

Reaction Prediction: The Suggestions of the Beppe Program

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The Beppe project represents a modeling experiment that aims at contributing a better management of the prediction of reaction products. From this perspective, a completely theoretical system has been initially studied, independent of the result control given by experimental data. The connected program realized until now can evaluate the different aspects of the molecular reactivity; consequently, it can generate some of the reaction products starting from a molecular ensemble and give a set of numerical rules to estimate both the result reliability and the possibility to get different results using different experimental procedures.

INTRODUCTION

Time has passed since the first approach¹ to reaction prediction appeared in the literature. Since then some other works have described different ways to confront the problem. Some of them are much more related to reaction retrieval² and classification systems;³ some of them are part of programs born to solve different problems⁴ (e.g., synthesis planning); some of them really aim at suggesting reaction products.⁵ From this last perspective, it is possible to further divide the experiences: those that use a high level of abstraction (privileging new fascinating ideas to reality),^{3,5c} those that use elaborated data (privileging experience knowledge to generality),¹ and those that use calculated physical data (trying to furnish both general and reliable answers).^{5a,b} The question is "Is it necessary to have a new approach?"; the answer is positive. Chemical reactivity is still the chance given to chemists to show their artistic capacity, permitting the development of new interpretations and predictions of molecular behavior.

Therefore, many theoretical chemists have their own possibility of introducing models for either explaining the well-defined interaction of two molecules (i.e., where starting and final products are known) or suggesting the possible result of their combination (i.e., enumerating the most feasible product molecules). All of the approaches represent models for chemical reactivity, and their utility is always assured, even if their reliability can be discussed.

Beppe would like to be another, hopefully useful, contribute to the field. It is not as sophisticated as *ab initio* approaches, but reliability, general applicability, and open mind are among its objectives.

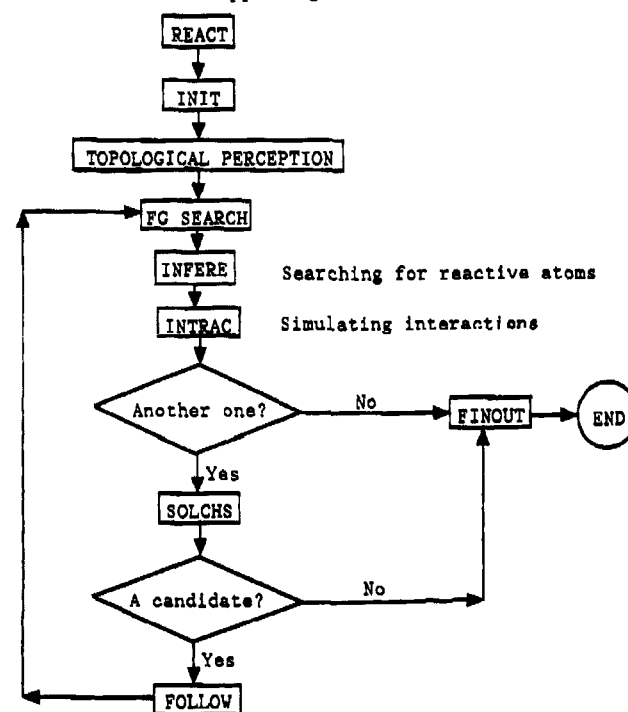
It is based on a general description of atoms and atoms in molecules that uses a set of atomic and molecular properties. A set of procedures⁶ for calculating these properties for both isolated atoms and interacting molecules gives the opportunity of modeling the changes of the studied microworld. The production of the intermediate and final structures, the evaluation of their reliability, and the discussion of the available alternatives complete Beppe's philosophy.

The integration of this program with some other procedures^{7,8} we have at our disposal is a future development toward a unitary system.

