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Perturbation Theory Modeling of Intramolecular Carbolithiation Reactions

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Abstract: PT-QSRR models are Quantitative Structure-Reactivity Relationship (QSRR) models based on Perturbation Theory (PT) that may be useful for multi-objective optimization in organic synthesis. In this communication, we summarize some of the more important results and conclusions obtained in our previous research / review paper about PT-QSRR models published in *Curr. Top. Med. Chem.,* **2013**, *13*, (5), 1713-1741. I this previous work, firstly we reviewed general aspects and applications of both perturbation theory and QSPR models. Secondly, we formulate a general-purpose perturbation theory for multiple-boundary QSPR problems. In this previous work, we developed a new QSPR-Perturbation theory model that classify correctly >100,000 pairs of intra-molecular carbolithiations with 75-95% of Accuracy (Ac), Sensitivity (Sn), and Specificity (Sp). The model predicts probabilities of variations in the yield and enantiomeric excess of reactions due to at least one perturbation in boundary conditions (solvent, temperature, temperature of addition, or time of reaction). The model also account for changes in chemical structure (connectivity structure and/or chirality patterns in substrate, product, electrophile agent, organolithium, and ligand of the asymmetric catalyst).

Keywords: Organometallic addition; Carbolithiation reactions; Asymmetric synthesis; Perturbation theory, QSRR models

1. Introduction

In the wider sense Perturbation Theory (PT) methods starts with a known exact solution of a problem and continue adding "small" terms to the mathematical description in order to approach a solution to a related problem without known exact solution. On the other hand, solving Quantitative Structure-Property Relationships (QSPR) problems may be important to study the chemical reactivity of compounds in organic synthesis. QSRR techniques involve: (1) numerical codification of molecular structure, and stage (2) search of a quantitative connection between the structure and reactivity. QM and/or Graph theory are computational techniques typical of stage (1); while Statistical and/or Machine Learning (ML) techniques are commonly used in stage (2). In this work, we give one example of the new theory to predict enantiomeric excess and yield in a set of intramolecular carbolithiation reactions.

PT-QSRR of intra-molecular carbolithiations

A particular class of reaction of high interest in organic synthesis is the so-called carbolithiation. The carbolithiation reaction offers an attractive pathway for the efficient construction of new carbon-carbon bonds by addition of an organolithium reagent to non-activated alkenes or alkynes, with the possibility of introducing further functionalization on the molecule by trapping the reactive organolithium intermediates with electrophiles. The intramolecular variant of this reaction has been applied mainly with alkyl- and alkenyllithiums, though there are also some examples of cycloisomerization of alkenyl substituted aryllithiums, generated by metal-halogen exchange. In particular, this type of intramolecular carbolithiation reaction has found application in the synthesis of both carbocycles and heterocycles, with a high degree of regio- and stereoselectivity in the formation of five-membered rings, although its application to larger rings is still not general. When alkenes are used, up to two contiguous stereogenic centers may be generated, which may be controlled by using chiral ligands for lithium, and so opening new opportunities for application of this methodology to asymmetric synthesis. Bailey and Groth reported independently the intramolecular carbolithiation of *N*-allyl substituted *o*-haloanilines in the enantioselective synthesis of indolines, Barluenga described the preparation of dihydrobenzofurans in high *ee*, starting from allyl *o*-haloaryl ethers. Lete *et. al.* previously reported the preparation of 4-substituted 2-phenyltetrahydroquinolines from *N*-alkenylsubstituted 2-iodoanilines via intramolecular carbolithiation reactions. We developed a QSPR model for a very large set of input-output perturbations in the enantioselective intramolecular carbolithiation reactions via aryllithiums generated by halogen-lithium exchange (*see* **Figure 1**).

