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Amphiphilic conetworks: Definition, synthesis, applications

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Abstract

The emerging field of amphiphilic conetworks (APCNs) is critically reviewed. A definition of APCNs is proposed and discussed in depth. The field of APCN science, born in 1988, is delineated and differentiated from similar constructs (e.g. interpenetrating networks, grafted networks). Among the justifications for sustained scientific/technological interest in APCNs are hosts of high-technology applications, some in commercial use and some under development. A large amount of information scattered throughout the scientific and patent literature is collected and analyzed, and the strategies for the synthesis of APCNs are identified, systematized, and evaluated. It is concluded that syntheses published to date, including those of extended-wear soft contact lenses, can be subdivided into three main groups: free radical induced polymerizations, ionic living polymerizations, and chemical combinations of hydrophilic and hydrophobic prepolymers. The strengths and weaknesses of these strategies are analyzed. Conclusions in regard to APCN synthesis and network topology are reached. The review concludes with a brief glimpse into the future.

Keywords: Amphiphilic; Network; Conetwork; Hydrogel; Interpenetrating network, Synthesis strategies; Contact lenses

Contents

Abbreviations: A, acrylate; AAc, acrylic acid; AAm, acryl amide; APCN, amphiphilic conetwork; BA, *n*-butyl acrylate; Bd, butadiene; BMA, *n*-butyl methacrylate; BzMA, benzyl methacrylate; CL, caprolactone; DMAAm, dimethyl acrylamide; DMAEMA, dimethylaminoethyl acrylamide; EtA, ethyl acrylate; GMA, 2,3 propandiol-1-methacrylate; HEA, hydroxyethyl acrylate; HEMA, hydroxyethyl methacrylate; HI, hydrophilic; HO, hydrophobic; IPN, interpenetrating network; (D,L)LA, lactic acid; $M_{c,HI}$, molecular weight of hydrophilic segment between crosslinking sites; $M_{c,HO}$, molecular weight of hydrophobic segment between crosslinking sites; MA, methacrylate; MAAc, methacrylic acid; MAAm, methacrylamide; MMA, methyl methacrylate; MW, molecular weight; MWD, molecular weight distribution; NIPAM, *N*-isopropyl acrylamide; P, poly; PBMA, poly(*n*-butyl methacrylate); PDMS, polydimethylsiloxane; PDXL, poly(1,3-dioxolane); PEG, poly(ethylene glycol); PIB, polyisobutylene; PROx, poly(2-alkyl-2-oxazoline); PSt, polystyrene; PTHF, polytetrahydrofuranp; PNVP, poly(*N*-vinyl pyrrolidone); PODVE, poly(octadecyl vinyl ether); PPO, poly(propylene oxyde); PVCL, poly(*N*-vinyl caprolactam); PεCL, poly(ε-caprolactone); SEMA, sulfoethyl methacrylate; St, styrene; T_g, glass transition temperature; THF, tetrahydrofuran; Y, $SiPh(SiH_2)OEt$ = bis[(dimethylsilyl)oxy]-[(etoxydimethylsilyl)oxy]phenylsilane.

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1. Definition

A review ought to start with a definition.

While many individuals and groups are actively engaged in amphiphilic conetwork research, a rigorous definition of this class of complex materials has not yet been proposed. To fill this gap we propose the following definition:

Amphiphilic conetworks (APCNs) are two-component networks of covalently interconnected hydrophilic/hydrophobic (HI/HO) phases of cocontinuous morphology; as such they swell both in water and hydrocarbons, and respond to changes in the medium by morphological isomerization ('smart' networks).

In the vernacular, *APCNs are hydrogels that swell in hydrocarbons*.

