ONIUM IONS ARE NOT ON THE REACTION COORDINATE IN THE FORMATION OF HETEROCYCLES VIA ELECTROPHILE-INDUCED ALKENOL CYCLIZATIONS

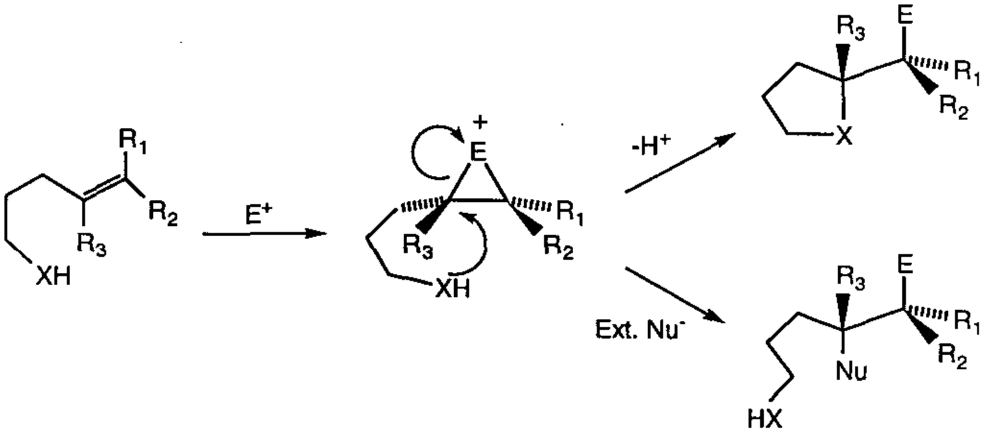
James Sperka and Dennis C. Liotta*

Department of Chemistry,
Emory University,
Atlanta, Georgia 30322, U.S.A.

Abstract - Semi-empirical molecular orbital methodology was used to determine the reaction surfaces for competitive intramolecular bromoetherification and intermolecular bromohydrin reactions. These reactions do not proceed through a bromonium ion intermediate. Instead, the additions involve the formation of a weak olefin / Br^+ π-complex which is subsequently captured by a proximate nucleophile.

Despite the development of many novel reaction protocols, the simple addition of electrophilic reagents to double bonds (the co-functionalization reaction) remains one of the most conceptually-important and synthetically - useful processes in modern organic chemistry. In addition, electrophile-induced intramolecular cyclizations have emerged as one of the most general methods available for the preparation of three, five and six-membered ring heterocycles.[1,2] Mechanistically, these co-functionaliztion reactions are thought to proceed through three membered onium ion intermediates which are subsequently opened in a *trans*-fashion by either an internal or external nucleophile (see **Scheme 1**).[3] The potential intermediacy of free carbocations was discounted long ago when it was observed that in simple cases, such as dibromide formation, no *cis*-products were found in the reaction mixture.[4]

Electrophile-induced intramolecular cyclizations are usually much faster than other potentially-competitive intermolecular addition processes and proceed with good regio- and stereocontrol.[5] For example, even in saturated aqueous dimethoxyethane, little, if any, halohydrin formation is observed during the haloetherifications of alkenols capable of internally forming three, five or six-membered rings. In the context of synthesis, the stereoselectivity observed in these cyclizations is often a function of: (a) the position and electronic characteristics of substitutents on the tether which links the nucleophilic and the olefinic portions of the system, (b) the chemical and physical properties of the electrophilic agent employed,[1] and (c) the degree of reversibility with which the onium ion intermediate is formed.[6]

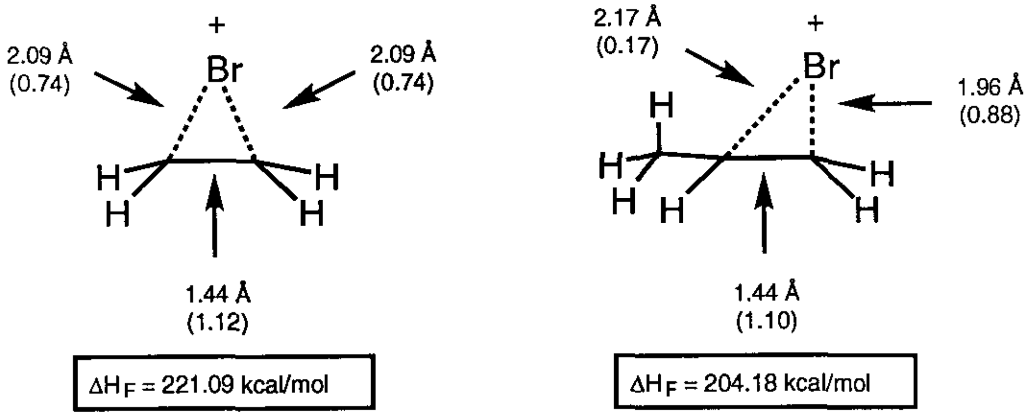


Scheme 1: The competition between intra- and intermolecular electrophilic additions to double bonds.