We propose herein, for the first time, a PT-QSRR model able to predict both the change in yield and enantiomeric excess for two pair of reactions after at least one change in chemical structure and/or perturbation of reaction variables of at least one of the molecules involved. After optimization of coefficients the best model found with LDA was:

$$\begin{aligned}\varepsilon_s(\mathrm{p_i}) = &-0.00105976 \cdot \mathrm{V}(\mathrm{product_i})_{\mathrm{icr}} \qquad (1)\\ &+ 0.13496123 \cdot \Delta\mathrm{V}(\mathrm{susbstrate_i})\\ &- 0.00000065 \cdot \Delta\mathrm{V}(\mathrm{solvent_i})\\ &+ 0.08477068 \cdot \Delta\mathrm{V}(\mathrm{electrophile_i})\\ &- 0.00029331 \cdot \Delta\mathrm{V}(\mathrm{ligand_i})\\ &- 0.00029331 \cdot \Delta\mathrm{V}(\mathrm{org.lithium_i})\\ &+ 0.01087415\end{aligned}$$

Here, $\varepsilon_s(p_i)_{rr}$ is called efficiency of reference and may be either the yield of this reaction $\varepsilon_s(p_i)_{rr} = yld(p_i)_{rr}$ or the enantiomeric excess of the same reaction $\varepsilon_0(p_i)_{rr} = ee(p_i)_{rr}$. The variables in the right side of the equation quantify multiple structural and physicochemical factors driven the yield and stereoselectivity of the reaction (see details on the original work). We consider the following six roles or types of molecules substrates, solvents, ligands of chiral catalysts, organolithium reactants, electrophiles, and products. As a results, we can calculate the effect of different perturbations $\Delta V(m_{qi})$ on the previous over reactivity for a given set of initial and final conditions (reaction of reference and query reaction). This is a very strong result because it determines that this is probably the first multi-objective optimization (MOOP) model for the effect of structural or condition perturbations in reactions.

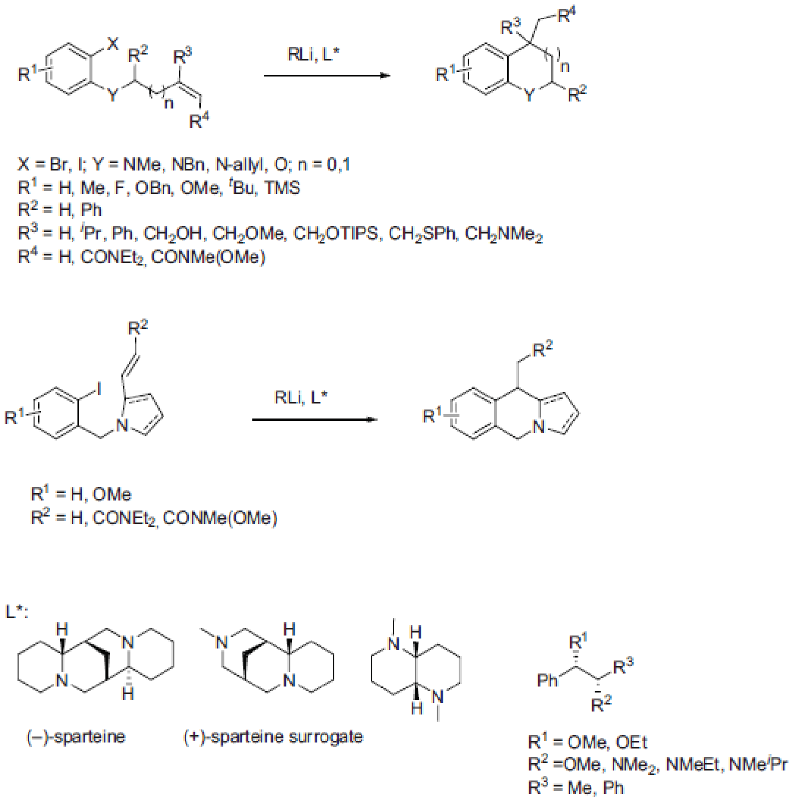

Figure 1. General scheme for intramolecular carbolithiations studied here.

4. Conclusions

It is possible to develop general models to predict the results of multiple input-output perturbations using ideas of QSPR analysis and perturbation theory. The new QSPR-Perturbation models may be used to study complex molecular systems. One the properties we can study are the yield and enantiomeric excess of reactions. These models may include perturbations in a very high number of input-output variables like (time, temperature, solvent, catalyst, assay, pharmacological experimental measures, molecular and cellular targets, and many others). The electronegativity values calculated with MARCH-INSIDE seems to be good molecular descriptors for QSPR-Perturbation theory.

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Conflicts of Interest

The authors declare no conflict of interest.

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