The three key coexisting characteristics of an APCN are: the simultaneous presence of HI and HO phases (two T_g's), covalent linkages between the phases, and phase cocontinuity (i.e. bipercolation). Phase cocontinuity is emphasized because the unique properties of APCNs cannot be explained by considering only the primary nature (HI and HO moieties) of the network segments; cocontinuity, i.e. the secondary organization or domain architecture of the system, must be part of the definition. Networks that contain dispersed, i.e. not cocontinuous, HI/HO phases are outside the scope of this definition. True, such systems may contain both HI and HO phases and exhibit two T_g's, however, since the phases are not cocontinuous, they *as a whole* do not exhibit amphiphilic character. Only if both the HI and HO phases are continuous are both water and hydrocarbons (or two solvents of very different polarities) able to permeate/percolate separately or simultaneously from edge to edge of the *entire* construct; and only then can morphological isomerization (i.e. profound phase rearrangement) occur over the entire system. Indeed, HI/HO phase cocontinuity/bipercolation renders APCNs unique among amphiphilic systems.

APCNs are smart or intelligent: they respond in a predictable manner to the medium they are in contact with. Fig. 1 helps to visualize medium-mediated morphological isomerization of an APCN. The cartoon in the center of the figure indicates an APCN in the dry state with two-phase bicontinuous morphology. In a common good solvent (top cartoon) for both the HI and HO constituents, the entire system is swollen. The lower two cartoons indicate swelling by HI and HO solvents. In the HI solvent, only the HI phase is swollen while the HO phase is collapsed; the latter wants to separate and precipitate but is unable to do so because it is covalently bound to the swollen HI phase. Importantly, in spite of the swollen HI phase, the continuity of the HO phase is maintained on account of the relative composition of the HI and HO constituents in the system, and because of the covalent bonds that connect the phases. Conversely, in the HO solvent the HO phase swells but the continuity between the collapsed HI phases is still maintained in spite of the intrusion of the HO solvent. Phase rearrangement is dynamic (reversible) upon changing the milieu (see the $\leftrightarrows$ in Fig. 1) and may contribute to the biocompatibility of many APCNs (see below).

Since APCNs swell in water they are hydrogels (satisfy the definition of hydrogels [1]); however, they also swell in hydrocarbons. Therefore, a more relaxed definition of APCNs is: hydrogels that swell in hydrocarbons.

A further requirement is that each and every terminus of the HI and HO segments must be connected to the network so that every chain element contributes to the load-bearing capability of the APCN. Ideally, APCNs do not contain dangling ends. In reality, a few dangling chain ends are always present at the extremities of any network (ideal systems included),

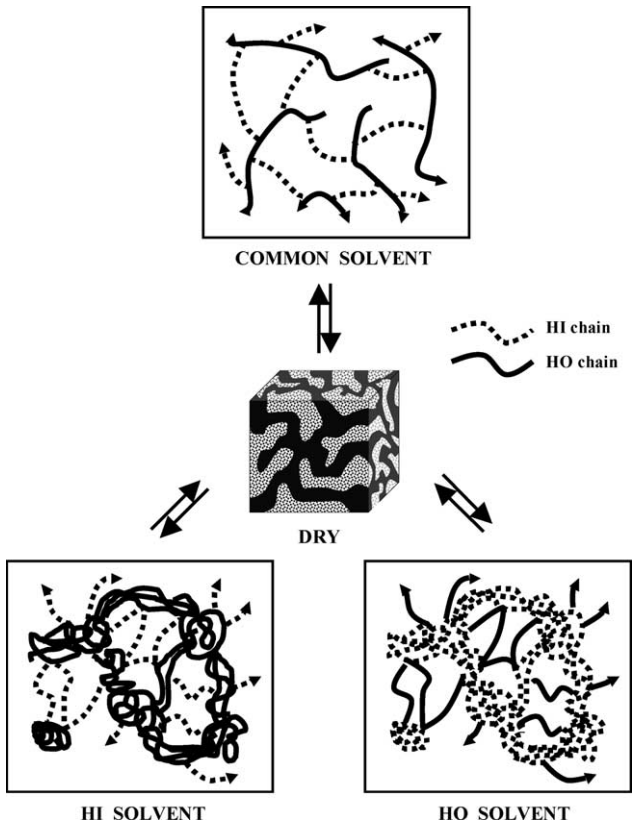
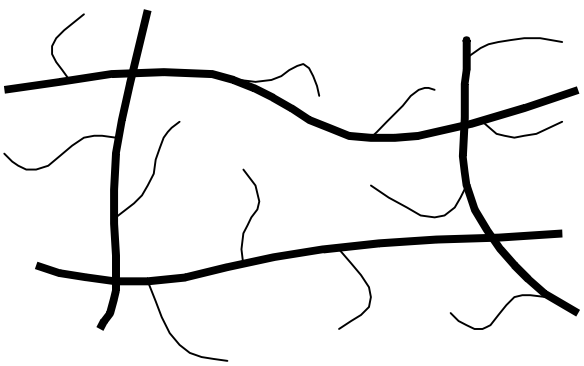


