

ORGANIC CHEMICAL REACTIONS

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Summary

Organic reactions have been used for preparing the huge amount of organic compounds so far known and will be used for the synthesis of new organic molecules in the future.

A detailed knowledge of organic reactions and their mechanism is therefore an essential tool for any scientist or technician involved with research and development of organic molecules in any scientific and technological field. This chapter is divided into two main parts. The first part introduces the reader to the basic and general knowledge of the organic reaction, including the chemical notation, the mechanism, thermodynamics and kinetics, a description of the main partners involved in the chemical transformation, and an introduction to the main topics of organic chemistry strictly related to reactions and reactivity. The second part is a description, organized by classes based on the mechanism, of the most important and common organic reactions. Many examples are given throughout the text with the help of a relevant number of figures. The person who reads this contribution should be able to classify and understand virtually any important organic reaction and gain the basics for organic synthesis research and development.

1. Introduction

Many millions of organic compounds are known today, either available in Nature (natural products) or prepared by Man (synthesis products). Each of these molecules has been obtained via a chemical reaction through the transformation of other organic molecules. Consequently, many different organic reactions have been and are used by scientists all over the world. During the XX century research has tremendously improved the amount of organic reactions available to the scientist. Today, not only a large variety of organic reactions is known but a detailed knowledge of their mechanism has been disclosed to allow a precise control of the chemistry of the products. Luckily, despite the large amount of known procedures, organic reactions present many similarities among themselves, such as the type of mechanism or the chemical nature of reactants and products. Thanks to these analogies, all of the organic reactions can be classified within a relatively small number of classes. A few classification strategies may exist, depending on the fact that the nature of mechanism, the structural change, or the type of reactive functional groups is considered. We will follow here the criterion based on the mechanism of the chemical transformation. A general section (Section 2) will precede the description of reaction categories in order to provide the reader with the basic knowledge and tools to understand, learn and apply the chemical reactions classified in Section 3.

2. The Organic Reaction

2.1. Chemical Reaction Notation: Equilibrium Arrows. Reactants and Products

A chemical reaction is a transformation where one or more reactants are partially or completely transformed into one or more products. According to the IUPAC Compendium of Chemical Terminology a reactant is a chemical substance that is consumed in the course of a chemical reaction, whereas a product is formed. The term reagent, sometimes used as a synonym of reactant, is commonly referred to the partner reagents which are added to the reaction mixture to bring about a reaction. In an organic reaction the reactant(s) and the product(s) are organic while the reagents may be organic or inorganic. Chemical reactions are commonly denoted as in Figure 1.

