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## Dynamers: dynamic molecular and supramolecular polymers

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## Abstract

Dynamers may be defined as constitutional dynamic polymers, i.e. polymeric entities whose monomeric components are linked through reversible connections and have therefore the capacity to modify their constitution by exchange and reshuffling of their components. They may be either of molecular or supramolecular nature depending on whether the connections are reversible covalent bonds or non-covalent interactions. They are formed, respectively, either by polycondensation with functional recognition or by polyassociation with interactional recognition between the connecting subunits. Both types are illustrated by specific examples implementing hydrogen bonding on one hand and acylhydrazone formation on the other. The dynamic properties confer to dynamers the ability to undergo adaptation and driven evolution under the effect of external chemical or physical triggers. Dynamers thus are constitutional dynamic materials resulting from the application of the principles of constitutional dynamic chemistry to polymer science.

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Keywords: Supramolecular chemistry; Constitutional dynamic chemistry; Molecular recognition; Hydrogen bonding; Acylhydrazone formation; Adaptation; Dynamic materials

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## 1. Introduction

The extension of the concepts and features of supramolecular chemistry [1–3] from discrete species to polymolecular entities is opening novel perspectives in materials science. It defines a field of supramolecular materials that rests on the explicit implementation of intermolecular interactions and recognition processes for controlling the build-up, the architecture and the properties of polymolecular assemblies as they emerge from their components through self-organization [1–4]. Such spontaneous but directed self-assembly is of major interest for the supramolecular design, synthesis and engineering of novel materials presenting novel properties.

Supramolecular chemistry is by nature a dynamic chemistry [5] in view of the lability of the noncovalent interactions connecting the molecular components of a supramolecular entity [1–3], which allows for incorporation, decorporation, rearrangement of partners in the supramolecular species. Importing such dynamic features into molecular chemistry requires shifting from stable to labile covalent bonds, so as to endow molecular species with the ability to undergo similar dynamic exchange and reorganization processes by virtue of the reversible formation and breaking of covalent connections.

This change in outlook amounts to take a standpoint opposite to the traditional one and consider that the lability resulting from reversible connections rather than being a drawback, gives access both to the richness of constitutional diversity and to the benefits of adaptability.



Fig. 1. Scope of constitutional dynamic chemistry, covering both molecular and supramolecular entities.

One may conjecture that an intriguing line of development of chemistry is thus being fueled by a basic paradigm shift from a constitutionally static to a *constitutionally dynamic chemistry* (CDC) [3], encompassing *both* covalent molecular [6,7] and non-covalent supramolecular entities (Fig. 1) [1,5,7]. These may be considered as, respectively, chemically dynamic, involving a reversible chemical reaction, and physically dynamic, based on physical non-covalent interactions.

### 2. Constitutional dynamic chemistry and materials

## Reversibility, exchange, diversity

Feeding-back the dynamic features, characteristic of supramolecular chemistry, into molecular chemistry implies looking at molecules as labile entities, in contrast to the usual longing for stability, and opens novel perspectives to covalent chemistry. It requires searching for reversible reactions that allow the making and breaking of covalent bonds, preferentially under mild conditions. These developments are embodied in the recent emergence of dynamic combinatorial chemistry as a powerful means for generating dynamic, effector-responsive molecular diversity [7,8].

Thus, *dynamic chemistry* comprises not only *motional dynamics*, but also *constitutional dynamics*, changes in constitution concerning the nature, number and arrangement of the components of a molecular or supramolecular entity, generating molecular and supramolecular diversity through reversibility of covalent bonds and of non-covalent interactions.

CDC is defined by chemical entities undergoing continuous recomposition, recombination, reorganization, construction and deconstruction by incorporation, decorporation or reshuffling of components, under the pressure of internal or external factors. The system may respond to such effects through selection of the most suitable components among those available by expressing the constituent(s) presenting best adaptation to a given situation (Fig. 2).

As supramolecular chemistry is by nature constitutionally dynamic, supramolecular materials are *dynamic materials* (DYNAMATs) [5]. Extending this notion to covalent species, CDC covers constitutional dynamic materials (CDMs) on both the supramolecular and the molecular levels.