Fig. 1. Effect of solvents on morphology of APCN.

however the effect on properties of a few dangling chains in an APCN is negligible. Networks obtained by the copolymerization of a monomer and a (monofunctional) macromonomer of differing philicities necessarily contain dangling chains and, therefore, are not true conetworks. For example, numerous workers synthesized hydrogels with dangling HO segments by copolymerizing/crosslinking water-soluble (meth)acrylates with (meth)acrylates carrying large HO substituents (C_4 and higher alkyl groups):



While such constructs may contain sufficient HO moieties for phase continuity and may exhibit amphiphilic characteristics over the entire system, the presence of the many dangling chains strongly reduces the mechanical properties (load-bearing capacity) of the network, i.e. they are not conetworks within the scope of our definition of APCNs.

APCNs are not interpenetrating networks (IPNs). It is instructive to examine the similarities and differences between APCNs and IPNs. The micromorphologies of these systems are similar because cocontinuity of both HI and HO molecules exists in both. The fundamental difference between APCNs and IPNs is in the nature of constraints between the phases: While in APCNs phase separation is constrained by chemical bonds, in IPNs the molecules/phases are constrained by physical forces, i.e. entanglements. APCNs exhibit massive phase segregation, comprise relatively large phases and exhibit two T_g's. In contrast, in IPNs the phase morphology is strongly synthesis dependent: the entangled macromolecules may lead to relatively small phases and, indeed, many IPNs exhibit only one T_g, intermediate between the T_g's of the two constituents [2–4]. In IPNs (or semi-IPNs) domain size is

mainly controlled by the crosslink density of the first-produced network, while in APCNs the size of the domains is controlled by the size (MW) of the HI and HO polymer segments. Due to this circumstance, the domain sizes and crosslink densities in APCNs can be varied independently (see also Section 6.2). Thus, low crosslink density (weakly crosslinked) APCNs with very small domain sizes can be readily prepared (e.g. soft transparent contact lenses). Phase separation is an important issue in both APCNs and IPNs. While, by definition, an APCN is always swellable in both water and hydrocarbons, an IPN may not swell in any solvent if the two constituent networks of the IPN are both tightly crosslinked. Differences in micromorphologies lead to significant macroscopic differences between APCNs and IPNs.

2. A note on terminology

The first APCNs were born in 1988 (see Section 4) and since that time authors have used various expressions (amphiphilic networks, segmented networks, etc.) or circumlocutions to name these complex constructs [5,6]. We are using and recommend the terminology of Ivan, who coined the term 'amphiphilic conetworks'. The suffix 'co' in front of the word 'network' calls attention to the presence of two network constituents (i.e. HI and HO) and distinguishes APCNs from networks obtained by crosslinking amphiphilic copolymers (i.e. copolymers of HI and HO monomers).

The expression 'amphiphilic networks' is often employed and, indeed, was used in the titles of a series of some 30 publications by one of us [7], however, the word 'conetwork' better expresses the concept and will be used in the future.

