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Reaction Classification by Similarity: the Influence of Steric Congestion

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Abstract: Recently we introduced a new methodology that can classify reactions using similarity measures. The classification has the following properties: is hierarchical, is property based, uses similarity. We are now considering the addition of steric demand: a fast methodology for calculating steric hindrance is presented, the obtained descriptor is used in the calculation of a steric similarity index between reactions, and it is used inside the existing classification scheme to group together either reaction with similar steric demand, or reactions with both similar electronic and steric properties.

INTRODUCTION

Reaction classification is an implicit action of chemists' brains that always bursts when chemists are considering a molecular transformation. It is so natural that often it passes unobserved, leaving the chemist mind before s/he can make a sense of it. This characteristic, combined with the reluctance of chemists to explicitly rationalize their intuitions, caused a very scarce attention in the literature for reaction classification.[1] In addition, we must consider two different ways to look at the problem: reaction classification for storage, retrieval, and naming, and reaction classification for organizing reactivity. In the first case, a great deal of the solution is represented by the determination of a convenient formalism to univocally describe structural changes and, possibly, reaction mechanisms, not as fundamental atomic transformations but as pictorial electron - bond movements. This aspect is extremely important and of great benefit to the chemists' community, because it permits the elimination of ambiguities and redundancies.[2] In the second case, on the other hand, the electronic properties of molecules are the topic. Consequently, it can happen that either reactions formally similar become member of different groups, or viceversa. Also this reaction classification mode is important, because it permits the prediction of reaction courses and/or of reaction products. Indeed, the solution of this second mode is more articulated because chemical reactivity is much more complex than its formal description.[3-8]

In a recent work we challenged the reaction classification problem introducing our approach based on similarity analysis.[9] The method considers the electronic aspect of reactions and hierarchically classifies them. The obtained classification scheme was successfully used for the comparison of organic synthesis plans.[10] During and after its development we realized that an important aspect of chemical reactivity remained unsolved:

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the role of the molecular geometry. In fact, it is well known that many reactions, electronically allowed, don't take place because of the presence of steric congestion, or, on the contrary, the final result of a reaction is unexpected for the same reason. We are worried by this issue of chemical reactivity since many years[11] and we are still searching for a sound solution. However, we can at least try to classify steric congestion in reactions.

To this end, we are going to present a simple but effective way of reaction classification by steric congestion,[12] using an appropriate descriptor and a method for its use; of course, the classification stays inside the similarity approach we already reported, in order to get a consistent complete system.

Steric congestion in two dimensions

Molecular geometry is typically a three dimensional issue; it depends on the relative disposition of the atoms in space. Consequently, it has been often confined inside the complex and hard field of conformational / configurational aspects. However, many purely two-dimensional approximations have been introduced in order both to reduce the computational effort and to provide an alternative methodology for studying geometrical properties.[13-16] Even molecular shape has been represented by two-dimensional descriptors.[17]

The selection of a two-dimensional descriptor in the present case is justified by two principal purposes: first, the customary aim at leaving the conformational problem far from our study; secondly, the appeal of the different message that the dimensional reduction bears. It is clear that ignoring the third dimension we introduce an important simplification, but the idea of getting the fundamental data in a less resolved space is also stimulating.

In our preceding work in the field of synthesis planning we have already used an approximated steric descriptor to order the bond breaking sequences.[18] The descriptor is calculated from the molecular topology using a method for classifying the atom steric congestion. Atoms are assigned to steric classes by their substitution level and by the substitution of their first shell neighbours. G is a step function calculated by equation 1

$$G(i) = f(\alpha, \beta_M, \beta_T) \qquad G = \text{congestion class} \qquad (1)$$

where α is the number of atoms directly connected to atom (i), β_M is the highest number of atoms connected to a single atom in the alpha sphere, and β_T is the sum of the atoms connected to the alpha sphere. Eight different classes are defined (as exemplified in Figure 1) and a numerical value is assigned to each of them.

These values consider the steric congestion of an atom as a separate entity, but, for our purpose, this is not sufficient. We thus introduced a steric congestion calculated using the congestion of the atom and of its neighbours. This is simply obtained summing their G values (equation 2). The calculation could have been extended over further atomic sphere, but we think that the significance of the calculation wouldn't have improved.

$$Gf = \sum_k G(i)_k \qquad (2)$$

Reaction steric congestion

Equation 2 gives the extended atomic steric congestion for any atom in a molecule; but we would like to

2) Reactant steric demand; it concerns the steric congestion present on reactants. A reaction is influenced by this congestion and can even give different results. This is the classical understanding of steric congestion by chemists; i.e. the more a reacting atom is congested, the more difficult is its transformation.