## CONSTITUTIONAL DYNAMIC CHEMISTRY

MOLECULAR DYNAMIC CONSTITUTIONAL DIVERSITY SUPRAMOLECULAR > chemical systems undergoing continuous exchange/recombination/reorganization under the pressure of internal external factors

> deconstruction and reconstruction

SELECTION through Dynamic Constitutional Diversity responding to the pressure of internal/external factors

Fig. 2. Constitutional dynamic chemistry, constitutional diversity generation and selection.

Dynamic materials may be defined as materials whose constituents are linked through reversible connections (non-covalent or covalent) and are able to continuously reorganize through assembly/disassembly processes and exchange of components in a given set of conditions, usually under thermodynamic control [5,7], but eventually involving kinetic bottlenecks or traps.

#### 3. Dynamers: constitutional dynamic polymers

Focusing on a specific class of materials, polymers, one may designate under the term DYNAMERS, dynamic polymers [9,10], polymeric materials exhibiting reversible formation and component exchange. They comprise both the supramolecular polymers [10-13] that are dynamic by nature and molecular polymers that are dynamic by intent, due either to the presence of a non-covalent or to the introduction of a covalent reversibility cassette (Scheme 1). Their formation and dynamic character result either from recognition-directed reversible polyassociation of components through complementary interactional groups (supramolecular, non-covalent, physical, interactional recognition) or from reversible polycondensation of components through *complementary* functional groups (molecular, covalent, chemical, functional recognition), respectively (Fig. 3). In view of the ability of dynamers to build up by self-assembly [1–4] and to select in principle their components in response to external stimuli or to environmental factors, they behave as *adaptive materials* [5,7,10].

Dynamers may be obtained from hetero- or homocomplementary monomers (Fig. 4) by the usual type of polymerization processes (Fig. 5). They may be of either main chain type, as those pictured below, or involve reversible side-chain attachment. They display a number of particularly attractive features for polymer chemistry. The present description will draw mainly from work performed in the laboratory of the author.

#### 4. Supramolecular dynamers

Supramolecular polymers are defined as the entities generated by the polyassociation of molecular monomers bearing complementary binding groups capable of connecting through the usual non-covalent interactions implemented in supramolecular chemistry: electrostatic, hydrogen bonding, donor-acceptor, Van der Waals as well as metal ion coordination.



Scheme 1. Schematic representation of main-chain dynamers in which complementary ditopic monomers are linked by either supramolecular or molecular reversibility cassettes X, Y, and Z, conferring dynamic character through reversible connections, noncovalent interactions or reversible covalent bonds, respectively. X, Y, and Z may be the same or different. In conventional polymers, they represent covalent bonds that are not reversible in the conditions considered.

## DYNAMERS

DYNAMIC POLYMERS



Fig. 3. Dynamers: dynamic (reversible) polymers of molecular (covalent) and supramolecular (non-covalent) nature.

## DYNAMER CHEMISTRY

## Generation of DYNAMIC POLYMERS

 $\Rightarrow$  Divalent, Trivalent, Tetravalent monomers :

Fig. 4. Dynamer chemistry: types of main-chain dynamers.

## DYNAMER GENERATION – DYNAMIC MATERIALS



Fig. 5. Dynamer generation processes.

A number of reviews have been devoted to supramolecular polymers [10–15]. The presentation below will be limited to entities based on hydrogen bonding investigated in the author's laboratory. A more detailed description may be found in Refs. [10, 11] (Chapter 14).

The first system studied involved the molecular recognition-directed polyassociation of chiral ditopic molecular monomers comprising a tartaric acid-type spacer bearing two complementary triple hydrogen bonding patterns derived from uracil, TU<sub>2</sub>, and from 2,6-diaminopyridine,  $TP_2$  (Fig. 6). Whereas the starting compounds were solids, the process resulted in the formation of liquid crystalline polymeric entities presenting a thermotropic mesophase over an exceptionally wide temperature ranger (over 200°) [16]. Very long helical fibers, based on a triple helix superstructure resulting from helical wrapping of three supramolecular strands, were observed by electron microscopy [17]. Related rigid-rod polyassociations gave lyotropic mesophases [18].

Supramolecular polymers have been obtained with various other types of interaction patterns between

monomers, from a single hydrogen bond between a carboxylic acid and a pyridine unit [15,19] to four hydrogen bonds between self-complementary heterocyclic groups. In particular, in the latter case, the extended entities formed display a number of interesting physico-chemical features [13,20]. Modifications of the liquid crystalline properties have been induced in ternary mixtures by means of chiral additives [21].