In this paper we present the results of a study which employs semi-empirical methods (*i. e.*, AM1 Hamilitonian within MOPAC, version 5.00) to calculate the reaction surfaces of several bromoetherification reactions. By utilizing this approach, we are able to rigorously locate the transition states and activation energies of competing intra- and intermolecular reactions (*i. e.*, tetrahydrofuran and bromohydrin formation, respectively) in the addition of bromine to 1-penten-5-ol in the presence of water.

Construction of the various reaction surfaces involves the following general protocol: (a) calculation of the initial geometries of starting materials and products using the MMX force field as implemented in PCMODEL,[7] (b) minimization of these geometries with the AM1 Hamilitonian[8] in MOPAC 5.00[9] and (c) systematic variation of crucial bond lengths involved in the reaction to map out a crude rendering of the surface. Although the angle of the attacking nucleophile and one of the C-Br bonds were partially restricted to maintain proper trajectory and promote bonding respectively, all other bond lengths and angles were allowed to optimize during the surface mapping. From the representation of the reaction surface the maxima and minima can be easily located in an approximate sense and then subjected to further characterization.

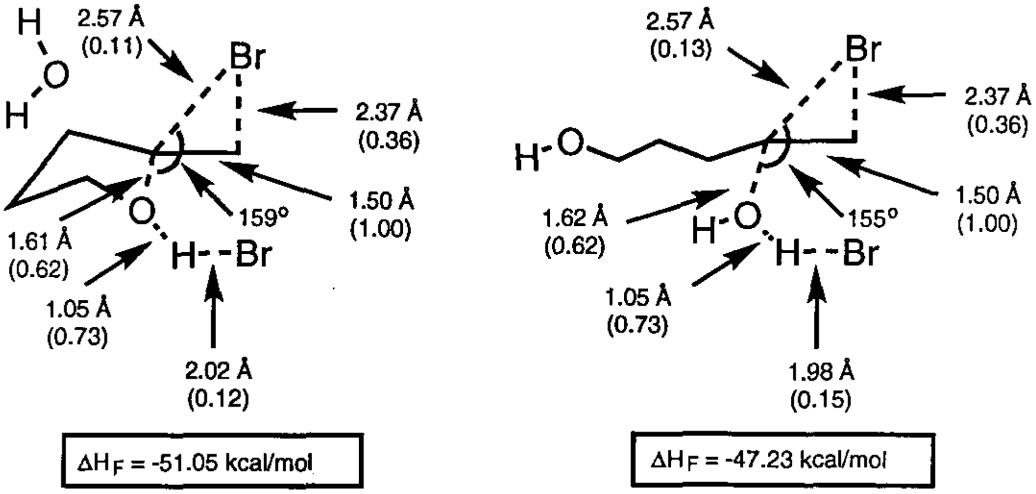
The major point of interest, the saddle point, appears on the surface as a valley flanked by various higher energy peaks which are adjacent to the reaction coordinate. Locating the transition state, which is usually found in this region, is accomplished using Bartel's Non Linear Least Squares Method (NLLSQ).[9] This method reduces the gradient norm by finding a change in sign of the gradient that identifies either a saddle point or a local or global minimum. At these inflection points the geometry is stable enough for further characterization which is done using a Force calculation.[9] In order to qualify as a legitimate transition state, the various maxima on the surface must exhibit one (and only one) negative force constant. In addition, the lowest energy vibration must largely include only the atoms directly involved in bond making or bond breaking. Conversely, reaction intermediates (minima) exhibit all positive force constants, the first five of which are typically very close to zero.[9] For calibration purposes, several simple onium ions were evaluated to obtain bond length and bond angle information. In particular, the bromonium ions, C_2H_4Br and C_3H_6Br (**Scheme 2**), were characterized as described above. The calculated geometries of these species are consistent with one's intuitive expectations for olefin / electrophile complexes. For example, the ethylene / Br^+ complex is symmetrical with its C-Br and C-C bond lengths somewhat longer than those observed for C-Br single bonds (1.93 Å) and C-C double bonds (1.34 Å). Similarly, the propylene / Br^+ complex is unsymmetrical with its C_2-Br bond considerably longer than its C_1-Br counterpart, an observation which fits nicely with the well-known preference for nucleophiles to react with these complexes at the more substituted carbon (Markovnikov's rule).



Scheme 2. Relevant bond lengths, heats of formation and bond orders for the bromonium ions of ethylene and propylene.