PROCEDURE DESCRIPTION

The flow of the program is roughly sketched in Scheme I. It can be divided into three main parts: (1) the location of

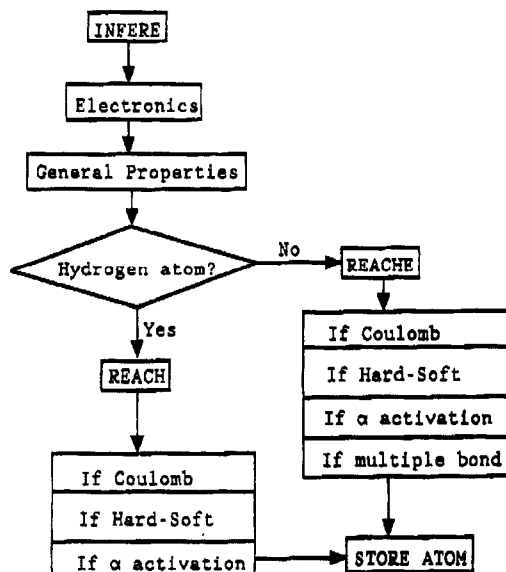
Scheme I. Flow of Beppe Program^a



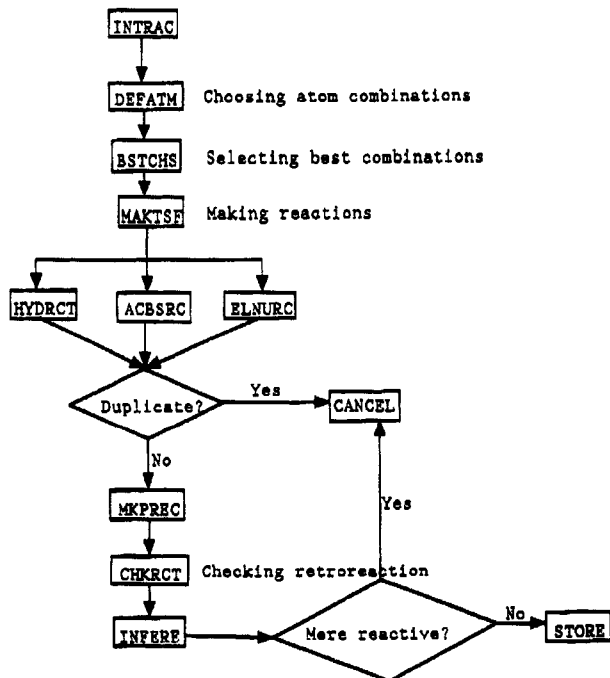
^a REACT is the main routine. INIT is the block that initializes all the needed variables. TOPOLOGICAL PERCEPTION extends the perception of the molecule. FG SEARCH identifies functionalities. INFERE and INTRAC are described in Schemes II and III. SOLCHS chooses the solutions that can be further processed. FOLLOW updates the variables using the new molecules. FINOUT is the main output routine.

the reactive sites, (2) the transformation of the starting molecules into the products, and (3) the evaluation of the results and their acceptance or rejection. A brief description of each part follows.

(1) **Reactive Atom Choice.** The logical flow of this part is sketched in Scheme II. The location of the reactive atoms is based on the calculation of some atomic and molecular descriptors that are combinations of variables calculated by previously realized routines.⁶ Hydrogen atoms are defined reactive if they are either potential protons or potential hydrides; the causes of their reactivity can depend directly on their electronics (either Coulomb-like or hard-soft activation) or on the use of the reactivity of their α atoms. Heavy atoms are defined reactive if they are either acids (bases) or nucleophiles (electrophiles); they have reactivity dependencies

Scheme II. Logical Flow of Reactive Atom Location^a

^a REACH and REACHE examine hydrogen and heavy atoms, respectively.

