Computational analysis of the radical addition to isonitriles and study of the stereoelectronic interactions in the stereochemically non-rigid compounds

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Annotation

The relevance of the work.

Computational analysis and modeling of intermolecular interactions in organic reactions play a critical role in various fields of modern chemistry. Understanding the mechanisms of chemical reactions has been an important and active area of computational organic chemistry. Close collaborations between experimentalists and theorists represent a growing trend. Recent decades have witnessed the increasing connection between computational and experimental chemistry to solve many organic problems. In addition, it allows one to trace trends in changes in the reactivity of compounds in relation to their structure. To achieve this connection, a series of compounds of various structures are studied to identify general structure-reactivity patterns. This knowledge is commonly implemented as a solution of many problems of a fundamental and applied nature.

Identifying the reasons for the donor–acceptor dichotomy of many functional groups. If one needs to change a donor into an acceptor represents a major challenge in this analysis. A chemical transformation is usually required—from something as simple and potentially reversible as protonation, or coordination with a Lewis acid etc. to chemical transformations, that is, reductions and oxidations. The utility of this thinking is illustrated by such concepts as in "umpolung," which switchs the reactant polarity for the design of new synthetic transformations. However, subtler and interesting situations exist in which the donor/acceptor properties of substituents and, hence, chemical reactivity, is controlled by using groups that can be either donors or acceptors depending on their orientation in space with respect to the rest of a molecule. To describe such examples, Dr. Igor Alabugin introduced the concept of stereoelectronic chameleons. A typical example of chameleonic behavior is obvious in the conformation of the p-OMe substituted benzylic anion in which the usual planar conformation of non-crowded alkoxyaromatics is changed to the perpendicular orientation. The conformational change "inverts" the electronic character of the OMe group, converting it from a p-donor to a hyperconjugative s-acceptor.

Understanding these properties is impossible without a correct theoretical description of the processes taking place. An effective way to solve such problems is to analyze the stereoelectronic factors account for the apparent reversal of donor–acceptor properties of a variety of functional groups by a simple change of their orientation in space. Study of these conformational and translocational “stereoelectronic chameleons” with the focus on the situations in which the stereoelectronic “umpolung” unlocks useful ways of thinking about chemical reactivity and opens new doors for reaction design.

Scientific novelty and practical significance

Based on the detailed analysis of stereoelectronic intra- and intermolecular interactions for several classes of organic compounds, it was possible to draw conclusions about their influence on the structure of the molecules and their reactivity. Examples of new stereoelectronic chameleons were identified and described.

The crucial role of several weak, coexisting, multidirectional electronic interactions on the course of the reaction of isonitriles with radicals was demonstrated. The stereoelectronic analysis revealed that interesting hidden differences between isonitriles and alkynes in their radical addition transition states. The ability of the isonitrile group to act as both a donor and an acceptor of electron density and easily react with both electrophilic and nucleophilic radicals was explained.

It was observed that the polarity of the X_3CO- (X = H, F) group essentially depends not only on the nature of X, but also on the conformation of the X_3CO-Ar fragment. Examples of the properties of "stereoelectronic chameleons" for amide groups, enamines, carbenes, fluorine atoms have been found. Methods for changing the fundamental property of amides - planarity caused by conjugation of a lone pair of a nitrogen atom with a carbonyl group - are systematized in order to give these functional groups an unusual reactivity.

It has been demonstrated that the framework of the concept of "stereoelectronic chameleons” allows to describe, explain and, in some cases, predict the stability and reactivity of a wide range of common organic functionalities. New reactivity patterns that arise from spatial anisotropy that can be modulated by conformational flexibility were described.

The main goals of the present work were to study the mechanism of radical addition to isonitriles; analyze the effects of stereoelectronic effects on stability, reactivity and intermolecular bonding of conformationally non-rigid compounds containing such fragments as methoxy group, halogens, amide and aminoalkenyl substituents. In order to achieve these goals, **the following tasks** are set and solved in the dissertation work:

- Scientific justification of the differences in the mechanisms and products of the radical addition reactions to isonitriles compared to alkenes and alkynes;
- Stereoelectronic analysis of the reaction of radical addition to isonitriles; study of the influence of the nature of the radical on the reaction rate;
- Assessment of the influence of stereoelectronic effects on the structure and reactivity of a number of model systems containing groups with different in magnitude and/or opposite in sign inductive and conjugation effects (F, AlkO, $CONR_2$, CH = NR and others).

The main provisions for the defense:

- Stereoelectronic explanation of significant differences in the reactions of addition of radicals to alkynes in comparison with isonitriles;
- Stereoelectronic analysis of the radical addition reaction to arylisonitriles demonstrates the role of weak intermolecular interactions in determining the reagent approach trajectory and reaction rate;
- The importance of using the concept of stereoelectronic effects when describing the structure and properties of functional groups and organic compounds, such as amides, carbenes, methoxy group, halogen atoms;
- Expanding the applicability of the concept of "stereoelectronic chameleon", which is defined as an atom or functional group exhibiting electronic effects that depend on the relative spatial arrangement of two different molecules or two fragments within one molecule;
- Detailed description of a wide range of functional groups that can exhibit the properties of "stereoelectronic chameleons".