Iteroselectivity, the missing sibling of chemo-, regio- and stereoselectivities

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Abstract: Iteroselectivity is the selectivity that governs the number of repeating chemical transformations on a substrate bearing multiple identical reactive functions or when the reactive function is regenerated like in the case of polymerization. This new concept of selectivity is defined and compared with the classical chemo-, regio- and stereoselectivities encountered in chemical synthesis. Examples of iteroselective reactions are given ranging from very common reactions such as electrophilic aromatic substitutions to advanced methods involving large supramolecular complexes.

Introduction

Selectivity plays a crucial role in organic synthesis. Selective reactions are most commonly categorized as chemoselective,¹,² regioselective¹,³ and stereoselective.¹,⁴ There is, however, one type of selectivity commonly encountered in various reactions (e.g. substitutions, polymerizations, etc.) that does not fit in these three categories. The purpose of this work is to present the selectivity observed when a reaction can occur at least twice on a substrate (e.g. the alkylation of ethylene glycol, see Figure 1) but stops selectively after a given number of iterations. In 2014, we proposed to name this selectivity “iteroselectivity”⁵ and, since then, this term was used in various articles.⁶,⁷,⁸,⁹,¹⁰,¹¹,¹²,¹³,¹⁴ To the best of our knowledge, the concepts arising from this type of selectivity have not been yet properly named and defined in the literature.

Herein, we propose to define properly this type of selectivity, to compare it to the three main types of selectivity in organic synthesis, and to list some concrete examples from the literature.

Discussion

Definition of iteroselectivity and related concepts. Iteroselectivity is defined as the preferential formation of products (i.e. iteromers) differing by the number of repeating chemical transformations the starting substrate underwent, where preferential means different from a normal products distribution (vide infra).⁵ The term iteromer was chosen instead of iteroisomer, which has to be banned, to name the different products of an iteroselective reaction. Indeed, the repeating chemical transformations involve the formation of non-isomeric products unlike the regioselective, stereoselective and some chemoselective reactions which lead to constitutional isomers or stereoisomers. Repeating chemical transformations designate reactions happening on a same chemical function x leading to a same chemical function y. We originally proposed the name “iteroselectivity” as this type of selectivity concerns iterative processes such as the modification of a given number of functional groups iteratively. The iteroselectivity discussed herein applies only to one-
pot reactions involving iterative chemical steps and should not be confused with sequential multi-step processes such as peptide syntheses relying on protection/deprotection steps.

The iteroselectivity may originate from a wide diversity of phenomena such as electronic, steric, supramolecular effects, or even difference in solubilities. Iteroselectivity under kinetic control involves a modification of the reactivity after a given number of iterations, i.e. activating or deactivating one iteromer in regard to other iterations of the chemical reaction, thus accumulating an iteromer regardless of its relative stability compared to other iteromers. A thermodynamic control is only seen at equilibrium in reversible reactions in which the most stable iteromer(s) will form preferentially.

In the case of stereoselectivity, the absence of selectivity is trivially defined as a 1:1 ratio between two stereoisomers. This is sound in the case of enantiomers that both have the same stability but this is an arbitrary decision in the case of diastereomers as these isomers display different relative stabilities and a diastereomeric excess (de) of 0% is thus unexpected under any condition. Similarly, defining a normal distribution of iteromers implies arbitrary decisions. We propose to define the normal distribution of iteromers as the distribution obtained after complete consumption of the limiting reactant(s) for iterative irreversible reactions with identical kinetic constants and partial first order kinetic for each reactant (see details in the Supporting Information). These arbitrary choices ensure that the normal distributions are relatively simple to calculate, invariant to changes in concentration, and that complete per-functionalization results from an excess of reagent to the number of functional groups on the substrate. Yet, we are conscious that these choices lead to a poor description of a normal distribution of iteromers in reversible reactions at equilibrium. Further considerations are discussed in the Supporting Information. Rebek Jr and co-workers previously described the normal distribution in a similar way to evaluate the iteroselectivity of a reaction over time.\textsuperscript{15}