3) Product steric demand; it concerns the steric congestion present on products. In a kinetically controlled reaction, as is the favourite of chemists, this congestion is unimportant. However, its role is crucial just in the balance between kinetical and thermodynamical control. Therefore, its analysis could be interesting.

The three classification modes can be used: separately, thus classifying reactions under a precise aspect; hierarchically, permitting the subclassification of reactions; in connection with the electronic classification, grouping reactions that are both geometrically and electronically similar.

RESULTS AND DISCUSSION

The discussion of the method performance will be presented with the aid of some examples. The example selection has been operated so as to cover the majority of organic reactions and, at the same time, many different steric instances. The results are reported in the following Tables that are divided by reaction class and substructure types.

The reactions covered are: eliminations (Table 1); substitutions (Tables 2, 3, and 4); additions (Table 5); cycloadditions (Table 6); enolizations (Table 7). From the viewpoint of the variation of congestion during the reaction we have: reactions which don't show a great congestion change (substitutions); reactions which show a congestion decrease (eliminations); reactions which show a congestion increase (additions and cycloadditions); reactions which show either a congestion increase or a congestion decrease (enolizations); thus, all the possibilities are covered. The discussion initially presents each reaction class and then we will try a more comprehensive comparisons.

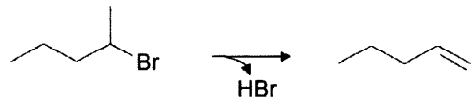
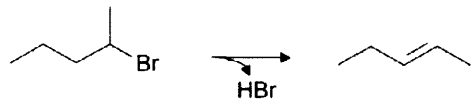
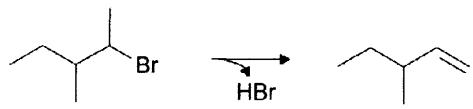
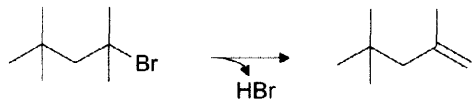
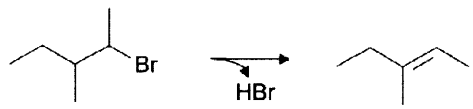
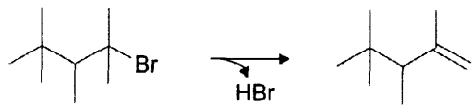
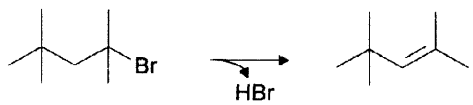
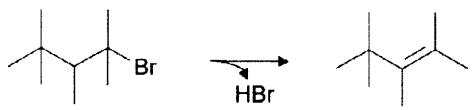
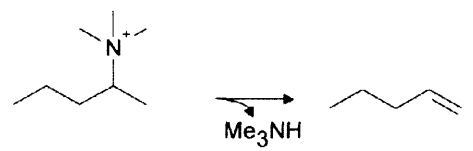
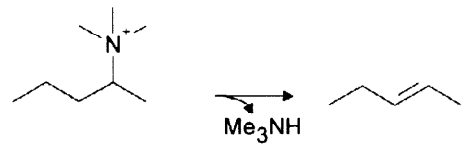
Eliminations

The elimination of acid bromide from alkyl bromide has been chosen as the prototype of this class. As expected, all the reactions show a decrease in steric congestion. Here we report some examples with different steric demand. The result is very clear and all the reactions are inserted in the expected group. More interesting is to look at potential isomeric products. Reaction pairs are: E1-E2, E3-E5, E4-E7, E6-E8, E9-E10. All of them give an identical indication: elimination toward more substituted double bonds have a greater decrease in steric congestion; however, the measure of the decrease depends on the structure. There are cases where more congested reagents differ less with respect to the formed isomers than less congested reagents (e.g. E3-E5 and E4-E7). It is interesting to note that a compound that typically gives a Hofmann elimination (E9-E10) shows a greater difference between potential isomeric products than its Saytzev counterpart (E1-E2). This predicts a diverse classification of the two transformations, as expected. But these data haven't any special relapse on the isomer amount experimentally found that is determined by several concurrent causes: reaction conditions and the consequent reaction mechanism, steric congestion of the reagent, type of reaction control. Looking at the RRG and PRG values a principal aspect must be noted: the congestion value depends on the reaction also for the reagent / product analyses. In fact, because steric congestion is measured only for the reacting atoms and

because they are selected by the pair reagent / product, the congestion is not that of a single atom and, therefore, the accessibility to an atomic center is not directly correlated to the present calculation.

We can in all affirm that the result concerning this reaction group is well adequate, most of the time in line with expectations.