We do not favor the expression 'segmented networks' as used by Belgian and French authors because the terms 'segmented' and 'network' are redundant (every network is built of segments).

3. Why APCNs?

Why should one be interested in APCNs? This review answers this rhetorical question and provides justification for continued interest in APCNs.

First and foremost, APCNs are useful. Their usefulness has already been amply demonstrated by the world-wide acceptance of extended-wear soft contact lenses, and other promising applications are being diligently explored by scores of investigators. Next, APCNs exhibit a combination of unprecedented properties whose exploitation will certainly lead to unexpected new applications. Finally, from the vantage point of pure or basic science, APCNs pose intellectual challenges to the experimental polymer chemist to develop practical syntheses, and to the theoretician to describe quantitatively the unusual phenomena APCNs engender.

APCNs revolutionized the field of contact lenses. Today every extended-wear soft contact lens in use or under development is an APCN. While scientists in extended-wear soft contact lens research do not usually regard themselves APCN researchers, in fact they are! And their contributions to this field under consideration are fundamentally important. A discussion of extended-wear soft contact lenses is of course far beyond the scope of this short review, and the reader is referred to the books, reviews and literally hundreds of patents and publications on this subject; however, in the final analysis extended-wear soft contact lenses are APCNs, and must be included in this discussion to the extent they have enhanced our understanding of and shaped research in the field of APCNs.

The fact that extended-wear soft contact lenses are APCNs was clearly brought in focus in a landmark publication by Nicolson and Vogt of CIBA Vision Co. [8]. Without divulging proprietary information, they evaluated a large amount of clinical findings and came to the conclusion that for an extended-wear soft contact lens to move on the cornea (i.e. be comfortable on the eye of the wearer) it must be cocontinuous in respect to water (salt solution) and oxygen (a hydrophobic gas). It was established that percolation of water through siloxane hydrogels starts when the water content in the lens reaches ca. 20% [1]. Cocontinuous morphology in contemporary extended-wear contact lenses is achieved by the skillful combination of a highly HI phase (usually PDMAAm and PNVP) with the highly HO oxyphilic PDMS phase. The continuous HI phase provides wettability, comfort, and on-eye lens movement, whereas the continuous PDMS phase provides the needed high oxygen permeability essential for the healthy eye (PDMS has by far the highest oxygen permeability among elastomers [9,10]). The mechanical properties of the lens are mainly controlled by the overall HI/HO composition and crosslink density.

The family of materials containing cocontinuous polysiloxane and hydrophilic phases are termed siloxane hydrogels in the soft contact lens literature. Modern extended-wear soft contact lenses are siloxane hydrogels, and are invariably APCNs [8,11–20].

Silicon hydrogels are synthesized by crosslinking amphiphilic telechelic macromonomers. (The reader is cautioned that the term 'macromer' is used incorrectly

in both the scientific and patent literature of soft contact lenses. The correct term is 'telechelic macromonomer'; the term 'macromer', the abbreviation of macromolecular monomer, connotes the presence of only one polymerizable terminal function, and the word Macromer® (coined by Milkovich) is a trade name of the Sartomer company. For clarity and consistency, we advocate using the terms 'terminally-functional (or telechelic) macromonomer', or for brevity's sake 'telechelic macromer').

APCNs hold promise as controlled implantable drug delivery devices. It was shown that certain APCNs imbibed with various drugs (theophilline, etc.) exhibit delayed drug delivery profiles, and in certain cases yield desirable zero-order drug delivery kinetics [21–26]. Jerome and coworkers obtained APCNs by benzoyl peroxide initiated copolymerization of HEMA with MA-telechelic poly(ε-caprolactone) or poly(-D,L)lactic acid. Cocontinuity was shown by swelling in water and chloroform, and the kinetics of drug release (dexamethasone) was studied [27]. Rimmer and coworkers prepared various APCNs for biological applications, most recently for supports for cell proliferation [28,29]. Tiller and coworkers investigated thin film APCNs for antimicrobal coating, and showed that the biocide was released into the environment over a long period of time [30,31]. The same researchers found that peroxidases entrapped in the hydrophilic domains of APCNs exhibited increased activity and stability. Increased activity was attributed to the large hydrophilic/hydrophobic interphase in the APCN [32,33].

