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

Roy Lavendomme1,2,* and Ivan Jabin2,*

SUMMARY
Iteroselectivity is the selectivity that governs the number of repeating chemical transformations that occur on a substrate bearing multiple identical reactive functions or when the reactive function is regenerated, like in the case of polymerization. This 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 regioselective,1,3 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 given reaction can occur at least twice on a substrate (e.g., the alkylation of ethylene glycol; see Figure 1A) but stops selectively after a given number of iterations i. This is distinct from selectivity imposed through sequential reactions,5 and it applies only to one-pot reactions. In 2014, we proposed to name this selectivity "iteroselectivity"6 (Figure 1B), and since then, this term has been used in various articles.7–15 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 and related concepts, to compare it with the three main types of selectivity in organic synthesis (see Figure 1).

Figure 1. Iterative reactions that may show iteroselectivity
(A) The alkylation of ethylene glycol is a simple example of iterative reaction. The substrate and potential products are named iteromers. i corresponds to the number of iterations.
(B) Substrates bearing several identical functions can react iteratively in a single pot. Iteroselectivity arises when one or several products are predominantly formed against the expected outcome if reaction kinetics were equal for each iteration.

1Center for Ordered Materials, Organometallics and Catalysis (COMOC), Department of Chemistry, Ghent University, Krijgslaan 281-S3, 9000 Ghent, Belgium
2Laboratoire de Chimie Organique, Université libre de Bruxelles (ULB), Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium
*Correspondence: roy.lavendomme@ulb.be (R.L.), ivan.jabin@ulb.be (I.J.)
https://doi.org/10.1016/j.xcrp.2022.101121
DEFINITION OF ITEROSELECTIVITY AND RELATED CONCEPTS

Iteroselectivity and iteromers
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 product distribution (see below). The products of an iterative reaction are not isomers and thus must be named iteromers instead of iteroisomers. Repeating chemical transformations designate reactions occurring on equivalent starting functional groups yielding equivalent final functional groups (e.g., alkylation of primary alcohols under the same conditions affording ethers). 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 multistep processes such as peptide syntheses relying on protection/deprotection steps.

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 with other iteromers. Thermodynamic control is only seen at equilibrium in reversible reactions in which the most stable iteromer(s) will form preferentially.

Calculating the degree of iteroselectivity
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 thermodynamic 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 in absence of iteroselectivity 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 (see details in Note S1). The evolution of the concentration of iteromers under this definition is illustrated in Figure 3 for a tetra-functional substrate. 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 Notes S1 and S2, including formulas to calculate the normal distributions and precalculated tables for convenience. Rebek Jr. and co-workers previously described the normal distribution in a similar fashion to evaluate the iteroselectivity of a reaction over time despite not using the terminology and definitions introduced herein.16

To determine the degree of iteroselectivity, we introduce the concept of iteromeric excess \( \text{ite} \) by analogy to enantiomeric and diastereomeric excesses (see Note S3). Since the ratio of each iteromer can be different under a normal distribution, we define the \( \text{ite} \) 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 \( r_{\text{normal}} \) that both range from 0 to 1 (Equation 1). The \( \text{ite} \) ranges from 0 to 100% for positive iteroselectivity, and from \(-\infty\) to zero for negative iteroselectivity. Conveniently, in presence of an excess of reagent, \( r_{\text{normal}} \) equals zero for any product other than the per-functionalized product, and therefore, the \( \text{ite} \) equals the yield \( r_{\exp} \).

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

It is noteworthy that for any intermediate iteromer (i.e., neither the starting substrate nor the per-functionalized product), \( r_{\text{normal}} \) is always smaller than 0.37 per the definition of normal distribution (e.g., the ratios of AB, AB2, and AB3 in Figure 3). Consequently, any synthesis of intermediate iteromer in yield greater than 37%
shows positive iteroselectivity. This condition is sufficient to describe a reaction as iteroselective, and reporting the $ite$ is informative but optional. 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.¹

Iteroselectivity in polymerization

Interestingly, iteroselectivity is not limited to reactions only modifying existing functions on a substrate but also applies to oligo- and polymerizations (Figure 4). 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. Iteroselectivity is better suited to describe the selective formation of short oligomers, while for large polymers, the established concept of degree of polymerization is more appropriate. Indeed, large polymers are generally synthesized in batches of various lengths that are better described by their average length or weight rather than a precise number of iterations.