Scheme III. Logical Flow of Product Realization and of Their Evaluation^a

^a DEFATM chooses reactive atom pairs. BSTCHS evaluates the reactivity level. MAKTSF makes the products. HYDRCT, ACBSRC, and ELNURC explicitly analyze hydrides, acid-base, and electrophile-nucleophile interactions, respectively. MKPREC, CHKRCT, and INFERE analyze the feasibility of the examined reaction and decide its acceptance.

similar to H atoms, but the calculated descriptors must be compared with different thresholds.

All the reactive atoms are then combined in correct pairs (i.e., pairs where atoms have compatible reactivity), the pairs are ordered by their activity (the sum of the partner activities), and the analysis goes toward the second part of the program.

(2) **Making Products.** The logical flow of this and of the successive part is reported in Scheme III. This part transforms the starting molecules into the products, breaking and making bonds. During this phase some more descriptors are calculated for the intermediate structures, and these quantities are passed

to the next section. The work of the present part is straightforward, and care is taken only to avoid unwanted or duplicated results.

(3) **Checking Reactions.** The third part does the most important operations that are responsible for the effectiveness of the procedure. The evaluation of the descriptors of the products, their comparison and their acceptance or elimination, furnishes the final set of results that are then shown to the chemist for his own evaluation. It is clear that the reliability of the approach is entirely dependent on what remains at the end of the analysis.

At the present stage, the only elimination chance is related to the activation of the retroreaction. In fact, only if the reaction activity is greater than a fixed high threshold or if it is greater than half of the retroreaction activity is the solution accepted.

All the other calculated descriptors are used only for comparison purposes, permitting the suggestion of particular conditions in order to favor the wanted product, but they are not used to suggest the most probable product. A future improvement will try to save only those products that are in agreement with all the requirements chosen at the beginning of the analysis (e.g., thermodynamically controlled reaction or kinetically controlled reaction).

Algorithms. The algorithms used for the calculation of the descriptors are briefly reported in the following.

(1) Electronic Energy.

$$E = \sum_i E_i$$

$$E_i = k_3(A + B + C) - k_2 N_3$$

$$k_3 = -k_1 / (Z^{0*} R_{cov}^0)$$

where k_1 and k_2 are constants depending on the atom type; Z^{0*} is the effective nuclear charge of the isolated atom for a complete electronic shielding; R_{cov}^0 is the atomic covalent radius of the isolated atom. The sum is on all the atoms.

$$A = (N^2 + aN - 2NN_1 - 2bNN_2 + N_1^2 + 2bN_1N_2 - aN_1 + b^2N_2^2 - abN_2)N_3$$

$$B = 0.5(-2aN + 2aN_1 + 2abN_2 - a^2)N_3^2$$

$$C = (a^{2/3})N_3^3$$

where a , b , and c are Slater's coefficients; N is the atomic number; and N_i is the shell occupation number.

(2) Electrostatic Interaction Energy.

$$elstatic = \sum_i [Q_i Q_j / (R_i + R_j)]$$

where Q_i and Q_j are calculated partial atomic charges, and R_i and R_j are calculated atomic covalent radii. The sum is on all the bonded atom pairs.

(3) **Electronic Energy of Charged Intermediates.** This is the electronic energy calculated as previously shown, but using a molecular structure where the reacting bonds have already been made or broken and the reacting atoms have been positively or negatively charged.

(4) Hardness Interaction.