To determine the degree of iteroselectivity, we introduce the concept of iteromeric excess \( ie \) by analogy to enantiomeric and diastereomeric excesses. Since the ratio of each iteromer can be different under a normal distribution, we define the \( ie \) based on the difference between the ratio of the iteromer \( i \) obtained experimentally \( r_{exp} \) (that can be assimilated to the yield) and the normal ratio \( r_{normal} \) (equation 1). The \( ie \) ranges from 0 to 100% for positive iteroselectivity, and from \(-\infty \) to 0 for negative iteroselectivity. Conveniently, in presence of an excess of reagent, \( r_{normal} \) equals 0 for any product other than the per-functionalized product and, therefore, the \( ie \) equals the yield.

\[
ie = \frac{r_{exp} - r_{normal}}{1 - r_{normal}} \times 100\% \quad (1)
\]

Cases of perfect normal distribution are extremely rare or possibly inexistent. As such, most reported reactions are at least mildly iteroselective. Therefore, we recommend to refrain emphasizing the iteroselective character of a reaction unless “high” iteroselectivity is observed. The term iterospecificity should be avoided to describe complete iteroselectivity as recommended by IUPAC for other selectivities.\textsuperscript{1}

Interestingly, iteroselectivity is not limited to reactions only modifying existing functions on a substrate but also applies to oligo- and polymerizations (Figure 2). Indeed, a polymerization is an iterative reaction involving a repeating chemical transformation in which the reacting function is regenerated after each iteration. Therefore, a reaction leading to a major oligomer comprising a definite number of repeating units is iteroselective. Some of the most striking examples of iteroselective oligomerization are (i) the peptide synthesis controlled by the complex ribosome activity in biological organisms\textsuperscript{16} (Figure 2a) and (ii) the syntheses of oligomeric macrocycles such as cucurbiturils,\textsuperscript{17} calixarenes,\textsuperscript{18} or pillararenes\textsuperscript{19} which are, in some cases, templated by metal cations or solvent molecules to form iteroselectively a macrocycle of definite size (Figure 2b for calixarenes). Note that,
for $n$ repeating units, the number of iterations $i = (n - 1)$ for linear oligomers but $i = n$ for oligomeric macrocycles due to the additional iteration closing the macrocycle. For homo-polymerizations, the normal distribution would consist of a single polymer of maximum length, thus the normal ratio for any given length of polymer is essentially 0 and the $ie$ is conveniently equal to the yield.

**Comparison between iteroselectivity and other main selectivities**

**a) Iteroselectivity vs regioselectivity**

![Diagram showing iteroselectivity and regioselectivity comparison]

Figure 2. Examples of iteroselective oligomerizations. a) peptides as linear oligomers, b) calix[n]arenes as oligomeric macrocycles. $i$: number of iterations.

Figure 3. Comparison between iteroselectivity and regioselectivity for the $S_i$Ar of anisole.
Iteroselectivity and regioselectivity are fundamentally different but complementary. Indeed, while the former leads to iteromers and the latter leads to regioisomers, several regioisomers may arise at each iteration of an iterative reaction. One simple example is the electrophilic aromatic substitution of functionalized benzene rings (Figure 3). If one considers the Friedel–Crafts alkylation of anisole, it is usually fair to assume that it will generate ortho/para-alkylated anisoles with relatively good regioselectivity (ortho and para positions) and iteroselectivity (from mono to trialkylated anisoles). In contrast, the nitration of anisole expresses a similar regioselectivity (ortho and para positions favored) but the iteroselectivity is greatly enhanced due to the strong deactivation imparted by nitro groups leading mainly to mononitro anisole in mild reaction conditions. In this last case, the iteroselectivity is driven by electronic effects with a deactivating kinetic control.

Another example is the functionalization of oligomeric macrocycles such as cyclodextrins or calixarenes which was studied for decades to seek efficient iteroselective and regioselective reactions (Figure 4). While most reactions to functionalize oligomeric macrocycles are not highly iteroselective or regioselective, some examples stand out and are described in the last section (vide infra).

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**Figure 4.** Comparison between iteroselectivity and regioselectivity for the functionalization of phenolic positions of calix[4 and 6]arenes.

### b) Iteroselectivity vs stereoselectivity

Similarly to the comparison with regioselectivity, iteroselectivities are orthogonal but complementary since several stereoisomers may arise after each iteration of a reaction. A simple case such as an S_{N}1 reaction performed on an enantiopure dibromoalkane can illustrate this complementarity between the two selectivities (Figure 5).
c) Iteroselectivity vs chemoselectivity

Considering the definition of iteroselectivity proposed herein that concerns repeating chemical transformation on the same chemical function, iteroselectivity is fundamentally different from chemoselectivity that concerns the selectivity between different chemical functions. A lack of chemoselectivity in a potential iterative reaction would lead to side products which are out of the iterative process studied (Figure 6). Thus, iteroselectivity and chemoselectivity differ to such an extent that they cannot be used in a concerted manner to describe the products of a reaction as opposed to the complementarity between iteroselectivity and regio- or stereoselectivity discussed above.