There is a good chance that APCN membranes will find use in clinical medicine, for example as immunoprotecting membranes in the bioartificial pancreas. Briefly: it was postulated that a bioartificial pancreas (i.e. a device comprised of living insulin-producing animal cells protected by an immunoisolatory membrane and implanted into diabetic humans) could correct diabetes. A huge amount of very expensive research is being carried out, mainly by medical professionals, in this direction. The key component of the bioartificial pancreas is a semipermeable membrane whose function is to encapsulate and thus protect foreign (porcine, bovine) insulin-producing pancreatic tissue from the onslaught of the host's immune system. Immunoprotecting membranes must allow the rapid ingress of water, nutrients, glucose, etc. to keep the cells alive, however, at the same time they must allow the rapid exit of insulin and metabolic wastes. The bioartificial pancreas is an implanted dual sensor and delivery device: it senses the prevailing glucose level in the blood of the host, and a drug delivery device, which produces and delivers the correct amount of insulin dictated by the prevailing glucose concentration. APCNs combine all the needed characteristics (biocompatibility, biostability, non-fouling surface, controlled mesh size, semipermeability, mechanical properties, sterilizability, etc.) required of an immunoisolatory membrane [34–43]. Indeed, experiments have demonstrated that a bioartificial pancreas (a semipermeable tubule prepared of a well-defined APCN and containing porcine pancreatic islets) significantly reduced hyperglycemia of a diabetic rat [44]. Needless to state, a functioning bioartificial pancreas would be of immense benefit to humankind.

In addition to biological/medical applications, APCNs are being explored for various industrial applications. For example, Wooley and coworkers developed APCNs for minimally-adhesive surface coatings to protect the hulls of marine vessels [45–47]. The coatings were prepared by crosslinking hyperbranched fluoropolymers with 14–55% NH_2–PEG–NH_2 segments. Surface rearrangement was demonstrated by contact angle measurements. Belgian–French investigators prepared APCN membranes by the copolymerization of MMA with MA-telechelic poly(1,3-dioxolane), and examined the use of these membranes for dehydration by pervaporation of water/ethanol mixtures [48]. Other possibilities may include oxygen enrichment membranes, membranes for batteries, filtration, water-remediation, surface modification, etc.

4. A brief historical note, and a glimpse at APCN research world-wide

It often happens in science: when the time is ripe, things get discovered. Evidently, the time was ripe for the discovery of APCNs in 1988 when these systems were first described almost simultaneously by Weber and Stadler in Germany [5], and Kennedy and coworkers in the US [6]. Fig. 2 reproduces the original sketches that appeared in these publications. Just a brief glance at these two cartoons, drawn an ocean apart, reveals the virtual identity of the proposed concepts. The German investigators prepared PEG fitted with 1,2,4-triazoline-3,5-dione endgroups that react rapidly and quantitatively with the double bonds in PBd, and used this telechelic PEG for crosslinking PBd. The American group obtained APCNs by free-radical initiated copolymerization of select water-soluble acrylates with a methacrylate-ditelechelic PIB macrocrosslinker (MA-PIB-MA). Both groups recognized the

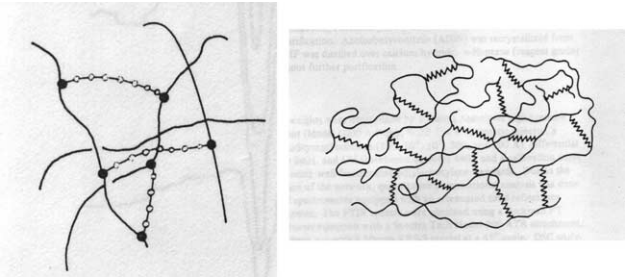


Fig. 2. First notions of APCNs: sketches from 1988.

anisotropic nature of their materials (i.e. the absence of macroscopic phase separation), and HI/HO phase cocontinuity was proven by swelling experiments with both water and hydrocarbons. Most regrettably, Stadler died and his lead was not taken up by other investigators. Kennedy and his group pursued this breakthrough and contributed a series of close to 30 publications and patents to the science and technology of APCNs [6,7,21–26,34–43,49–62].