$$HS_{int} = \sum_i |h_i - h_j|$$

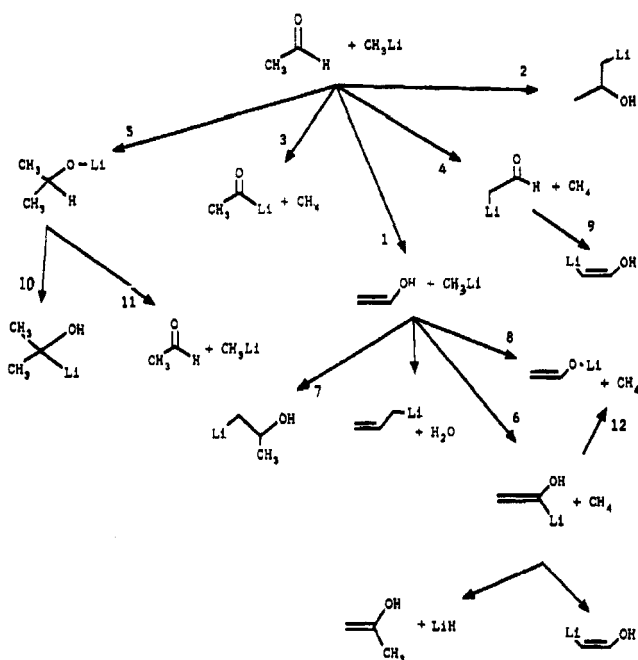
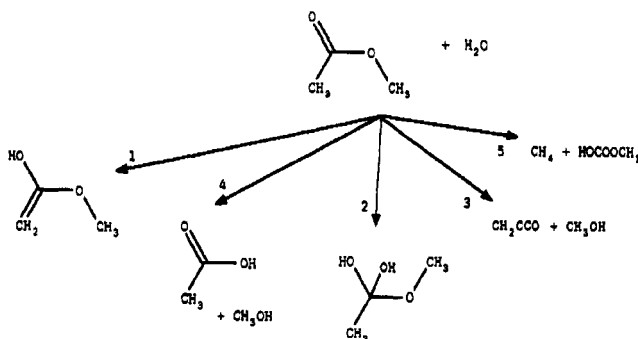
where h_i and h_j are the calculated hardness of the atoms, and the sum is on all the bonded atom pairs.

RESULTS AND DISCUSSION

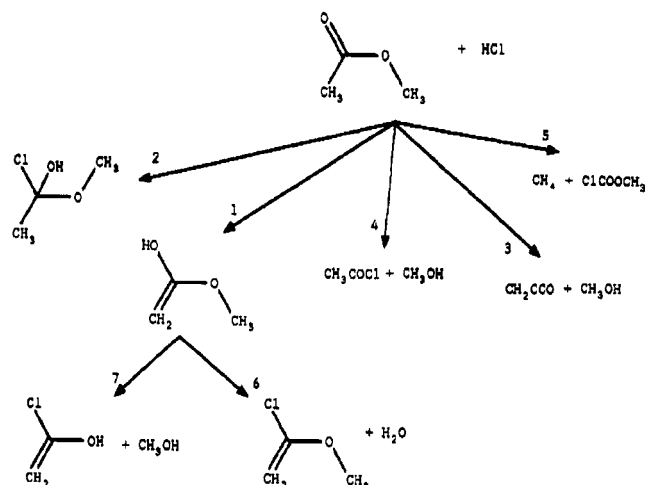
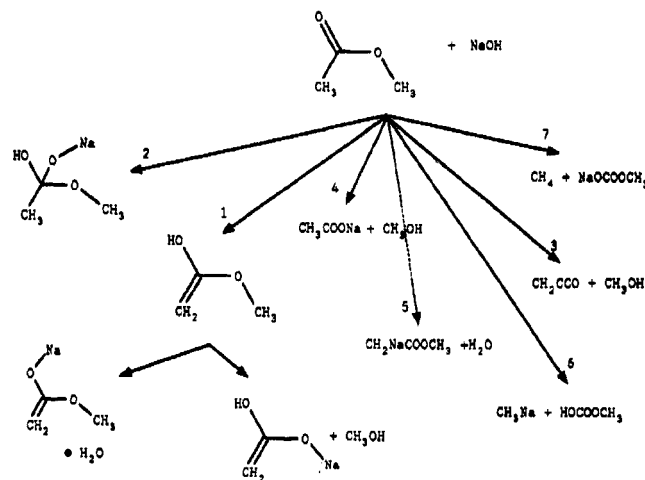
The reaction set used to preliminary test the reliability of the procedure is reported in Table I; all the molecule pairs