Supramolecular polymeric fibers and a variety of materials have been obtained from the association of two homoditopic heterocomplementary monomers through sextuple hydrogen bonding (Fig. 7) [22]. Fiber formation was shown to be strongly influenced by stoichiometry, as well as by the addition of end-capping agents and of tritopic cross-linking units (Fig. 7), which led to very pronounced changes in morphology of the material observed by electron microscopy.

This system also produced highly viscous *supramolecular gels* in organic solvents of low polarity and displayed interesting rheological properties as a function of shear, temperature, concentration, stoichiometry and additives [23].



Fig. 6. Supramolecular polymer  $(TP_2,TU_2)_n$  generated by recognition-controlled polyassociation of heterocomplementary monomers  $TP_2$  and  $TU_2$ , derived from tartaric acid, through triple hydrogen bonding.



Fig. 7. Ditopic complementary monomers, monotopic end-capping agents and tritopic cross-linking monomer bearing complementary patterns for sextuple hydrogen bonding. (Bottom) Main-chain supramolecular polymer generated via sextuple hydrogen bonding.

Janus-type recognition groups, such as barbituric or cyanuric acid and triamino-pyrimidine or -triazine derivatives, represent a special type of cross-linking unit by virtue of their ability to interact through both their hydrogen bonding faces. The incorporation of two such complementary groups into ditopic molecular monomers provides entries towards the generation of 'ladder' or 'double-ribbon' polyassociations (when only a single ditopic component is used) or of twodimensional supramolecular polymeric networks (from two complementary ditopic components) (Fig. 8).

Indeed, monomers in which two such groups are grafted onto tartaric acid spacers (e.g. replacing P and



# 2-D Supramolecular Polymers via H-Bond

Fig. 8. Two-dimensional supramolecular polymers generated from tartaric acid-derived monomers bearing Janus-type recognition groups presenting complementary sextuple hydrogen bonding patterns.

U units in  $TP_2$  and  $TU_2$ , see Fig. 6) generate very high molecular weight aggregates that may be characterized by various physical methods [24].

The generation of the supramolecular assemblies usually involves hierarchical self-organization along a conditional sequence of steps, as is the case for the  $(TU_2 + TP_2)$  assemblies (Fig. 6), which undergo first formation of a  $(TU_2 - TP_2)_n$  supramolecular strand, then columnar triple helical wrapping and finally, lateral association by side-chain entangling into helical fibers.

Supramolecular columnar discotic liquid crystals may be generated in a two stages process. Thus, the tautomerism induced self-assembly of three units of the lactam-lactim form of disubstituted derivatives of phthalhydrazides yields a disk-like trimeric supermolecule. Thereafter, these disks self-organize into a thermotropic, columnar discotic mesophase [25].

Along the same lines, a bow-shaped molecule bearing a self-complementary quadruple hydrogenbonding array generates, in hydrocarbon solvents,

highly ordered supramolecular sheet aggregates that subsequently give rise to gels by formation of an entangled network (Fig. 9) [26]. The process exemplifies the generation, by hierarchical selfassembly, of highly organized supramolecular materials presenting novel collective properties at each level of organization.

Generation of supramolecular fibrils and fibers has been found to result from stacking-promoted, hierarchical self-organization of molecular strands



Fig. 9. Formation of a ribbon-type supramolecular polymer by polyassociation of a self-complementary, bow-shaped monomer through quadruple hydrogen bonding.

presenting an enforced [27,28] or an effector induced [29] helical conformation.

## 5. Molecular dynamers

Molecular dynamers, reversible covalent polymers, open a range of perspectives to polymer chemistry. Even though exchange reactions have long been known in macromolecular chemistry (see pp. 902–915 in Ref. [6]) and have been put to use even in large scale industrial processes (involving, e.g. transesterification), the exploitation of reversible polymerization has been hampered by the difficulties in controlling the process. The primary focus of polymer methodology has been on trying to avoid exchange reactions and to produce chemically as well defined as possible, unique polymers, in particular for industry. Taking the opposite standpoint consists in deliberately pursuing constitutional diversity rather than emphasizing unicity. It involves to explore the generation of diversity through reversibility, which allows component exchange leading to highly diverse populations, combinatorial libraries of polymeric constituents in dynamic equilibrium (Fig. 10). Reversible reactions are presently receiving increasing attention and provide a means for developing new materials exhibiting unusual features. Recent covalent polymers investigated for their reversible properties have included entities based on various reactions such as: transesterification [30-33], transetherification [34], Diels-Alder reaction [35,36], [2+2] photodimerization [37], radical reaction [38] and boronate ester formation [39].