Some of the most striking examples of iteroselective oligomerization are (1) the peptide synthesis controlled by the complex ribosome activity in biological organisms¹⁷ (Figure 4A) and (2) the syntheses of oligomeric macrocycles such as cucurbiturils,¹⁸ calixarenes,¹⁹ or pillararenes,²⁰ which are in some cases templated by metal cations or solvent molecules to form iteroselectively a macrocycle of definite size (Figure 4B 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 (see Note S1), so the normal ratio for any given length of polymer is essentially zero and the $ite$ is conveniently equal to the yield. For hetero-polymerizations, the normal distribution is more complex to calculate, but some cases are covered in Note S1.

**COMPARISON BETWEEN ITEROSELECTIVITY AND OTHER MAIN SELECTIVITIES**

**Iteroselectivity vs. regioselectivity**

Iteroselectivity and regioselectivity are fundamentally different but complementary. Indeed, while the former leads to iteromers and the latter leads to regiosomers, several regiosomers may arise at each iteration of an iterative reaction. One simple example is the electrophilic aromatic substitution ($S_{E}\text{Ar}$) of

---

**Figure 4. Examples of iteroselective oligomerization**

(A) Peptides as linear oligomers. The iteroselectivity originates from the complex ribosomal activity. For linear oligomers of size $n$, there are $n - 1$ iterations $i$.

(B) Calix[n]arenes as oligomeric macrocycles. Metal cations are used to template the formation of macrocycles with matching sizes iteroselectively. For cyclic oligomers of size $n$, there are $n$ iterations $i$ due to the additional iteration closing the macrocycle compared with linear oligomers.
functionalized benzene rings (Figure 5). 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 itero-selectivity (from mono to trialkylated anisoles). In contrast, the nitration of anisole expresses a similar regioselectivity (ortho and para positions favored), but the itero-selectivity is greatly enhanced because of the strong deactivation imparted by nitro groups leading mainly to mononitro anisole in mild reaction conditions. In this last case, the itero-selectivity is driven by electronic effects with a deactivating kinetic control.

To describe the products and selectivity of such reactions that involve both itero-selectivity and regioselectivity, it is necessary to express both the itomeric excess i and the ratio of regioisomers. Following with the example of the S$_E$Ar in Figure 5, let us consider the reaction of anisole with 1 equiv of alkylating agent leading to the monoalkylated products in ortho and para positions (20% and 60% yield, respectively). Both regioisomers correspond to the first iteration, so the r$_{exp}$ for $i = 1$ is the combined yields of both products (20% + 60% = 0.8). r$_{normal}$ is 0.368 (see precalculated Table S4 in the supplemental information). The result of the reaction for $i = 1$ can be described completely with $ite_i = 100\% \times (0.8 - 0.368)/(1 - 0.368) = 68\%$ (itero-selectivity), and the ratio between all three possible regioisomers functionalized in ortho/meta/para positions is 1:0:3 (regioselectivity).
Another example of reactions involving both types of selectivity is the functionalization of oligomeric macrocycles such as cyclodextrins or calixarenes, which was studied for decades to seek efficient itero- and regioselective reactions (Figure 6). While most reactions to functionalize oligomeric macrocycles are not highly iteroselective or regioselective, some examples stand out and are described in the last section (see below).

![Figure 6. Comparison between iteroselectivity and regioselectivity for the functionalization of oligomeric macrocycles](image-url)

During the functionalization of phenolic positions of calix[4 and 6]arenes, several regioisomers can be formed at different iterative steps.
Iteroselectivity vs. stereoselectivity
Similarly to the comparison with regioselectivity, itero- and stereoselectivities are orthogonal but complementary since several stereoisomers may arise after each iteration of a reaction. A simple case such as a first-order nucleophilic substitution (S_N1) performed on an enantiopure dibromoalkane can illustrate this complementarity between the two selectivities (Figure 7). To describe completely the outcome of such reaction presenting both itero- and stereoselectivities, it is necessary to express both the iteromeric excess \( \text{it} \) and the ratio of stereoisomers \( \text{dr} \) (or \( \text{ee}/\text{de} \) when applicable) for a given iteration \( i \).