Table I. Complete Reaction Set Used as Test Set

$\text{CH}_3\text{CHO} + \text{CH}_3\text{Li}$	$\text{CH}_3\text{CHNH} + \text{CH}_3\text{Li}$	$\text{PhCHO} + \text{CH}_3\text{Li}$
$\text{CH}_3\text{COCH}_3 + \text{CH}_3\text{Li}$	$\text{CH}_3\text{CNHCH}_3 + \text{CH}_3\text{Li}$	$\text{PhCOCH}_3 + \text{CH}_3\text{Li}$
$\text{CH}_3\text{COOH} + \text{CH}_3\text{Li}$	$\text{CH}_3\text{CNHOH} + \text{CH}_3\text{Li}$	$\text{PhCOOH} + \text{CH}_3\text{Li}$
$\text{CH}_3\text{COOCH}_3 + \text{CH}_3\text{Li}$	$\text{CH}_3\text{CNHOCH}_3 + \text{CH}_3\text{Li}$	$\text{PhCOOCH}_3 + \text{CH}_3\text{Li}$
$\text{CH}_3\text{CONH}_2 + \text{CH}_3\text{Li}$	$\text{CH}_3\text{CNHNH}_2 + \text{CH}_3\text{Li}$	$\text{PhCONH}_2 + \text{CH}_3\text{Li}$
$\text{CH}_3\text{CHO} + \text{H}_2\text{O}$	$\text{CH}_3\text{CHO} + \text{HCl}$	$\text{CH}_3\text{CHO} + \text{NaOH}$
$\text{CH}_3\text{COCH}_3 + \text{H}_2\text{O}$	$\text{CH}_3\text{COCH}_3 + \text{HCl}$	$\text{CH}_3\text{COCH}_3 + \text{NaOH}$
$\text{CH}_3\text{COOH} + \text{H}_2\text{O}$	$\text{CH}_3\text{COOH} + \text{HCl}$	$\text{CH}_3\text{COOH} + \text{NaOH}$
$\text{CH}_3\text{COOCH}_3 + \text{H}_2\text{O}$	$\text{CH}_3\text{COOCH}_3 + \text{HCl}$	$\text{CH}_3\text{COOCH}_3 + \text{NaOH}$
$\text{CH}_3\text{CONH}_2 + \text{H}_2\text{O}$	$\text{CH}_3\text{CONH}_2 + \text{HCl}$	$\text{CH}_3\text{CONH}_2 + \text{NaOH}$
$\text{CH}_3\text{CHO} + \text{NaH}$	$\text{CH}_3\text{CHO} + \text{NH}_3$	$\text{CH}_3\text{CHO} + \text{H}_2\text{S}$
$\text{CH}_3\text{COCH}_3 + \text{NaH}$	$\text{CH}_3\text{COCH}_3 + \text{NH}_3$	$\text{CH}_3\text{COCH}_3 + \text{H}_2\text{S}$
$\text{CH}_3\text{COOH} + \text{NaH}$	$\text{CH}_3\text{COOH} + \text{NH}_3$	$\text{CH}_3\text{COOH} + \text{H}_2\text{S}$
$\text{CH}_3\text{COOCH}_3 + \text{NaH}$	$\text{CH}_3\text{COOCH}_3 + \text{NH}_3$	$\text{CH}_3\text{COOCH}_3 + \text{H}_2\text{S}$
$\text{CH}_3\text{CONH}_2 + \text{NaH}$	$\text{CH}_3\text{CONH}_2 + \text{NH}_3$	$\text{CH}_3\text{CONH}_2 + \text{H}_2\text{S}$

**Figure 1.** Product tree for the reaction $\text{CH}_3\text{CHO} + \text{CH}_3\text{Li}$. Unnumbered arrows refer to discarded solutions.**Figure 2.** Product tree for the reaction $\text{CH}_3\text{COOCH}_3 + \text{H}_2\text{O}$.