Table 1. Elimination reactions

ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
E1		3.75	2.63	-1.12
E2		4.46	3.24	-1.22
E3		4.16	2.89	-1.27
E4		4.73	3.05	-1.68
E5		5.55	3.71	-1.84
E6		5.64	3.36	-2.28
E7		10.34	6.39	-3.95
E8		11.41	6.86	-4.55
E9		7.62	3.30	-4.32
E10		10.70	4.81	-5.89

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

Substitutions

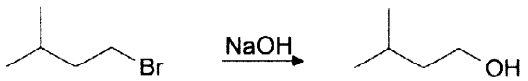
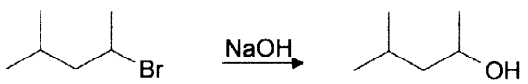
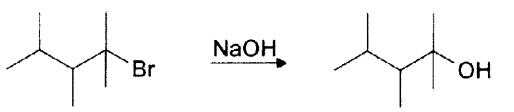
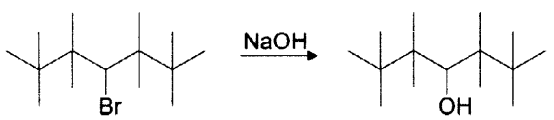
The substitutions are shown in three Tables because they cover three different prototypical cases: the exchange of two fundamentally similar groups on chains (Table 2) and on rings (Table 3), and the exchange of

a small group with a bigger one (Table 4) on rings. In the first two cases the variation of steric congestion is relatively small (0.0 - 0.38), whilst in the third the course is clearly more articulated.

It is interesting to note the difference between the values of Tables 2 and 3. Because the calculation is differently made on ring structures the values are constantly greater in Table 3; but the differences are very similar. On the contrary, if the substitution is performed using a more demanding group the values are more affected (Table 4).

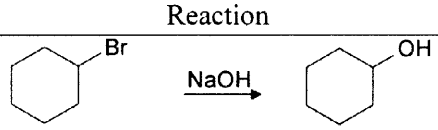
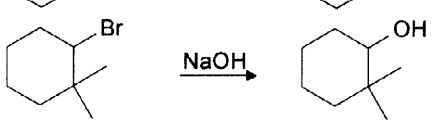
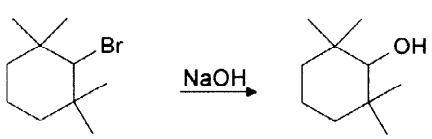
We must also point to a drawback of the two-dimension procedure; in fact, the congestion on rings is not influenced by their conformations / configurations. For example, the introduction of a new substituent in alpha position has always a bigger effect than in the beta position. The weight of this factor can be however considered introducing one of the existing descriptors.[19]

Table 2. Substitution reactions

ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
S1		1.35	1.35	0.0
S2		1.82	1.89	0.07
S3		2.88	3.26	0.38
S4		5.60	5.67	0.07

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

Table 3. Substitution reactions

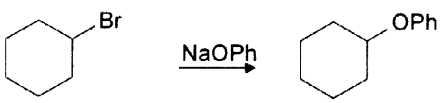
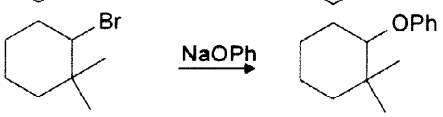
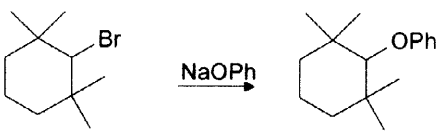
ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
CS1		2.06	2.26	0.20
CS2		3.07	3.27	0.20
CS3		4.85	5.05	0.20

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

This class permits to evince that the influence of steric considerations clearly separate reactions that would have been grouped together using only electronic considerations.

It is also possible to compare substitution reactions to elimination reactions. The steric influence on these two types of transformations is clearly different because eliminations decrease steric demand whereas substitutions don't show great changes. However, the difference is much greater for those compounds that are more crowded (compare S2 to E3 and S3 to E8) according to a higher probability for the elimination to compete with the substitution. It is worth noting that the reaction classification only assigns the reaction to different classes without predicting a particular product; the application that uses the classes should take care of the calculated differences.

Table 4. Substitution reactions

ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
OC1		2.64	3.17	0.53
OC2		3.28	4.29	1.01
OC3		4.41	5.77	1.36

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

Additions

Two classes of additions have been selected as prototypes: the 1,2-addition of MeLi on carbonyl compounds and the 1,4-addition of MeLi on α,β unsaturated carbonyl compounds. The analysis has been carried on without separately considering the two classes.

In addition reactions the steric congestion obviously increases, but, in parallel with eliminations, the perturbation is strongly related to the situation of the reagent / product.

