POLARITY RULES IN COMPUTER DESIGN OF HETEROCYCLES

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Abstract

Qualitative polarity rules for heterocyclic ring synthesis via polar reactions of cyclization or recyclization are discussed. The main idea is the application of general definition of consonant and dissonant structures to acyclic chains and cyclic heteroaromatics and analysis of interconversion of this two combinatorial properties. Appearance of dissonant structure from consonant one seems to be forbidden process. Brief review of recent author's works show prospects of application this rules to computer assisted heterocyclic synthesis.

One actual problem of computers assisted organic synthesis is prediction of optimal routes for the synthesis of the given heterocyclic target. Usual principles of heterocyclic synthesis include two general methods of the target structure formation: 1) by cyclizations of acyclic precursors, 2) by ring transformations of another heterocycles. Most of such reactions are usually polar on nature, and permit one to clearly identify the disposition of electro- and nucleophilic centers in the target and reactants. The goal of this communication is to provide the general qualitative analysis of polarity rules for these methods of heterocyclic synthesis, and to prove their usefulness in computer synthesis planning.

Heteroaromatic systems can be roughly classified into the two large classes:

The ***consonant heteroaromatic structures*** are: those with even-membered rings (e.g. pyridines), and/or with alternating disposition of heteroatoms (e.g. pyrimidine), and/or with "normal" disposition of polar donor and acceptor groups.

"Normal" disposition means ***odd chain*** betweeen any pair of electronegative heteroatoms X, independently on their presence as endo-cyclic heteroatom in the ring, donor atom as the exo-group, or terminal electronegative atom of acceptor group. Any consonant structure can be presented as bichromatic graph, so that any electronegative heteroatom has the same color. The color may be associated with alternation of formal charges (+ and -), of acceptor/donor and/or of electro-/nucleophilic centers in consonant molecule.

The ***dissonant heteroaromatic structures*** are: those with odd-membered rings (e.g. azoles), and/or with even-membered rings and non-altemating disposition of heteroatoms (e.g. pyrazines, pyridazines), and/or with even-membered rings and non-alternating disposition of polar exo-groups or polar groups and endo-heteroatoms (e.g. 3-hydroxypyridines).

The dissonant structures either can not be presented as bichromatic graphs at all (like in the case of azoles), or such presentation may cause different colors for heteroatoms of the same polar nature (like in pyrazines or 3-hydroxypyridines).

Evidently, this dichotomy is natural generalization of the distribution of chains into two - consonant and dissonant - types, first proposed by Evans[1], and former discussed by Seebach[2] and Ho[3] under another terms. Meanwhile, these two equivalence classes in heterocyclic chemistry correspond to two different types of structure and reactivity of heteroaromatic rings. For example, pronounced polarity alternation in the consonant structures is responsible for consonant action of exo- and endo-heteroatoms in orientation toward external electro- or nucleophilic attack. In the dissonant structures such selectivity is usualy uncertain.

By the other hand, polar structure of open-chain precursors for every class is dramatically different. Thus, there are only few examples where the consonant structures are synthesized from two dissonant chains; most examples of two-component synthesis include two consonant components. On the contrary, usual route to dissonant structure is the combination of consonant and dissonant chains.

The simple mnemonical rule can be used to clearize general difference between the consonant and dissonant structures. Consonant structures can be globally associated with some sort of ***eveness*** (manifested in bichromatic structure of graphs), e.g. with properties of even numbers, while the dissonance correspond to the global ***oddness,*** e.g. properties of odd numbers. Thus, three global properties of consonant structures are parallel to the parity of sum of any pair of numbers:

Even + Even = Even	Consonant + Consonant = Consonant
Even + Odd = Odd	Consonant + Dissonant = Dissonant
Odd + Odd = Even	Dissonant + Dissonant = Consonant

This analogy is, evidently, some sort of oversimplification, since the consonance is simply absence of conflicts (even chains between heteroatoms), while the dissonance may be measured by the number of such conflicts. As the result, there is also possibility to combine two dissonant species to form "more dissonant" one. An attempt to give quantitative measure of dissonance (including also conflicts between the hydrogen atoms) is discussed in our other communication at this conference.

Nevertheless, this analogy shows, mat it is impossible to get a dissonant structure from two consonant ones, and we failed to find counter-examples to this rule in the synthesis of heterocycles. By the other hand, action of something consonant ***conserves*** initial (consonant or dissonant) property. One can say that the consonant structures in mathematical sence tend to form closed set under the action of consonant reagents. Action of dissonant molecule usualy tend to ***change*** initial (consonant or less dissonant) structural feature.

The discussed analogy is rather global rule that may be applied to different aspects of computer chemistry of heteroaromatics, in particular to simulating the qualitative aspects of synthesis and reactivity of consonant and dissonant heteroaromatics. Two main applications discussed in the poster communication are the cyclization and recyclization reactions of the consonant heteroaromatics.

CYCLIZATIONS

As the example of application of such rules to synthesis planning of concrete heterocyclic structure we consider ring formation of pyridines from open chains. Over 600 examples of reactions were carefully selected from literature, and arranged into the database[4,5].

Analysis of relationship between the consonant and dissonant structure of open chain reagents and the resulting substituted cycles brought no counter-examples to the above rules. However, the main type of dissonant cyclic structures, resulted from dissonant open chains were only the pyndines with acceptor carbonyl (carboxyl) function at the a or g position. In all other cases consonant arrangement of functions around the pyridine ring simply originate from consonant structure of open chains. As a result, it was claimed, mat the optimal polarity of pyridine precursors should be of the same type, as in pyridine (polarity conservance rule).

Computer program Heterocycland that generate possible consonant precursors of consonant azines was recently elaborated[6]. Application of this program for design of new methods of pyridine ring synthesis has permitted us to predict the polar structure of open chain for last unknown 5+1 cyclization. this prediction has been proved experimentally in the new quinoline synthesis[7].

RECYCLIZATIONS

Recently we developed general mathematical formalism for description of heterocyclic ring transformation reactions (the Ring-Bonds Redistribution Graphs Model)[8-9]. The key idea of this approach is the use of reaction graphs to classify heterocyclic rearrangements into hierarchic system, one important level of such hierarchy includes the identification of electro- and nucleophilic centers in the side chain of heterocycle as the useful criteria of estimating the polar structure of product.

Again, analysts of heterocyclic precursors of consonant azines showed, that they are always consonant. By the other hand, dissonant azines required dissonant (usualy azole) heterocyclic precursors, and often tend to undergo ring transformations to dissonant azines. This model implemented into the computer program GREH has permited us to predict previously unknown reactions of ring interconversion of azoles and azines[10]. So, the proposed rules, implemented as the algorithms of computer programs, play a role of good empirical filter to select reasonable cyclic or acyclic precursors of heteroaromatic structures from the unreasonable ones.

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