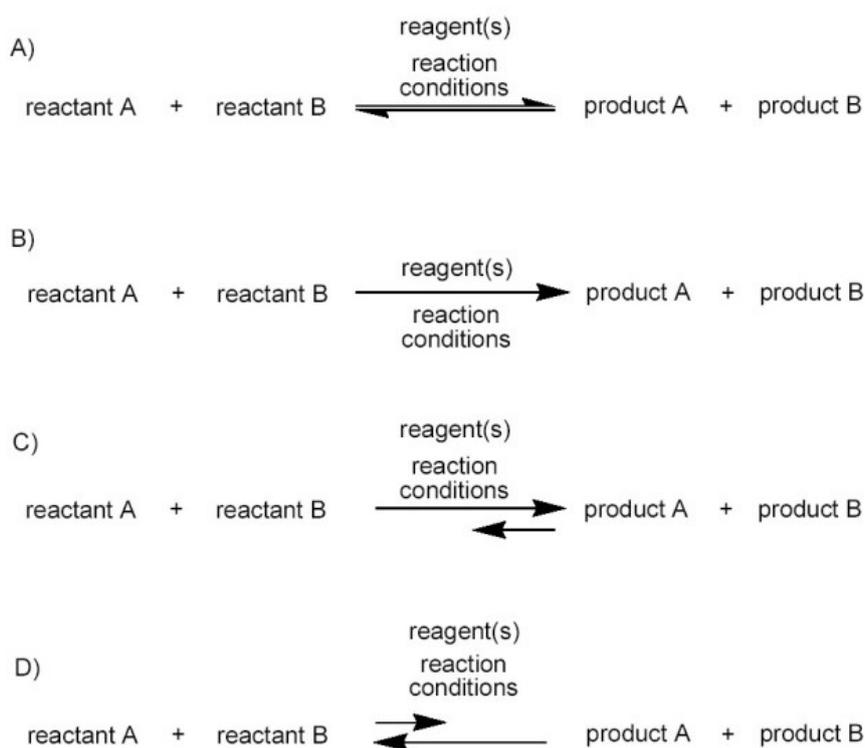


Figure 1: Commonly used symbolisms for organic chemical reactions. A) Generic reaction. B) Reaction largely shifted towards the formation of the product(s). C) Reaction mostly shifted towards the formation of the products. D) Reaction little shifted towards the formation of the products.

All reactions are equilibria (Section 2.3.). The equilibrium concentration of all reagents and products is determined by the reaction free energy and equilibrium constant. An equilibrium reaction is a reversible transformation; a double arrow pointing to opposite directions is inserted between reactants and products. However, many organic reactions are almost completely shifted towards the products and the residual concentration of the reactants at the end of the reaction is negligible. This happens when the equilibrium constant is very high. For those reactions a single arrow may be used pointing to the direction of the predominant species at the equilibrium.

It is worthy noting that in a chemical reaction one or more bonds are always broken and/or formed and one or more atoms change their relative position. In a resonance (or mesomerism) between two or more Lewis formulae (limit resonance structures) only electrons move. A resonance is not a chemical transformation; all of the structures refer to the same chemical species. In a resonance description a double-ended arrow is used (\leftrightarrow).

2.2. Mechanisms of Organic Reactions: The Arrow Notation

The symbolism shown in Figure 1 shows the chemical structures of the reactant(s) and of the product(s) but does not give any information about the way the reaction proceeds. More detailed information is given by the reaction mechanism. A mechanism is the

actual process of the chemical transformation. It shows how chemical species react and how the products are formed, the motion of atoms and electrons from one species to the other, which bonds are broken and formed, and the number of elementary steps involved in the whole reaction. It gives you the structure of all the intermediates and sometimes that of the transition states. A mechanism of a reaction must fit all the experimental data, first of all the chemical nature of the formed products. The gross mechanism of most common organic reactions is today known. However, many details are still unknown, due to the large number of variables involved. For many reactions even the gross mechanism has not been determined yet in an unambiguous manner and two or more hypotheses may be present.

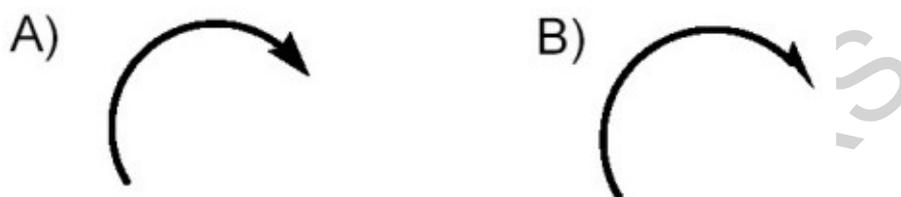


Figure 2: Curved arrows used for showing electrons motions in mechanisms. A) Motion of an electron pair. B) Motion of a single electron.

Mechanisms show the motion of electrons involved in bond breaking and bond making. These electrons are valence shell electrons and may be either bond or non-bond electrons. Motion of electron is shown using curved arrows. Depending on the number (either one or a pair) of electrons involved in a single motion, two types of curves have been defined (Figure 2).

Mechanisms are extremely important in Organic Chemistry. If the mechanism is known it is possible to predict the structures of the products, interpret the way a reaction proceeds, or figure out why a reaction is not successful. The mechanism of a given reaction is closely related to the chemical nature of the functional groups involved. Therefore the mechanism is invariable for similar compounds and may be applied to a potentially infinite number of chemical species with different substitution pattern far from the reaction center. The reaction classification given in Section 3 is based on the mechanism.

There are three types of mechanisms depending on the way bonds are broken and made:

- heterolytic
- homolytic
- pericyclic.

A general example of each type is depicted in Figure 3.