gave results comparable to those discussed in the following. The principal aim of the test set was to control the program skill in analyzing interactions between molecules either with gradually changing structures (aliphatic carbonyls, aromatic carbonyls, or nitrogen-modified carbonyls) or that use different parts of the program [using the same group of carbonyl derivatives reacting with a potential carbanion (MeLi), an amphiprotic solvent (H_2O), a strong acid (HCl), a strong base (NaOH), a hydride (NaH), a weak base (NH_3), or a soft acid (H_2S)]. Four examples have been chosen for the discussion, and the resulting reaction trees are sketched in Figures 1–4, respectively. The calculated corresponding descriptors are reported in Tables II–V. [In the tables the

**Figure 3.** Product tree for the reaction $\text{CH}_3\text{COOCH}_3 + \text{HCl}$.**Figure 4.** Product tree for the reaction $\text{CH}_3\text{COOCH}_3 + \text{NaOH}$. Unnumbered arrows refer to discarded solutions.**Table II.** Solution Summary for Reaction $\text{CH}_3\text{CHO} + \text{CH}_3\text{Li}$

sol ^a	energy ^b	elstatic ^b	transit ^b	HS _{int} ^b	activat ^b
0	97.8772	-0.5295	0.0000	0.3245	0.0000
1	94.7211	-0.6489	94.9273	0.3031	0.1561
2	95.7708	-0.8633	94.9611	0.2769	0.1932
3	<u>98.2961^c</u>	-0.0365	99.7037	0.3128	0.2178
4	<u>98.0009</u>	-0.7621	98.6152	0.3217	0.2500
5	96.3384	-1.1794 ^c	97.7452	0.1976 ^c	0.3036 ^c
6	95.0052	-0.3354	95.2149	<u>0.2836</u>	<u>0.2377</u>
7	95.7708	-0.8633	94.7150	0.2769	0.2019
8	95.4089	-1.0289	100.3723	0.2243	0.2656
9	94.9094	-0.7343	95.0405	0.2987	0.2564
10	95.8377	-0.3178	95.7679	0.2479	0.5381
11	97.8771	-0.5295	99.9570	0.3245	0.5156
12	96.2951	-0.4280	97.2294	0.2422	0.2929

^a The solution numbers correspond to the structures sketched in Figure 1. ^b All the values reported are in arbitrary units. ^c Best values are underlined.

“best values” are the highest (energy, elstatic, activat) or the lowest (HS_{int}) absolute values of each column. Transit does not have “best values” because its use is still mainly qualitative.]

The results can be discussed from two viewpoints: (1) the program behavior and (2) the chemical feasibility. In the Introduction, a doubt was raised on the necessity of a new program, and it still requires an answer. As a first remark, the level of autonomy of the program must be emphasized. Beppe can make its own decisions based on its own calculations only; no human guide is needed; no statistical treatment is used. The program simulates, as far as possible at the present

Table III. Solution Summary for Reaction $\text{CH}_3\text{COOCH}_3 + \text{H}_2\text{O}$

sol ^a	energy ^b	elstatic ^b	transit ^b	HS _{int} ^b	activat ^b
0	161.3330	-1.4848	0.0000	0.3029	0.0000
1	158.2083	-1.3877	158.4191	0.2908	0.1973
2	159.1720	-1.5990 ^c	158.3286	0.2370 ^c	0.2234 ^c
3	160.2193	-1.4352	160.1112	0.2651	0.1370
4	161.3374 ^c	-1.4341	160.0900	0.3019	0.1631
5	161.0738	-1.3870	160.8881	0.2657	0.1498

^a The solution numbers correspond to the structures sketched in Figure 2. ^b All the values reported are in arbitrary units. ^c Best values are underlined.