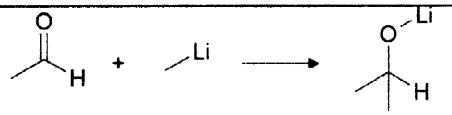
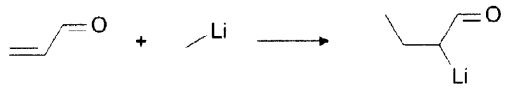
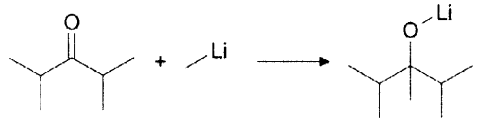
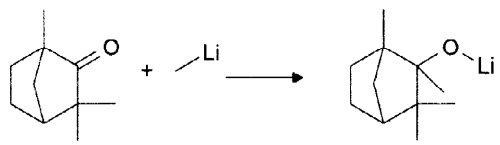
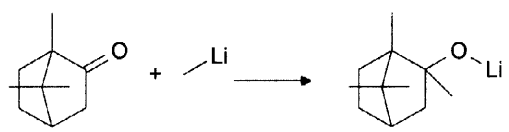
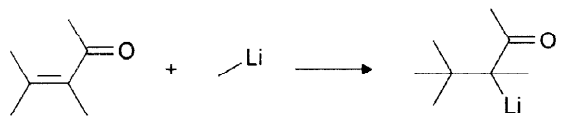
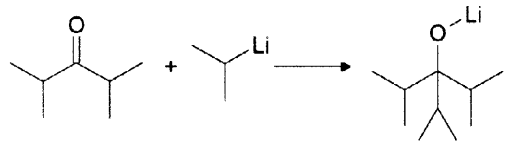
Only few principal points. First, apparently the 1,4-additions requires greater steric availability, as showed by their positions in the lists. Second, comparing reactions A2 and A5, we can also note that the steric demand of both reagent partners is important. Finally, two highly congested ketones, A3 and A4, that score high in reagent classification, don't show a great change of their congestion after addition of MeLi in agreement with expectations.

The whole classification is, in any case, interesting, showing good responses, sensitive to the steric congestion differences.

Cycloadditions

Cycloadditions are in a reaction class that definitely changes structural steric demand; in addition, the cyclicity of the molecule is also changed. Therefore, they represent a good test of our classification scheme. In order to test this particular situation we analyzed some prototype reactions: additions to substituted 1,3-dienes and to cyclopentadienes.

Table 5. Addition reactions

ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
A1		1.26	2.92	1.66
MA1		2.76	4.71	1.95
A2		1.90	6.95	5.05
A3		4.83	9.98	5.05
A4		4.03	9.56	5.53
MA2		3.86	10.27	6.41
A5		2.60	9.96	7.36

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

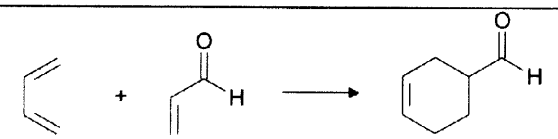
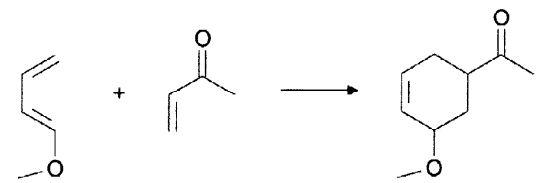
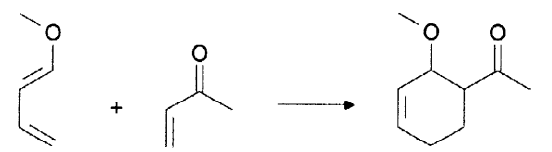
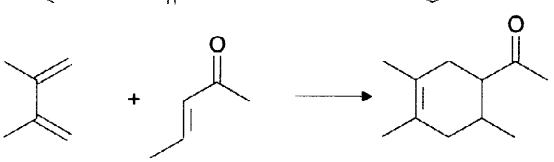
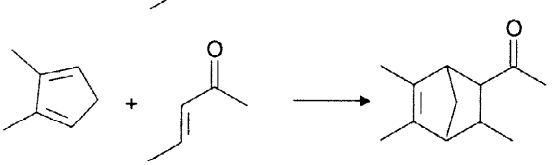
The TRGs score quite high showing good sensitivity to the steric congestion changes. Looking at reactions DA4 and DA5 it is possible to note that the different level of cyclicity puts the two reactions into two different groups. Concerning the regioselectivity in Diels-Alder reactions it is well known that it is mainly managed by electronic effects; therefore the influence of steric congestion is absolutely of secondary importance. Nevertheless, looking at reactions DA2 and DA3 we can note that the two possible regioisomers ("orto" and "meta") show different steric requests with DA2 increasing less the geometric congestion. This result is in contrast with the experimental finding, demonstrating once more that cycloadditions are not governed by steric congestion.