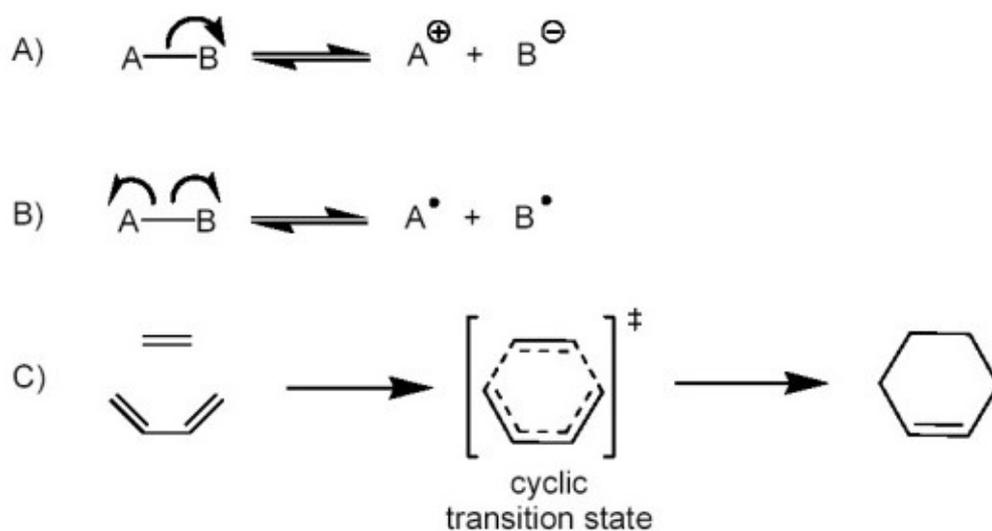


Figure 3: Reaction mechanism type depending on the nature of bond breaking and making. A) Heterolytic. B) Homolytic. C) Pericyclic.

In heterolytic reactions the bonds are broken in such a way that the bond electron pair is assigned completely to one fragment. These reactions are also called *ionic reactions*, since ionic reactants, products, or intermediates are usually involved.

When the bond is broken in a homolytic manner one bond electron remains with one fragment and the other bond electron with the other. Free radical intermediates are therefore involved and these transformations are consequently called *radical reactions*.

Finally, a third type of organic reactions not belonging to any of the previous two classes exists. No ionic or radical intermediates are formed during these transformations. They proceed in one single concerted step, with no intermediates, characterized by a cyclic transition state where bonds are simultaneously broken and formed. Accordingly, it is improper to describe the mechanism by using a curved arrow notation (Figure 2), though this representation is sometimes used for sake of convenience. This mechanism is correctly pictured via interaction of frontier molecular orbitals (FMO). Being cyclic transition states involved these reactions are called *pericyclic*.

2.3. Thermodynamics and Kinetics: Reaction Equilibrium and Reaction Rate

When we look at an organic reaction (generally speaking, any chemical reaction) we have to take into account two main concepts: the equilibrium and the rate of the reaction.

The conversion between reactants and products is governed by the *reaction free energy* ΔG , that is the difference between the free energy of the products and that of the reactants. A reaction is thermodynamically allowed when the free energy of the products is lower than that of the reactants, that is, ΔG is negative. When ΔG becomes equal to zero the equilibrium is reached and an equilibrium constant K_{eq} of the reaction

can be defined as a function of ΔG° , the variation in the standard free energies. The equilibrium constant K_{eq} is the ratio between the equilibrium concentration of the products and that of the reactants. The free energy has two components, the enthalpy H and the entropy S . Whereas ΔH of a reaction refer to the energy difference between the products and the reactants, ΔS is related to the disorder of the reaction. When a reaction equilibrium is studied, both factors must be taken into account. For instance, an important gain in entropy occurs when the number of products molecules is larger than that of the reactants.

A favorable thermodynamics is a necessary but not sufficient condition for a reaction to take place. In fact, the equilibrium can be reached in a relatively fast or low manner. If the rate is very low (for instance, months or even years or centuries) the net result is that the reaction basically does not proceed, even if thermodynamically allowed. Both the thermodynamics and kinetics must be favorable, that is the reaction must have a negative ΔG and should occur in a relatively fast manner. As far as kinetics is concerned the reactants must go through an energy barrier, called *the free energy of activation* ΔG^\ddagger . Once this energy is gained, partial bond breaking and bond making takes place giving a local high energy geometry, the *transition state*, which then evolves to the intermediate/product. The lower is the free energy of activation, the faster is the reaction.