Table IV. Solution Summary for Reaction $\text{CH}_3\text{COOCH}_3 + \text{HCl}$

sol ^a	energy ^b	elstatic ^b	transit ^b	HS _{int} ^b	activat ^b
0	158.0609	-0.7600	0.0000	0.3740	0.0000
1	154.9442	-0.6975	155.1521	0.3635	0.1936
2	155.9283	-0.9042	155.1104	0.3122 ^c	0.3208 ^c
3	156.9491	-0.7228	156.8438	0.3364	0.1350
4	158.1346 ^c	-0.8152	156.8306	0.3890	0.2622
5	157.8690	-0.6978	157.6039	0.3530	0.2498
6	155.0065	-0.9201 ^c	154.7842	0.3729	0.2311
7	155.0126	-0.8436	154.7914	0.3714	0.2220

^a The solution number corresponds to the structures sketched in Figure 3. ^b All the values reported are in arbitrary units. ^c Best values are underlined.

Table V. Solution Summary for Reaction $\text{CH}_3\text{COOCH}_3 + \text{NaOH}$

sol ^a	energy ^b	elstatic ^b	transit ^b	HS _{int} ^b	activat ^b
0	160.7399	-2.3041	0.0000	0.4627	0.0000
1	157.6175	-2.2186	157.8271	0.4521	0.1994
2	158.7480	2.5607 ^c	159.6132	0.4008 ^c	0.8654 ^c
3	159.6227	-2.2417	159.5189	0.4250	0.1381
4	160.9450 ^c	-2.4857	159.4616	0.4735	0.2003
5	160.1886	-2.0638	160.1506	0.5347	0.7798
6	159.7864	-1.6597	157.8375	0.4990	0.7903
7	160.6655	-2.4490	160.2355	0.4363	0.1865

^a The solution number corresponds to the structures sketched in Figure 4. ^b All the values reported are in arbitrary units. ^c Best (see text) values are underlined.

stage, the behavior of a chemist that, using calculations and a standard model, suggests probable reaction products. In the case of a complete theoretical development, Beppe could furnish the best reaction tree; however, the results are subjected to approximations related both to the complexity of the solution space and to the still partial understanding of the chemical reactivity.

This is accounted for by the diversification of the analysis; five different situations can be examined; (a) a complete energetic control, i.e., the product with the lowest electronic energy is preferred (descriptor: energy, its absolute value is reported in the tables); (b) a starting material kinetic control, i.e., the atoms with the highest activation react giving the preferred product (descriptor: activat); (c) an intermediate energetic control, i.e., the atom interaction which gives the most stable charged intermediate (v.i.) is preferred (descriptor: transit); (d) a hard-soft control, i.e., the product with the lowest difference in hardness between its atoms is preferred (descriptor: HS_{int}); and (e) an electrostatic control, i.e., the product with the highest electrostatic stabilization is preferred (descriptor: elstatic; negative values mean stabilization). Moreover any kind of combinations between them is possible. This permits two different advantages: the possibility of interpreting the results and the possibility of suggesting a control of the reaction toward the desired direction. The program can already eliminate most of the unreliability (e.g.,

excluding those products likely to give a retroreaction, i.e., where activat of the reacting atoms in the product is greater than twice their activat in the starting molecules; prosecuting the examination of those products that have a tendency to furnish second level results, i.e., those products that have |transit| > |energy|; eliminating duplications). The rest of the work is the future improvement. A regulated expert system is foreseen which will offer, as a final result, all the good features of the present version plus a much more clever connection between its separated parts.

Some comments on the chemistry. Very simple examples have been chosen in order to facilitate the discussion.