Since 1988 a large number of investigators have entered the field and generated a large quantity of information concerning APCNs. Table 1 identifies representative groups currently active in APCN research world-wide.

The science and technology of APCNs owes tremendous debts to industrial scientists working in the field of soft contact lenses, particularly extended-wear soft contact lenses. Even the briefest historical note would not be complete without taking note of the landmark contributions of Salamone and Kunzler and their coworkers at the Bausch and Lomb Company [11–18], and of Nicolson and coworkers at CIBA Vision Corporation [19,20,63,64].

The rapidly expanding filed of APCNs was first reviewed (close to 80 references) by Patrickios and Georgiu, researchers who made significant original contributions to the field [65–70]. The authors focused on the synthesis, characterization, structure, and modeling of APCNs, however, for some reason, they ignored the contributions made by investigators working in the soft contact lens industry.

Table 1
Leaders of representative groups active in APCN research

Gitsov (US)
Goethals-DuPrez (Belgium)
Ivan (Hungary)
Jerome (Belgium)
Kennedy (US)
Salamone-Kunzler (US)
Lutz (France)
Nicolson (US) Patrickios (Cyprus)
Peng (China)
Rimmer (UK)
Tiller (Germany)
Wooley (US)

5. Synthesis strategies

This section concerns the identification, and a discussion of the strengths and weaknesses of the various strategies developed for the synthesis of APCNs. Fig. 3 outlines the types of chemical reactions that have been employed and documented to date. The huge amount of information in the scientific and patent literature can be subdivided into three main groups and several subgroups, as indicated in Fig. 3.

The perennial problems synthesis researchers faced were how to engineer around the thermodynamic incompatibility of HI and HO constituents, and how to overcome the difficulty of uniting these constituents into a macroscopically homogeneous construct. The various synthetic strategies discussed below represent diverse methodologies devised to overcome these problems.

5.1. Random free radical copolymerization of monomers with telechelic macromonomers

Techniques that yield APCNs by free radical copolymerization of conventional small monomers with telechelic macromonomers can be subdivided into two large subgroups depending on the manner by which the radical is generated: i.e. thermally or photolytically-induced processes.

5.1.1. Thermal initiation

A large number of investigators synthesized APCNs by the copolymerization of selected monomers with telechelic macromonomers (macrocrosslinkers). The radicals were generated thermally by the use of