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.\(^1\) A lack of chemoselectivity in a potential iterative reaction would lead to side products that are out of the iterative process studied (Figure 8). 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.

EXAMPLES OF ITEROSELECTIVE REACTIONS FROM THE LITERATURE
A tremendous amount of iteroselective synthesis examples are 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 were calculated. Details of iteromeric excess calculations are provided in Note S4.

**Tosylation of polyethyleneglycols**

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

![Figure 9. Iteroselective mono-tosylation of PEGs](image)

Hydroxyl groups of PEGs can be activated by silver(I) oxide particles. The iteroselectivity originates from the unfavorable backfolding of the long PEG chain, which limits the chemisorption and activation to a single hydroxyl group per PEG.

![Figure 10. Multistep hetero-hexa-functionalization of α-cyclodextrin using an iteroselective mono-O-debenzylation reaction](image)

Iteroselective and regioselective di-O-debenzylation can also be achieved under harsher conditions.
presence of silver(I) oxide particles and potassium iodide (Figure 9). The iteroselectivity was rationalized by an activation of one of the two terminal OH groups through its chemisorption on the surface of the silver particles, with the other group remaining inactivated due to the entropically unfavorable backfolding of the PEG chain. For 1.0 equiv of tosyl chloride, the authors obtained a ratio of starting, mono-tosyl, and di-tosyl PEGs \((i = 0, 1, 2)\) of 179:733:88 (PEG-1500) and 158:762:79 (PEG-2000). The normal distribution for these iteromers under these conditions is 318:364:318 (see Table S1 in the supplemental information). Accordingly, the iteromeric excess for the mono-tosylated products are 58% (PEG-1500) and 63% (PEG-2000).

**O-debenzylation of cyclodextrins**

In the field of cyclodextrins, Sinaý and co-workers reported an iteroselective O-debenzylation of per-benzylated cyclodextrins with DIBAL-H (diisobutylaluminium hydride). Large excess of DIBAL-H (30–120 equiv) under mild or harsher conditions led to the mono- and di-O-debenzylations of per-benzylated \(\alpha\)-cyclodextrin bearing the reaction stops when only one phenolate is left unreacted. (A) Internal proton transfer assisting the carbamation of calixarenes and source of the iteroselectivity. (B) Example of iteroselective all-but-one carbamation of \(p\)-tBu-calix[6]arene. (C) Example of iteroselective and regioselective all-but-one carbamation of \(p\)-tBu-dihomoxxacalix[4]arene.

Figure 11. All-but-one carbamation of calixarenes

The reaction stops when only one phenolate is left unreacted. (A) Internal proton transfer assisting the carbamation of calixarenes and source of the iteroselectivity. (B) Example of iteroselective all-but-one carbamation of \(p\)-tBu-calix[6]arene. (C) Example of iteroselective and regioselective all-but-one carbamation of \(p\)-tBu-dihomoxxacalix[4]arene.
18 benzyl ethers in 64% and 82% yield, respectively (Figure 10). In both cases the ite corresponds 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, thus achieving both itero- and regioselectivity. Sollogoub and co-workers later employed the mono-O-debenzylation to achieve an impressive multistep hetero-hexa-functionalization of α-cyclodextrin that required high itero- and regioselectivities over each step (Figure 10).24

Carbamation of calixarenes
Over the last decade, we developed several strategies for the regio- and itero-selective modifications of calixarenes.8 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 11A).6,7,10 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 a 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 \( p\)-tBu-calix[6]arene with 18 equiv of tert-butyl isocyanate showed an ite of 91% equal to the yield (Figure 11B).6 It is noteworthy that the all-but-one carbamation can also lead to regioselectivity when multiple regioisomers are possible. The all-but-one carbamation of dihomooxacalix[4]arene leads to a single regioisomer among two possibilities, thus achieving high iteroselectivity (ite of 98%, equal to the yield) and regioselectivity (Figure 11C).7

Supramolecular protection
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.16,25–28 Unlike conventional covalent protecting groups modifying chemical functions, supramolecular protecting groups modify the environment and, consequently, the reactivity of the functional groups, which is the origin of the iteroselectivity. One remarkable example is the Staudinger mono-reduction of diazido alkanes in water (Figure 12).26 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 ite 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 guest29,30 or the host,31 but also reactions of the host with the guest.32–34