The major thrust of our study focused on determining the reactivity profiles for the intramolecular cyclization of the 1-penten-5-ol / Br^+ complex (**Scheme 1**, X = O, $R_1 = R_2 = R_3 = H$) as well as the competitive intermolecular hydration of the same complex (*i. e.*, bromohydrin formation). However, in addition to including water, it also proved important to have a "non-participating" counter ion present during the calculation. Without the counter ion, which in this case was chosen to be Br^-, it was virtually impossible to obtain meaningful data on either of these reactions. This is a direct consequence of evaluating these reaction profiles *in vacuo*. In the absence of solvation, charged centers seek out any available sources of excess electron density in order to distribute the charge over a larger volume. As a consequence of this, the process of internally solvating the starting olefin / Br^+ complex by the hydroxyl oxygen is so exothermic that in this case the barrier for its conversion to product is virtually non-existent (*i. e.*, $E_{act} \sim 0$). Fortunately, the simple addition of a counterion to the system reduces the separation of charge and thereby restores a more appropriate balance between electrostatic and orbital factors in the competing reactions.

In evaluating the competing intra- and intermolecular processes, the approach of the attacking nucleophile was varied systematically while the other nucleophiles present (*i. e.*, the other oxygen and the bromide) were allowed to interact freely. Although an extensive search for a bromonium ion intermediate or transition state was carried out, no suitable geometries were found. This was quite surprising since we knew from the study described in **Scheme 2** that the methodology employed had no difficulties dealing with bromonium ions *per se*.



Scheme 3. Relevant bond lengths, attack trajectory angles, heats of formation and bond orders (parentheses) for the intramolecular cyclization and intermolecular hydration transition states.

As a consequence, we extended the search to include π-complexes and were gratified to find saddle points for both the intra- and intermolecular processes that were characterizable from the surface plots (**Scheme 3**). In addition, the common starting materials and products for these reactions were also characterized. The two transition states which were located have many similarities. First, both C-Br bond lengths in the unsymmetrical transition states are considerably longer than those found in the propylene bromonium ion (2.37Å *vs.* 1.96Å and 2.57Å *vs.* 2.17Å, respectively). Conversely, the C-C bond lengths (1.50Å) in the transition states more closely resemble a normal C-C single bond (1.54Å) than the proplyene bromonium ion (1.44Å), to some extent as a consequence of their product-like character. Second, both transition states exhibit a high degree of C-O bond formation, suggesting the somewhat surprising conclusion that these reactions should be more appropriately viewed as concerted, rather than stepwise processes. Third, the counterion actually participates in the reaction by acting as a base for abstracting an O-H proton. However, we note that this involvement of bromide in the reaction may be an artifact of the calculation's neglect of solvation which effectively forces the counterion to be in relatively close proximity to the various reacting centers in order to minimize the separation of charge.

The enthalpy of activation for the intramolecular cyclization was found to be 3.8 kcal / mol lower in energy than the competing intermolecular hydration reaction. An energy difference of this magnitude is more than sufficient for rationalizing why tetrahydrofuran formation is overwhelmingly favored over bromohydrin formation. The difference in activation energies between the processes is most easily understood in terms of non-bonding interactions which occur with the carbon chain during the approach of the water molecule (Note: the C-O bond orders for both transition states are quite substantial (0.62)). In the intramolecular cyclization, these destabilizing interactions are significantly reduced because of the modest energetic penalty associated with orienting the internal nucleophile into the required trajectory.[10] In addition, the internal nucleophile is inherently more nucleophilic than water. One measure of this difference in nucleophilicity comes from examination of the p_z coefficients for each of the oxygens in the three highest occupied orbitals of the starting molecular array. For the internal oxygen these values are 0.041, 0.185 and 0.100 and for the water oxygen they are 0.001, 0.003, 0.009 for the HOMO-2, HOMO-1 and HOMO, respectively. These values clearly suggest that, all other things being equal, internal cyclization will be preferred electronically.

In conclusion, semi-empirical molecular orbital methodology was used to determine the reaction surfaces for competitive intramolecular bromoetherification and intermolecular bromohydrin reactions. These reactions do not proceed through a bromonium ion intermediate. Instead, the additions involve the formation of a weak olefin / Br^+ π-complex which is subsequently captured by a proximate nucleophile. These results are also consistent with empirical observations made earlier by us regarding the parallels between cyclization stereoselectivity and the reversibility of the initially-formed olefin / electrophile complex.[6] In particular, those reactions which involve strong olefin / electrophile interactions are expected to be inherently less selective than their weakly-associated counterparts since in the former the smaller degrees of C-O interactions attenuate differences which exist between diastereomeric transition states.

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10. The absolute values of the enthalpies of activation for both reactions (~ 40 kcal/ mol) are obviously too large for reactions which occur readily at room temperature or below. These errors are largely the result of the neglect of solvation which was previously discussed.

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