- Iteroselectivity vs chemoselectivity

Examples of iteroselective reactions from the literature

A tremendous amount of iteroselective synthesis examples is described in the scientific literature. However, it is difficult to search efficiently for these examples as they are not tagged as “iteroselective” and we have seen that iteroselectivity may apply to very simple reactions on small substrates as well as to more complicated cases. Therefore, the following list will not be exhaustive or representative of the diversity of substrates and reactions showing iteroselectivity but rather show recent and inspiring examples of highly iteroselective reactions. When possible, iteromeric excesses based on the reported yields and conditions have been calculated. Details of iteromeric excess calculations are provided in the Supporting Information.

Polyethyleneglycols (PEGs) have two terminal hydroxy groups separated by a long distance. It is thus difficult to selectively modify one of these two groups as the transformation of one group has no influence on the reactivity of the second one. The iteroselective mono-tosylation of PEGs was however successfully achieved in presence of silver(II) oxide particles and potassium iodide (Figure 7).
iteroselectivity was rationalized by an activation of one of the two terminal OH groups through its chemisorption on the surface of the silver particles, the other group remaining inactivated due to the entropically unfavorable backfolding of the PEG chain. For the mono-tosylation of PEG-1500 with 1.18 equiv. of tosyl chloride, we calculated an iteromeric excess of 70% from $r_{\text{norm}}$ and $r_{\text{exp}}$ of 34% and 80%, respectively.

![Figure 7](image1.png)

**Figure 7.** Selective-mono-tosylation of PEGs mediated by silver(I) oxide particles.

In the field of cyclodextrins, Sinaÿ and co-workers reported an iteroselective de-O-benzylation of per-benzylated cyclodextrins with DIBAL-H (diisobutylaluminium hydride).\(^{20}\) Large excess of DIBAL-H (30–120 equiv.) under mild or harsher conditions led to the mono- and di-O-debenzylation of per-benzylated $\alpha$-cyclodextrin bearing 18 benzyl ethers in 64% and 82% yield, respectively (Figure 8). In both cases the $ie$ correspond to the yield (64% and 82%) because the large excess of reagent should lead to the exclusive per-O-debenzylation under a normal distribution. The selectivity was rationalized by the limited number of bulky DIBAL groups allowed on the cyclodextrin narrow rim, thus leading to a maximum of two debenzylations at distant positions. Sollogoub and co-workers later employed the mono-O-debenzylation to achieve an impressive multistep hetero-hexa-functionalization of $\alpha$-cyclodextrin that required high itero- and regioselectivities over each step (Figure 8).\(^{23}\)

![Figure 8](image2.png)

**Figure 8.** Multistep hetero-hexa-functionalization of $\alpha$-cyclodextrin using an iteroselective mono-O-debenzylation reaction.

Over the last decade, we developed several strategies for the regio- and iteroselective modifications of calixarenes.\(^{7}\) As a representative example, we reported an iteroselective carbamation of calixarenes in aprotic solvents through the addition of an excess of tert-butyl isocyanate under basic conditions (Figure 9).\(^{5,6,9}\) The “all-but-one” iteroselectivity was rationalized by an internal proton assisted mechanism. This mechanism involves a phenolate attacking the isocyanate and a nearby phenol to provide a proton. When only one unreacted phenolic unit remains, the absence of nearby proton donor prevents the last addition. Interestingly, unlike other examples described herein this all-but-one
selective method does not lead to a specific number of iterations but depends on the number of starting reactive functions: \( i = m - 1 \) for \( m \) reactive functions. The reaction was shown to work efficiently on a wide scope of substrates including parent or partially functionalized calixarenes and homooxacalixarenes (typical yields >90%). The first example of this all-but-one carbamation on \( p\text{-tBu-calix}[6]\)arene with 18 equiv. of tert-butyl isocyanate showed a \( \text{ie} \) of 91% (equal to the yield).