All these concepts are conveniently depicted using energy vs. reaction profiles (Figure 4). The top profile is a one-step process, with no intermediates and one transition state corresponding to the single step from reactants to products. The total variation in free energy is negative (thus the reaction is thermodynamically possible). The shown free energy of activation is the energy barrier from reactants to products. A corresponding free energy of activation exists from the products to the reactants (not shown). The bottom plot refers to a two-step reaction which proceeds through an intermediate species. Each elementary step has its free energy of activation. In the example, the ΔG_1^\ddagger from the reactants to the intermediate is larger than that (ΔG_2^\ddagger) from the intermediate to the products. The first step is therefore kinetically more difficult than the second one and is called the slow step, or rate-determining step, of the reaction. Indeed, the rate of this step decides that of the whole process.

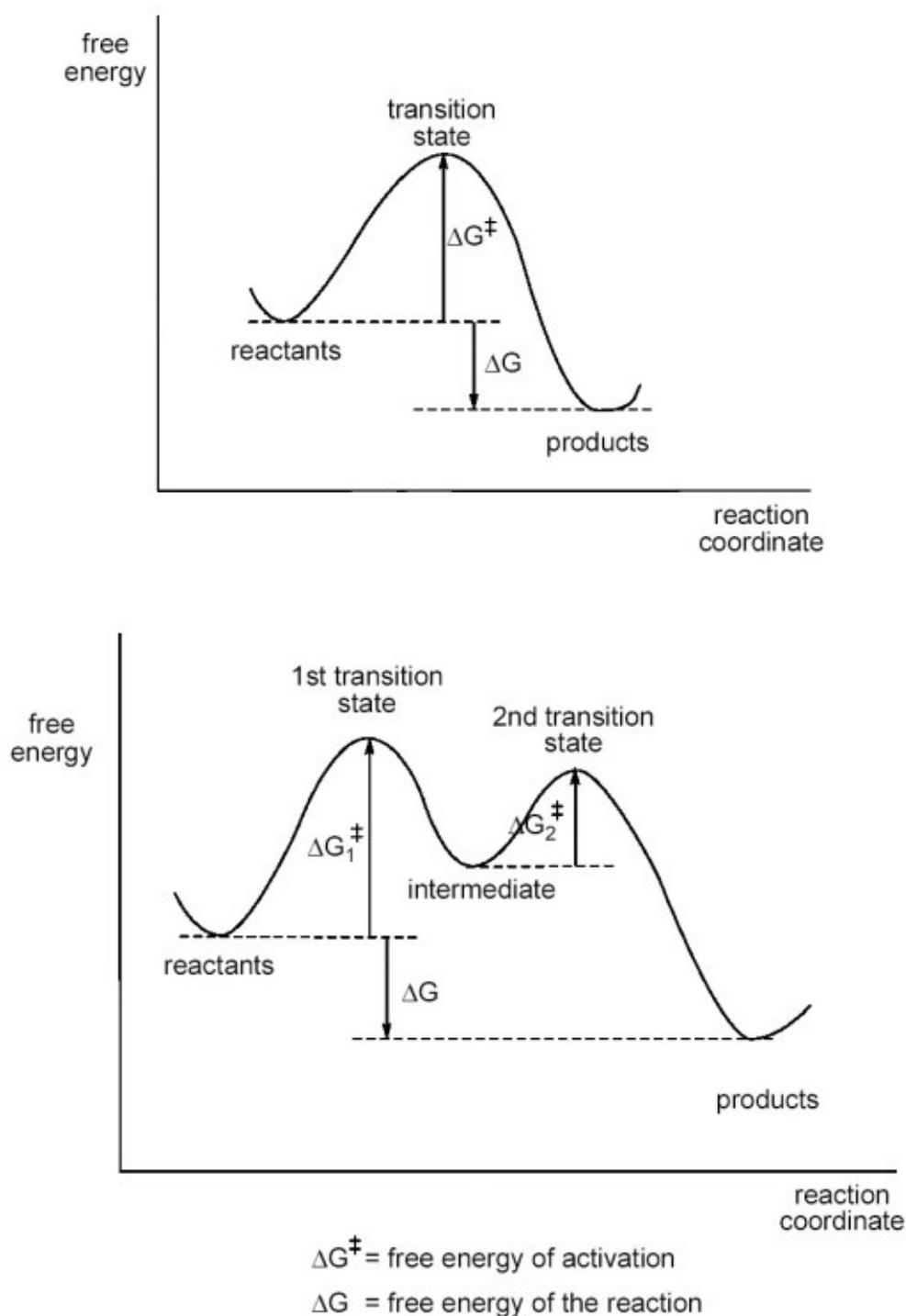


Figure 4: Energy vs reaction profiles for one- and two-step reactions.