Example 1. The interaction of acetaldehyde and MeLi gives five first-level products: three of them are expected [enolization (1), α -deprotonation (4), addition (5)]; one [carbonyl deprotonation (3)] is quite feasible; the last [addition of CH_2Li and a proton (2)] is unexpected. At the second level, the enol gives four products: addition of MeLi to the double bond, giving the same unexpected product (7) already discussed; deprotonation of the OH, giving the result complementary to the α -deprotonation followed by isomerization (8); the deprotonation of the carbonyl (6); and one product is hypothesized and then eliminated, the substitution of OH with CH_2Li . The addition product gives two products: a Li-H exchange (10) and a retroreaction (11). At the third level, the deprotonated enol gives three products; two of them are totally unexpected and promptly eliminated; the third is a Li-H exchange, giving the lithium enolate (12). Looking at the descriptors it is possible to observe that the activation of the starting materials drives toward the addition (activat = 0.3036, the highest of the first-level products) with subsequent Li-H exchange (activat = 0.5381, the highest of the second-level products); that the intermediate electronic energy favors both the carbonyl deprotonation (transit = 99.7037, greater than the target energy = 97.8772) and the addition followed by the retroreaction (transit = 97.7452 + 99.9570, the first one comparable with the target energy; the second one greater than the intermediate energy = 95.3384); that the product electronic energy favors the deprotonations (energy = 98.2961 for route 3 and energy = 98.0009 for route 4, but it must be emphasized that addition reactions are always disfavored in comparison with separated reagents); and that the Hard-Soft interaction suggests addition (HS_{int} = 0.1976), as does the electrostatics (elstatic = -1.1794). In conclusion, the most probable reaction is the addition, favored by three descriptors, that can compete with deprotonations and retroreactions. By comparing the differences between the energy and the transit descriptors, combined with the magnitude of activat, it can be seen that route 1 is probably a reversible reaction; that routes 2, 7, 9, and 10 are unlikely; that routes 3-5, 8, 11, and 12 have correct values; and that route 6 is on a borderline.

Examples 2-4. In order to compare the behavior of the same reagent in three different situations, methyl acetate has been treated with water, hydrochloric acid, and sodium hydroxide. The results are similar, furnishing similar reaction products. In all the cases, the addition products (route 2) are favored by all the descriptors less the electronic energy, that favors the lysis products (route 4). This is in agreement with a two-step mechanism where the first step is a tetrahedral intermediate and the final products can be obtained only by operating a movement toward the most energetically stable molecules. Wishing to extend the analysis, it is possible to observe also that the most activated reaction is the base addition [activat = 0.8654 compared with 0.2234 (H_2O) and with 0.3208 (HCl)], which is also favored by the electrostatic

interaction (elstatic = -2.5607 compared with -1.5990 (H₂O) and with -0.9042 (HCl)] and by the electronic energy of the final product [energy difference = 0.2051 compared with 0.0044 (H₂O) and with 0.0737 (HCl)]. By comparing the differences between the energy and the transit descriptors combined with the magnitude of activation, it can be seen that in examples 2 and 3 the intermediate electronic energy is always disfavored (transit always smaller than energy of the target), excluding route 1 where a reversible reaction is suggested. As an additional consequence route 4, energetically favored, is highly unlikely. In example 4, route 1 and probably route 3 can be considered a reversible reaction. Route 2 has correct values; therefore, route 4, which would be unlikely, could be reached through it. All the others can be discarded. In conclusion, the results are acceptable even if a complete discussion would require some deeper analysis to confirm the two-step mechanism.

All the reported examples are very simple, and their discussion is incomplete regarding both the real existence of some products and the reversibility of some reactions. They have been reported with the limited aim of illustrating the principal ideas that are behind the work methodology of the program.

CONCLUSION

A preliminary version of the Beppe approach to reaction product prediction has been reported, and some examples are commented on. Both the complete procedure description and a much more accurate discussion of the results will be presented as soon as the program will be usable on more complicated molecules. In fact, its main present limit is the high number of intermediate products, most of which are discarded in a successive phase, therefore, requiring too much computation time and disk storage.

ACKNOWLEDGMENT

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