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 \( C_{60} \) and \( C_{70} \) and achieve mono- to tetra-functionalization (Figure 13).35–39 In these reported complexes, the unfunctionalized fullerene guest is initially in free rotation
with all identical reactive sites showing equal reactivity (30 for C₆₀). 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-C₆₀ adduct with 4 equiv of diethyl bromo-
malonate, the ite calculated is 99% from r_normal and r_exp of 20 and 99%, respec-
tively. 36 It is noteworthy that this shadow mask strategy not only allows iteroselective
control but also regioselective control of the products. In the case exemplified in Fig-
ure 13, the shadow mask permits only the formation of the tetrakis-e,e,e,e-adduct as
ultimate product but other shadow masks were used to access different regio- and
iteroselectivities. 35–39

**Iteroselectivity in subcomponent self-assembly**

Nitschke and co-workers reported the iteroselective functionalization of tris-anilines
via a dynamic subcomponent self-assembly process (Figure 14). 40 Several supramo-
lecular structures can arise from the reported self-assembly including one kinetically
metastable intermediate formed by the condensation of two of the three amine func-
tions with an aldehyde to form imines stabilized by coordination to iron(II). The re-
main ing unreacted amine of the kinetically trapped iteroselectively di-protected
tris-anilines is then functionalized prior to disassembling the supramolecular struc-
tures. 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

**Figure 12. Iteroselectivity via supramolecular protection using cavitands**

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

**Figure 13. Selective fullerene functionalization via supramolecular protection**

Regio- and iteroselective tetra-functionalization of fullerene C₆₀ via a shadow mask strategy. There
are 30 equally reactive sites on the starting C₆₀.
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 2 equiv of 2-formylpyridine, the iteroselectivity calculated is 93% from $r_{\text{normal}}$ and $r_{\text{exp}}$ of 26 and 95%, respectively.

Figure 14. Iteroselective condensation of amines and aldehydes via self-assembly into supramolecular architectures
This is an example of kinetically controlled iteroselectivity. The ligands L of the metastable helicate $[\text{Fe}_2\text{L}_3]^{m+}$ are used as a bis-protected tri-amine to further functionalize the remaining free amine. The iteroselective step is the initial bis-condensation on the tri-amine reactant and not the final monofunctionalization that is achieved on a mono-amine ligand L.
Templated cyclooligomerization
The synthesis of oligomeric macrocycles is generally challenging as their size has to be controlled and the formation of linear polymers avoided. One of the most popular strategies is the use of a template that will drive the closure of the macrocycle with a defined number of monomers. A representative example is the synthesis of pillar[n]arenes using the solvent as a template (Figure 15). Ogoshi et al. showed that a small solvent such as 1,2-dichloroethane could serve as a suitable template for the small pillar[5]arene macrocycle (i = 5, yield = 71%), while the larger solvent chlorocyclohexane templates the formation of the large pillar[6]arene macrocycle (i = 6, yield = 87%). The oligomerization was shown to be reversible in presence of Lewis or Brønsted acids. Therefore, the iteroselectivity is under thermodynamic control. This templating strategy was successfully used to prepare larger macrocycles with reversible reactions (e.g., imine-based macrocycles) or irreversible reactions (e.g., porphyrin nanorings). Irreversible reactions, however, tend to lead to lower iteroselectivity due to the occasional formation of any smaller macrocycle or larger oligomer than the templated product.

To conclude, 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. The concepts described herein should lead to a better description of iteroselective processes in the literature, and we hope that they will be helpful in other fields than organic and supramolecular chemistries including biochemistry and inorganic chemistry.

SUPPLEMENTAL INFORMATION
Supplemental information can be found online at https://doi.org/10.1016/j.xcrp.2022.101121.

ACKNOWLEDGMENTS
We thank Prof. Vincent Dalla, Dr. Catherine Taillier, and Prof. Eric Monflier for fruitful discussions.

AUTHOR CONTRIBUTIONS
Conceptualization, R.L. and I.J.; formal analysis, R.L.; writing – original draft, R.L.; writing – review & editing, R.L. and I.J.

DECLARATION OF INTERESTS
The authors declare no competing interests.

REFERENCES