Enolizations

The last class of reactions that we used are enolizations. These are reactions that essentially move one or more atoms from one location to another in the molecule, i.e. they are isomerizations; consequently, the steric demand differences are sufficiently small and can be either positive or negative. In the set there are two kinds of reactions: real isomerizations (subset CEx) and acid-base enolizations (subset BEx). Most of the CEs are decreasing the steric congestion, as expected of a passage from an sp_3 C to an sp_2 C. On the contrary, acid-base

reactions are mostly increasing the steric congestion. The enolization case is particularly interesting because it allows to test the possibility of combining the calculated indexes to indirectly obtain the indexes of new transformations. For example, we can look at the reaction cycle reported in Figure 2; it represent the interactions that can take place when mixing an enolate and an aldehyde. Starting from the upper-left corner the

Table 6. Cycloaddition reactions

ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
DA1		1.86	2.94	1.08
DA2		2.10	3.40	1.30
DA3		2.10	3.78	1.68
DA4		2.27	4.57	2.30
DA5		2.86	6.71	3.85

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

C-enolate of isobutyraldehyde and acetaldehyde can give, going down, the O-enolate of isobutyraldehyde and acetaldehyde, or, going right, isobutyraldehyde and the C-enolate of acetaldehyde. The lower-left pair can then give isobutyradehyde and the O-enolate of acetaldehyde; the same result can be reached from the upper-right

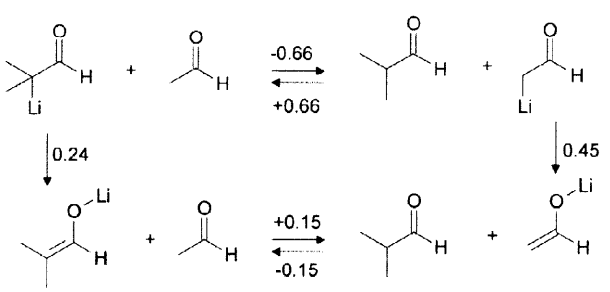
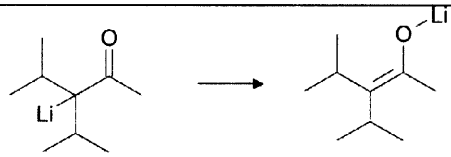
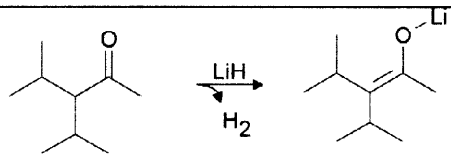
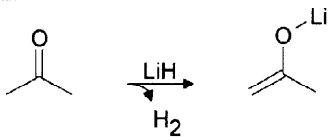
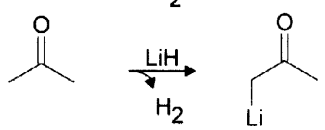


Fig. 2. Classification of reactions by TRG. Interactions between isobutyraldehyde and acetaldehyde: C-enolates, O-enolates, and starting reagents.

pair, thus closing the cycle. The corresponding TRGs are, clockwise from upper-left, -0.66, 0.45, -0.15, –0.24; their sum is equal to 0.6 that is very near to the calculated value of 0.66. However, other combinations give different values demonstrating that steric demand strictly depends on the order of reaction application.

Table 7. Enolization reactions

ID.[a]	Reaction	RRG[b]	PRG[c]	TRG[d]
CE1		5.88	3.23	-2.65
BE1		2.94	2.59	-0.36
CE2		1.92	2.08	0.16
BE2		1.25	1.67	0.41
BE3		1.51	2.23	0.72

[a]Reaction identification number. [b]Reagent steric congestion. [c]Product steric congestion.
[d]Difference of columns RRG and PRG.

Cross comparisons

As a final part of the discussion of our method we are interested in presenting some comparisons across reaction classes.

The first example concerns the comparison between different substitution reactions. In Figure 3 the course of the three indexes of the same substitution on cyclic and acyclic structures is shown. In the upper part two very similar transformations are compared by TRG; it is possible to note that they score differently. The middle and the lower parts show the different level of substituent complexity that are required to get similar values of RRG and PRG. In Figure 4 the comparison between different cyclic substitutions is reported. In the upper part it is shown how different is, by TRG, the response of the index for similar reactions with dissimilar reagents. In the rest of the Figure it is explained, in terms of RRG and PRG, the reason of this result. It is clear that the reagents do not affect the course of the reaction, but the products do. In fact, to have two similar PRGs the less demanding class must be burdened by heavy substituents.