One may distinguish (1) *self-contained reversible reactions* (*holo* reactions), where all atoms present in the starting compounds are also present in the product (e.g. the Diels–Alder reaction and cycloadditions in general, the Michael addition, hemiketal and aldol condensation, etc. and their retro processes); (2) *exchange reactions*, where isofunctional components are exchanged from starting compounds to products (e.g. transesterification, transimination, etc.); (3) *nonself-contained reversible reactions*, where an ancillary molecule (such as water) is formed (e.g. carbonyl-amine condensation, ester and amide formation, etc.).

Exchange and non-self-contained reactions may be manipulated or affected (e.g. their reversibility may be inhibited) by acting upon the ancillary compound or the isofunctional partner, whereas self-contained reactions respond to physico-chemical parameters (temperature, pressure, medium).

Among the known reversible covalent reactions [6-8], amino/carbonyl condensations to give C=N products such as imines, hydrazones and oximes (Scheme 2), are particularly attractive in view of the very wide range of structural variations available, the easy synthetic accessibility, the control through conditions of yields, rates and reversibility, as well as their role and potential for application in both biological/medicinal [7,8,40] and materials sciences.

## 6. Polyacylhydrazones

The formation of hydrazones and acylhydrazones by condensation of hydrazines and hydrazides,



### DYNAMER EXCHANGE PROCESSES

Fig. 10. Component exchange in dynamers.



Scheme 2. Reversible condensation reaction in imine and acylhydrazone formation.

respectively, with carbonyl groups has been implemented for the generation of biologically active substances [40,41] and of polymeric materials (polyhydrazones [42–45]; polyacylhydrazones [46– 50] and references in [9]). More specifically, acylhydrazone formation (Scheme 2) displays reversibility under mild conditions [41,51–53] with acid catalysis, regenerating the starting reagents. This reversibility can be exploited in the presence of additional aldehydes or hydrazides to produce new acylhydrazones as a result of aldehyde or hydrazide exchange promoted by acid catalysis and/or heat.

The acylhydrazone functionality provides both dynamic character, through the reversibility of the imine-type C=N unit, and hydrogen bonding sites through the amide group (Scheme 3). When dihydrazides are reacted with dicarbonyl compounds, polycondensation occurs and polyacylhydrazone polymers are formed (Scheme 4a) that present particularly attractive features: (i) they are strict alternating copolymers; (ii) they form in high yield under mild conditions; (iii) they are dynamic covalent polymers (molecular dynamers) due to the reversibility of the acylhydrazone bond, and (iv) they are therefore capable of exchanging their components; (v) they contain an amide group providing hydrogen bonding interactions, as in polyamides.



Scheme 3. Representation of the specific features of the acylhydrazone functionality displaying both a hydrogen bonding amide group and a reversible imino bond.

Thus, by virtue of the special properties of the acylhydrazone moiety, polyacylhydrazones may be considered as *reversible polyamides*, endowing this most important class of polymers with dynamic character and behavior of living polymer type (Fig. 11). Through monomer exchange, they allow the generation of novel, constitutionally modified alternating copolymers, exhibiting physical properties different from those of the original unexchanged polymer. They are able to incorporate, decorporate or reshuffle their constituting monomers, in particular in response to external stimuli and environmental physical or chemical factors (heat, light, chemical entities, etc.). They also offer the possibility of obtaining new crossover entities by mixing different dynamers. The polycondensation and exchange processes may be performed under mild and adjustable conditions. Thus, the features of polyacylhydrazone dynamers provide a powerful and easily implemented methodology for the generation of new materials presenting adaptive behavior.

A number of polyacylhydrazones have been prepared from selected dihydrazides and dialdehydes and shown to undergo exchange of both their components under various conditions (Scheme 4b,c) [9]. Remarkable mechanical properties have been obtained. Thus, the combination of specific difunctional monomers was found to afford either a very strong flexible film or a soft stretchy film; the latter could be converted into a strong hard film by dynamic incorporation of other monomers [54]. Bond crossover recombination between the components of neat polymer films was achieved in a dynamic polymer blend [55].

