} \beta_{ijk}E_jE_k + \sum_{jkl} \gamma_{ijkl}E_jE_kE_l + \ldots \qquad (1)$$

molecular axis, E_j is the jth component of the applied electric field, α is the linear polarizability, β the quadratic hyperpolarizability, and γ the cubic hyperpolarizability. The even order tensor, β, which is responsible for second harmonic generation (SHG) and frequency mixing, vanishes in a centrosymmetric environment. There are no environmental parity restrictions on the odd order

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