The second example concerns the comparison of substitutions and additions. In Figure 5 the comparisons by TRG, RRG, and PRG, are shown. The TRGs of the additions are expectedly greater because the perturbation

introduced in terms of steric congestion is greater. In fact, looking at the RRGs we note that the two classes behave similarly, whilst the PRGs indicate that the products are managing the difference.

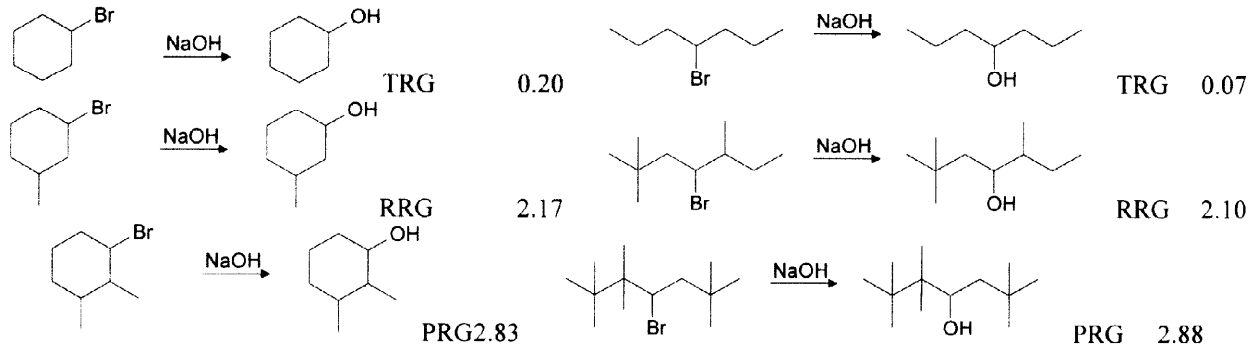


Fig. 3. Classification of reactions. Comparisons of acyclic and cyclic substitutions by TRG, RRG, and PRG.

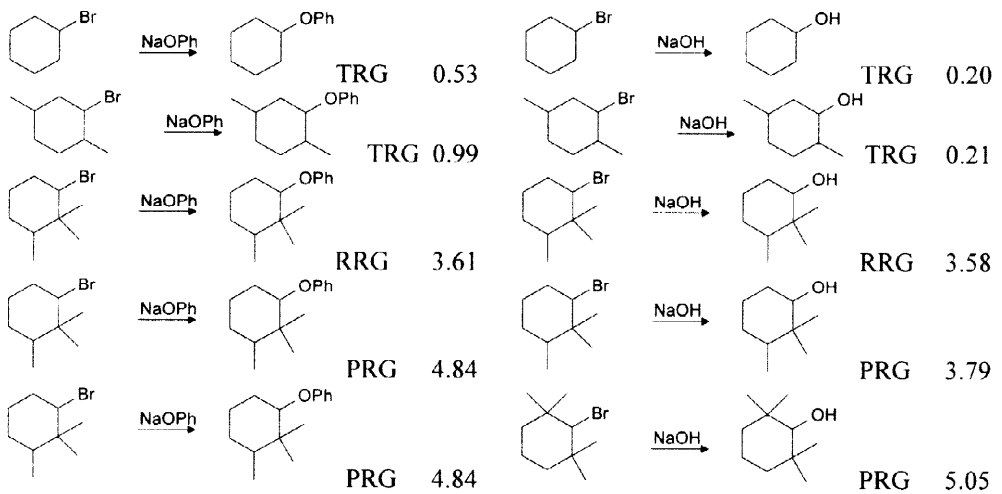


Fig. 4. Classification of reactions. Comparisons by TRG, RRG, and PRG of cyclic substitutions with different steric demand.