Similar formation and exchange experiments have also been performed with polyimines (Scheme 5) derived from various diamines and dialdehydes producing, in particular, changes in absorption and fluorescence spectra as well as in solubility in organic versus aqueous medium [56].



Scheme 4. (a) Generation of polyacylhydrazone dynamers by polycondensation; (b, c) monomer exchange reactions of polyacylhydrazones.

One may note that the polycondensation product of  $H_2NNHCO-(CH_2)_6$ -CONHNH<sub>2</sub> with OHC-(CH<sub>2</sub>)<sub>4</sub>-CHO represents a dynamic analog of nylon, which one might term '*dynalon*'.

It is clear that the dynamic polyamide features offered by polyacylhydrazones may be extended to other classes of polymers, in particular, dynamic polyureas and dynamic polyurethanes result from reaction of difunctional components bearing the corresponding groups, -NH-CO-NHNH<sub>2</sub> (or H<sub>2</sub>NHN-CO-NHNH<sub>2</sub>) and -O-CO-NHNH<sub>2</sub>, respectively, with a dicarbonyl component.

One may also stress that the amide and amine/ imine groups, present in the hydrazide/acylhydrazone functionalities, both play a major role in biological molecules and processes. Extension towards the generation of dynamic biopolymers (e.g. dynamic peptoids or dynamic nucleic acid analogs) are being conducted [57].

#### 7. Double dynamic polymers

Combining monomers that bear complementary non-covalent interaction units as well as complementary reversible functional groups allows the generation of polymers presenting *double dynamic behavior*, polymers that are dynamic on both molecular and supramolecular levels. This has for instance been realized by combining sextuple hydrogen bonding groups (Fig. 7) with acylhydrazone formation (Scheme 2) as illustrated in Fig. 12 [58]. Such developments implement dynamic features for both selection within mixtures of components and diversity generation via scrambling of monomers. Indeed, self-selection within a mixture of monomers is expected to occur between monomers bearing complementary functional groups or complementary recognition patterns. On the other hand, scrambling of compatible functions or recognition units generates dynamic diversity.

# 8. Implementation of dynamers towards driven evolution

The adaptive features presented by dynamers may be harnessed to achieve driven evolution of chemical systems.



## $\Rightarrow$ CONSTITUTIONAL DYNAMIC MATERIALS

Fig. 11. Polyacylhydrazones as dynamic, reversible, polyamides.



Scheme 5. Component exchange in polyimines.



Fig. 12. Double dynamic polymers containing both reversible hydrogen bonding patterns and reversible acylhydrazone covalent connections.

In order to realize adaptive capacity, a major factor is to establish fast equilibration between the constituents of the dynamic set. Lewis acid catalysis, in particular by scandium(III) ions, was found to very significantly accelerate component exchange in helical heterocyclic polyhydrazone strands, yielding dynamic constitutional diversity among helical constituents [59]. Subsequent addition of zinc(II) ions enforced an evolution of the equilibrating set of helical strands towards that constituent that was able to form a complex of  $[2\times 2]$  grid-type with the metal ions (Fig. 13). In this process, the scandium(III) ions act as generator of dynamic behavior, dynamogenic catalyst, whereas the zinc(II) ions are drivers, imposing a selection pressure.

In a second case, a library of polyimines was generated from an aromatic dialdehyde and two diamines, an aliphatic and an aromatic one; as expected, it contained mainly the polyimine of the aliphatic diamine (Fig. 14). Addition of zinc(II) ions, which bind preferentially to the more basic aliphatic amine groups, induced a decorporation of the aliphatic diamine leading to a constitutional reorganization, whereby the initial polyimine was converted into the fully aromatic one. In a further step, after completion of the exchange, the addition of excess zinc(II) ions provoked the appearance of an intense novel fluorescence [60].