In those reactions where two or more different products may be formed from the same reactants, each process has its own energy/reaction profile. In general, the product with the lower energy is associated to the transition state with the lower energy as well. The formation of such product is thermodynamically and kinetically favored with respect to the others. However, there are some cases where one product (e.g., A) has a lower energy than a second product (e.g., B) but the transition state leading to A is less stable

than that leading to B. The formation of A is thermodynamically favored whereas the formation of B is kinetically favored. The product A is called *thermodynamically controlled* and B *kinetically controlled* (Figure 5). The preferential formation of A rather than B, or vice versa, can be more or less successfully accomplished by running the reaction under *thermodynamic* or *kinetic control*, respectively. In the former case, the reaction is carried out at higher temperatures so to level off any kinetic deviation and allow the equilibrium to be established. The most stable product (A) will then be preferentially obtained. In the latter case the reaction is usually performed at low temperatures, so to maximize rate differences and stop the process well before the equilibrium is reached. The product with the lower energy of activation (B) will be preferentially formed.

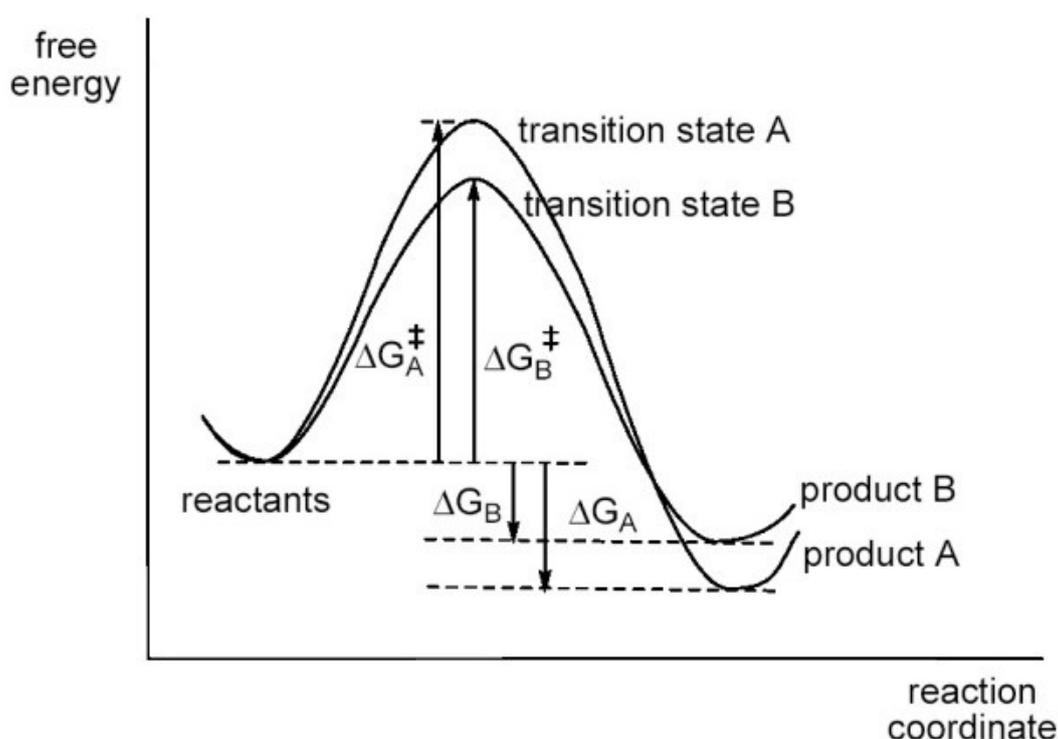


Figure 5: Thermodynamic and kinetic control: energy vs. reaction profiles.