**Figure 9.** All-but-one carbamation of calixarenes. The reaction stops when only one phenolate is left unreacted.

Rebek Jr and co-workers reported several cases of iteroselective reactions on di-functional molecules via a supramolecular protection of one reactive site within a deep cavitand.\(^{15,24,25,26,27}\) One remarkable example is the Staudinger mono-reduction of diazido alkanes in water (Figure 10).\(^{25}\) The diazido alkane guest is included in a resorcinarene-based deep cavitand with one of the two azides nesting in the cavity. The other azide protrudes from the cavity and can readily react with an excess of trimethylphosphine, affording the mono-amine product in 99% yield (the \( \text{ie} \) is equal to the yield). The further reaction of the unreacted azide is inhibited as this group is less polar than the amine and is thus preferentially hidden from the water. Such a strategy based on host–guest chemistry can be used to achieve regio- and iteroselective reactions on either the guest\(^{28,29}\) or the host,\(^{30}\) but also reactions of the host with the guest.\(^{31,32,33}\)

**Figure 10.** Iteroselective Staudinger reduction on a diazido alkane with one azide protected inside a deep cavitand.

In a similar fashion, recent advances in the functionalization of fullerenes showed the successful use of shadow masks to protect a given number of reactive positions of \( \text{C}_{60} \) and \( \text{C}_{70} \) and achieve mono- to tetra-functionalization (Figure 11).\(^{34,35,36,37}\) In these reported complexes, the unfunctionalized fullerene guest is initially in free rotation with all identical reactive sites showing equal reactivity (30 for \( \text{C}_{60} \)). Upon the first and subsequent functionalizations, the rotation of the fullerene in the complex is impeded, thus effectively deactivating reactive sites masked by the host. For the synthesis of the tetrakis-diethylmalonate-\( \text{C}_{60} \) adduct with 4 equiv. of diethyl bromomalonate, the \( \text{ie} \) calculated is 99% from \( r_{\text{normal}} \) and \( r_{\text{exp}} \) of 20% and 99%, respectively.\(^{35}\)
Regio- and iteroselective tetra-functionalization of fullerene $C_{60}$ via a shadow-mask strategy. There are 30 equally reactive sites on the starting $C_{60}$.

Nitschke and co-workers reported the iteroselective functionalization of tris-anilines via a dynamic subcomponent self-assembly process (Figure 12). Several supramolecular structures can arise from the reported self-assembly including one kinetically metastable intermediate formed by the condensation of two of the three amine functions with an aldehyde to form imines stabilized by coordination to iron(II). The remaining unreacted amine of the kinetically trapped iteroselectively di-protected tris-anilines is then functionalized prior to disassembling the supramolecular structures. This process is a clear example of kinetically controlled iteroselective reaction. It is important to note that the functionalization of the last free amine does not constitute the iteroselective reaction but rather the initial condensation of two amines with aldehydes. Indeed, in protection / functionalization / deprotection sequences, the substrate that bears several identical functions that can undergo an iterative transformation is the initial substrate before protection. The following functionalization reaction is merely a per-functionalization of the remaining reactive sites, thus not showing any iteroselectivity. This difference is crucial to not confuse a seemingly apparent overall iteroselective reaction and the true iteroselective protection step. For the bis-condensation of tris(4-aminophenyl)amine with two equivalents of 2-formylpyridine, the $i_e$ calculated is 93% from $r_{nor\text{m}}$ and $r_{exp}$ of 26% and 95%, respectively.

Figure 11. Itero- and iteroselective tetra-functionalization of fullerene $C_{60}$ via a shadow-mask strategy. There are 30 equally reactive sites on the starting $C_{60}$.

Figure 12. Iteroselective condensation of amines and aldehydes via self-assembly into supramolecular architectures.
Conclusion

Iteroselectivity is observed when a limited number of repeating chemical transformations occurs in regard to the maximum number of reactive sites on a substrate. It is surprising that this concept was not properly named and defined earlier considering its common occurrence in simple reactions such as the alkylation of diols or aromatic substitutions. Moreover, the numerous recent studies successfully achieving iteroselective reactions through advanced methods clearly show a great interest of the chemistry community for this type of selectivity. We have now lifted the lack of definition and naming convention. Additionally, we provided means for measuring the degree of iteroselectivity through the calculation of iteromeric excess. We hope the concepts described herein will lead to a better description of iteroselective processes in the literature.

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Notes
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