From a conceptual point of view, these results express a synergistic adaptive behavior: the addition of an external effector (e.g. zinc(II) ions) drives a constitutional evolution of the dynamic mixture towards the selection and amplification of that species that allows the generation of a (optical) signal indicating the presence of the very effector that promoted its formation in the first place. It embodies a 'constitutional dynamic self-sensing' process, that extends the range of self-processes [1] towards dynamic devices. Moreover, the self-sensing behavior, where an effector induces the upregulation of its own detector, amounts to a further step in the emergence, at the molecular and supramolecular levels, of dynamic systems of increasing complexity.

Dynamic component selection with expression of the optimal constituent may also be driven by selforganization of an extended polymolecular assembly. Thus, component selection driven by gel formation has been found to occur in a dynamic hydrogel gel, leading to the generation of the entity presenting highest viscosity [61].

Reversible polymerization can be directed by internal factors such as chain folding as found for specific polyimines [62].

### 9. Conclusion—outlook

The dynamic features of dynamers resulting in component exchange readily allow for the introduction of new difunctional complementary monomers into the polymer backbone at the expense of displacing monomer units initially present. The end result is the generation of a highly diverse dynamic combinatorial library [6,7] of alternating molecular or supramolecular copolymers, containing variable amounts of the new and the displaced monomers, whose properties differ from those of the original one (Fig. 15). Adequate selection of the monomeric components, in principle, makes possible the modulation of the properties of the polymer for specific purposes by incorporation/decorporation processes. For instance, alternating polyacylhydrazones copolymers are able to reversibly exchange their components against different ones, thus allowing the incorporation or decorporation of either a dihydrazide or a dicarbonyl monomer into the polymer backbone and leading to a set of copolymers presenting diverse compositions and properties. Such processes give access to doping and tuning of dynamer constitution by selective incorporation, decorporation, or reshuffling of different monomeric components yielding ultimately polymers with 'dial-in' properties. Physical properties that may change upon exchanging monomers include: solubility, hydrophobicity, hydrophilicity, molecular weight, absorbance, fluorescence, conductivity, castability, thermal behavior, viscosity, and elasticity. Designed modification of such features is both of basic interest and of significant potential in applied materials science, as is indicated for instance by the modification of mechanical properties of polyacylhydrazone polymers [54] and the formation of dynamic polymer blends [55] mentioned above.

Constitutional plasticity, as displayed namely by a dynamer library, is of special interest for the design of dynamic 'smart' materials. It may confer to materials the capacity to mend themselves and to undergo



Fig. 13. Generation of a dynamic library of helical strands by scandium(III) catalyzed hydrazone exchange and driven evolution towards formation of a  $[2\times2]$  metallosupramolecular grid-type architecture upon addition of Zn(II) ions. The helical polyheterocyclic strands are shown here in an extended linear form for clarity.



Fig. 14. Generation of a dynamic library of oligo-fluorenylimine polymers and zinc(II) driven component exchange and selection, converting the FlCy dynamer into the FlFl one.

self-healing, self-repairing processes [63–65], as found in biomolecular materials [66]. It also allows the expression/fine tuning of a given virtual (latent) property and/or the production of an adaptive response under the pressure of internal or external factors.

The ability of dynamers in particular and to constitutional dynamic systems in general to respond

## MAIN-CHAIN DYNAMERS





⇒ DYNAMIC DIVERSITY RESULTING FROM SCRAMBLING OF MONOMERS

Fig. 15. Generation of dynamic diversity in main-chain molecular or supramolecular dynamers by exchange or reshuffling of complementary components.

to external solicitations rests on the selection of the optimal components among those available in order to adapt to changing situations. It implements self-assembly and self-organization by selection [3], whereby the system selects the components that generate the best adapted materials.

Furthermore, the reversibility of dynamers makes these materials also of much value for the development of dynamic films and coatings, as well as for 'dynamic formulation', allowing slow release of active ingredients in pharmaceutical chemistry and medicine (controlled drug delivery), in agrochemistry, and in home and personal care.

Finally, dynamers present environmental and biological degradability, a feature of high potential interest in areas as different as biomedical applications [67] and waste management.

In conclusion, the operation of constitutional dynamics in polymer chemistry, and more generally in materials science, confers to the polymeric entity and to the material the ability to respond to external stimuli and to environmental conditions, i.e. adaptability, a major tenet of constitutional dynamic chemistry, that enables the development of adaptive chemistry [3].

The further exploration of these features may be expected to open wide perspectives for basic research in polymer science as well as to give access to a range of novel properties and applications in polymer technology.

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