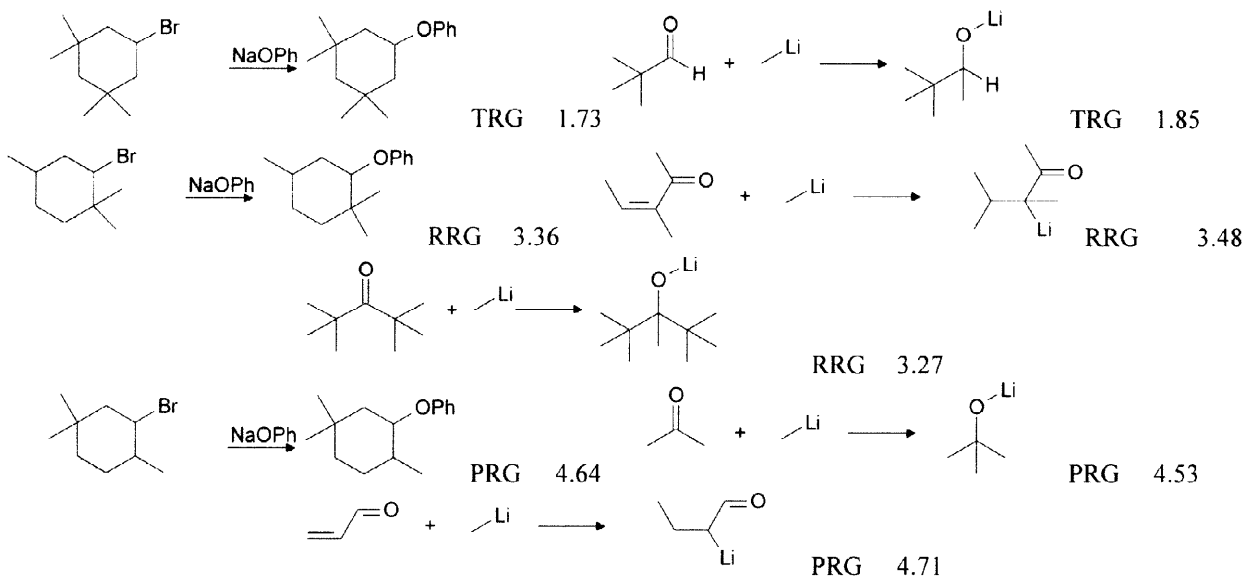


Fig. 5. Classification of reactions. Comparisons of additions and cyclic substitutions by TRG, RRG, and PRG.

The third example, sketched in Figure 6, concerns additions and cycloadditions. In this case, the TRGs indicate a similar course for the two classes, in agreement with the similar change introduced. In this case the responsible is the similar weight that reagents and products have in the two classes, as clearly shown in the Figure. However, we must remember that the cycloadditions affect more reacting centers than additions do.

The fourth example, sketched in Figure 7, compares by TRG an addition and an enolization. The greater change introduced by the last one is apparent looking at the very different complexity of the corresponding reacting atoms.

Finally, we would like to comment on the possibility offered by our procedure to compare different reactions. Taking a particular reaction as reference (see Figure 8, first, third, and fifth, lines) we can classify other reactions. In the shown cases, all the reactions are correlated with the reference, but this is absolutely not a requirement. It is worth noting that none of the other reactions can be classified together with the reference by TRG or PRG, and only the first one can be grouped by RRG, despite the similarity of the interested compounds.

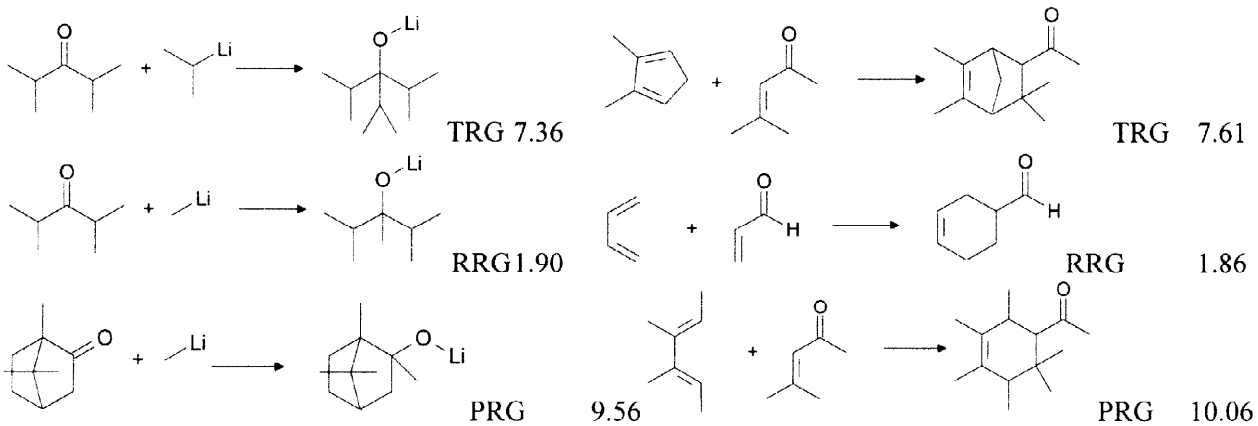


Fig. 6. Classification of reactions. Comparisons of additions and cycloadditions by TRG, RRG, and PRG.