Figure 6 shows an example of thermodynamically and kinetically controlled products. At lower temperatures the sulfonation of naphthalene (see: aromatic electrophilic substitution, Section 3.3.2.) gives the α -isomer, being the α position the most reactive site of naphthalene in the aromatic electrophilic substitution. However, this isomer is less stable than the β isomer because of steric interaction between the SO_3H group and the hydrogen atom at the position 8. Therefore the β isomer predominates at higher temperatures, under thermodynamically controlled conditions.

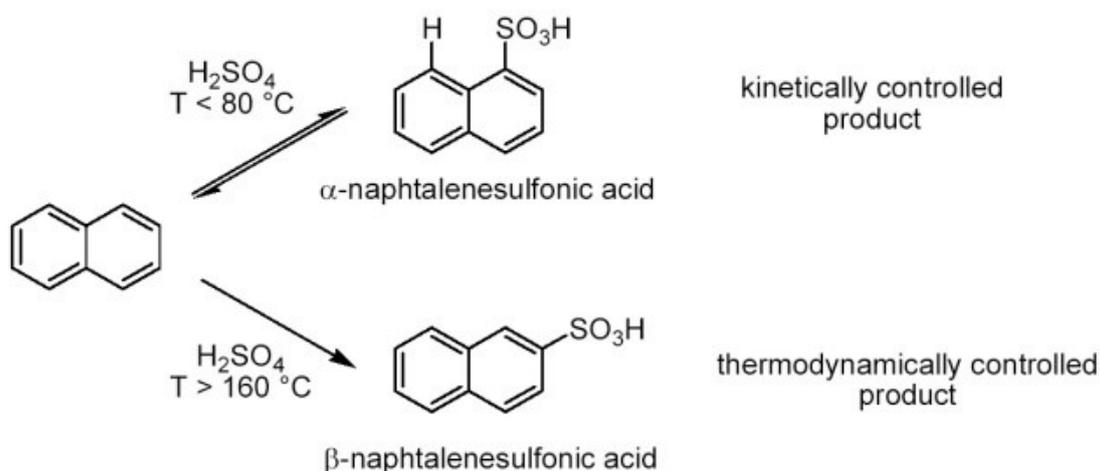


Figure 6: An example of thermodynamically and kinetically controlled products.

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Biographical Sketch

Abbotto, Alessandro was born in Milan in 1963, graduated in Chemistry from the University of Milan in 1989 (with honors). In 1990 he was awarded a prize (Dow Italy) for best student in Chemistry and Industrial Chemistry of the University of Milan. Graduate student from 1990 to 1993, receiving his Ph.D. in Chemistry from University of Milan (Mentor: Prof. G. A. Pagani). He worked at the University of Berkeley, CA (USA) (Mentor: Prof. Andrew Streitwieser) as a post-doctoral fellow (NSF funding) in 1994- 1995 and then at the University of Erlangen-Nuernberg, Erlangen (D) (Mentor: Prof. Paul v. R. Schleyer) with a NATO fellowship in 1995. He joined the Materials Science Faculty of the University of Milan in December 1995 as Assistant Professor in Organic Chemistry. In 1998 he moved to the University of Milano-Bicocca where he got an Associate Professor position in Organic Chemistry in 2001. Co-author of a university textbook in Heterocyclic Chemistry, ca. 80 papers in international scientific journals including 3 international patents, 11 invited lectures and ca. 100 communications at national and international meetings. Member of the Scientific Board of CMG (University of Milano Bicocca - Sapio Industrie network); application reviewer for national and international funding agencies (I-MIUR, I-INSTM, USA-NSF, CAN-CFI Canada Foundation for Innovation). Peer reviewer for many ACS, Wiley-VCH and other journals. Current scientific interests involve design, synthesis and characterization of organic and organometallic materials (including 1D-3D polar organic chromophores for nonlinear optics and multiphotonics, ion-templating multidimensional hybrid NLO-phores, multi-branched systems, hybrid organic-inorganic/metallic materials) for advanced applications in optoelectronics and (nano)photonics.