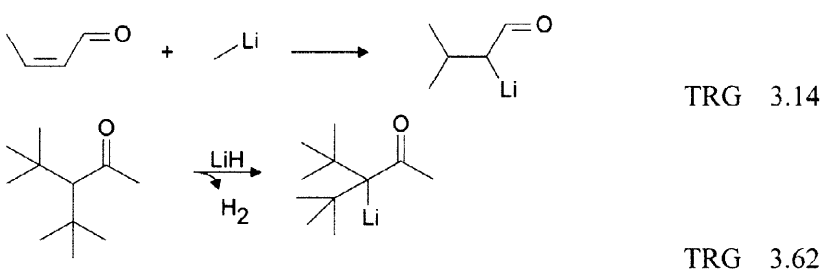


Fig. 7. Classification of reactions. Comparisons of additions and enolizations by TRG.

Van der Waals

For the sake of discussion we also analyzed few examples using the VdW strain energy calculated by MM2.[20] In Table 9 we show the results. It is immediately clear that the two methods are not alternative. In fact, our procedure only considers reacting center congestion to the aim of classification, whilst MM2 calculate the complete energy of the molecule to the fundamental aim of conformational search. Thus, we cannot expect correlated results. However, very qualitatively, the results show the same sense; i.e. strain energy

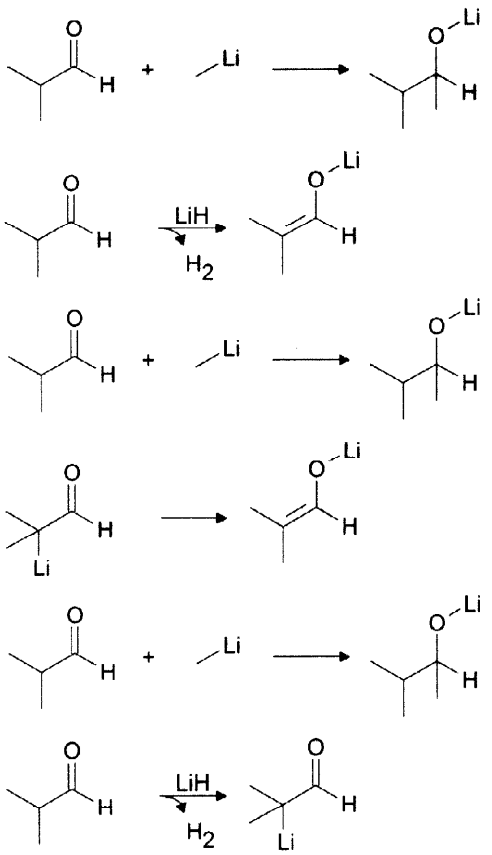


Fig. 8. Classification of reactions. Comparisons of different reactions by TRG, RRG, and PRG, using isobutyraldehyde as reference.

Table 9. Comparison of steric congestion and Van der Waals steric energy

Compound	Congestion[a]	Diff. (n+1-n)[b]	EVdW[c]	Diff. (n+1-n)[d]
CH_3COCH_3	1.01		4.08	
CH_2=C(OH)CH_3	1.46	0.45	4.72	0.64
$(iPr)_2CHCHO$	1.65		14.87	
$(iPr)_2$C=C(OH)H	1.89	0.24	10.13	-3.74
$(iPr)_2CHCOCH_3$	2.94		217.91	
$(iPr)_2$C=C(OH)CH_3	2.59	-0.35	103.94	-113.97
$(tBu)_2CHCOCH_3$	4.87		984.60	
$(tBu)_2$C=C(OH)CH_3	4.76	-0.11	664.94	-319.66
Et$CH(CH_3)C(CH_3)_2Br$	5.54 (7.63)		115.44	
Et$CH(CH_3)C(CH_3)$=CH_2	3.26	-2.28	41.86	-73.58
Et$C(CH_3)$=$C(CH_3)_2$	4.28	-3.36	72.70	-42.74

[a]Steric congestion of reaction center. [b]Difference of steric congestions between odd and even lines. [c]Strain energies calculated by MM2. [d]Difference of strain energies between odd and even lines.

decreases when reacting center congestion decreases. There is only one case that shows a divergent course, the comparison between isobutyraldehyde with its enol form.

CONCLUSION

We have presented a method for classifying reaction by their steric congestion. This represent an addition to our previous system for reaction classification, adding a hierarchical step. The influence of steric demand variations and the definition of steric congestion on both reactants and products represents an important element in the course of many reactions and it can become the fundamental cause of the reaction outcome. Consequently the availability of a methodology that explicitly consider this aspect adds great power to the standard reaction classification.

The complete system, thus realized, is property based and thus independent of the a priori definition of reaction classes. We would like to imagine that it can permit a new and diverse mode to look at reaction classification.

Acknowledgement

Partial financial support by the Consiglio Nazionale delle Ricerche, and by the Ministero dell'Universita' e della Ricerca Scientifica e Tecnologica, is gratefully acknowledged.

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