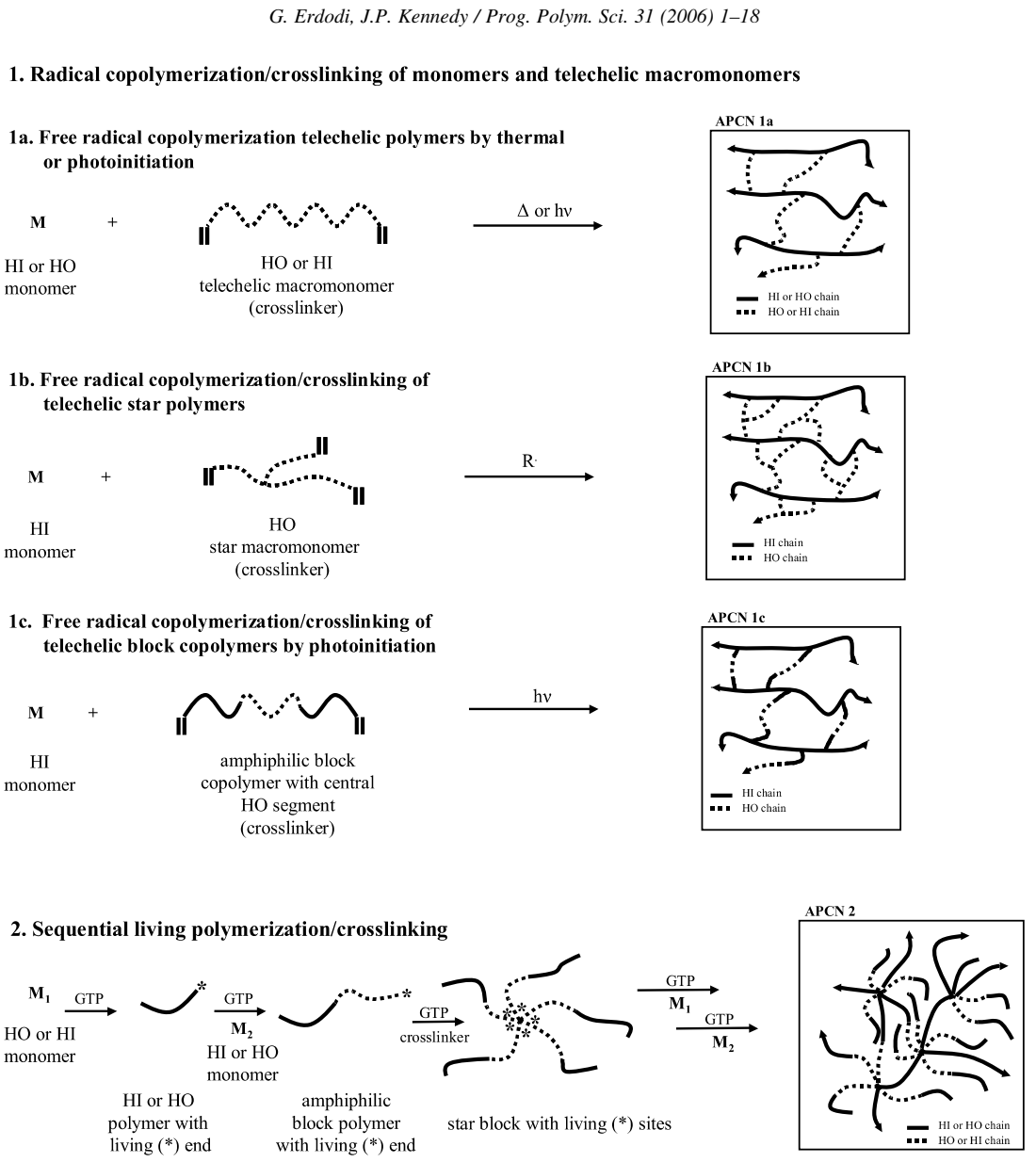


Fig. 3. Summary of strategies for synthesis of APCNs.

conventional azo or peroxy initiators; the monomers employed were either HI, in which case HO macrocrosslinkers were used, or HO in which case the macrocrosslinkers were HI. This strategy is symbolized by group 1a and 1b in Fig. 3. To overcome the incompatibility of the starting materials the copolymerizations were carried out in good solvents for both the monomer and the macrocrosslinker. This is essentially the same strategy first demonstrated to produce APCNs by Kennedy et al. (see Section 3). Table 2 lists combinations of monomers and telechelic macromonomer crosslinkers used, together with representative references.

The great advantage of this strategy is simplicity: the monomer and macrocrosslinker are dissolved in a common good solvent and a free radical initiator (typically an azo compound) is added. The relative concentrations of the two ingredients determine the overall composition of the APCN and the molecular weight of the main random copolymer chain. Sufficiently high MW HI main chains must be obtained to reach the gel point (for efficient crosslinking). The MW

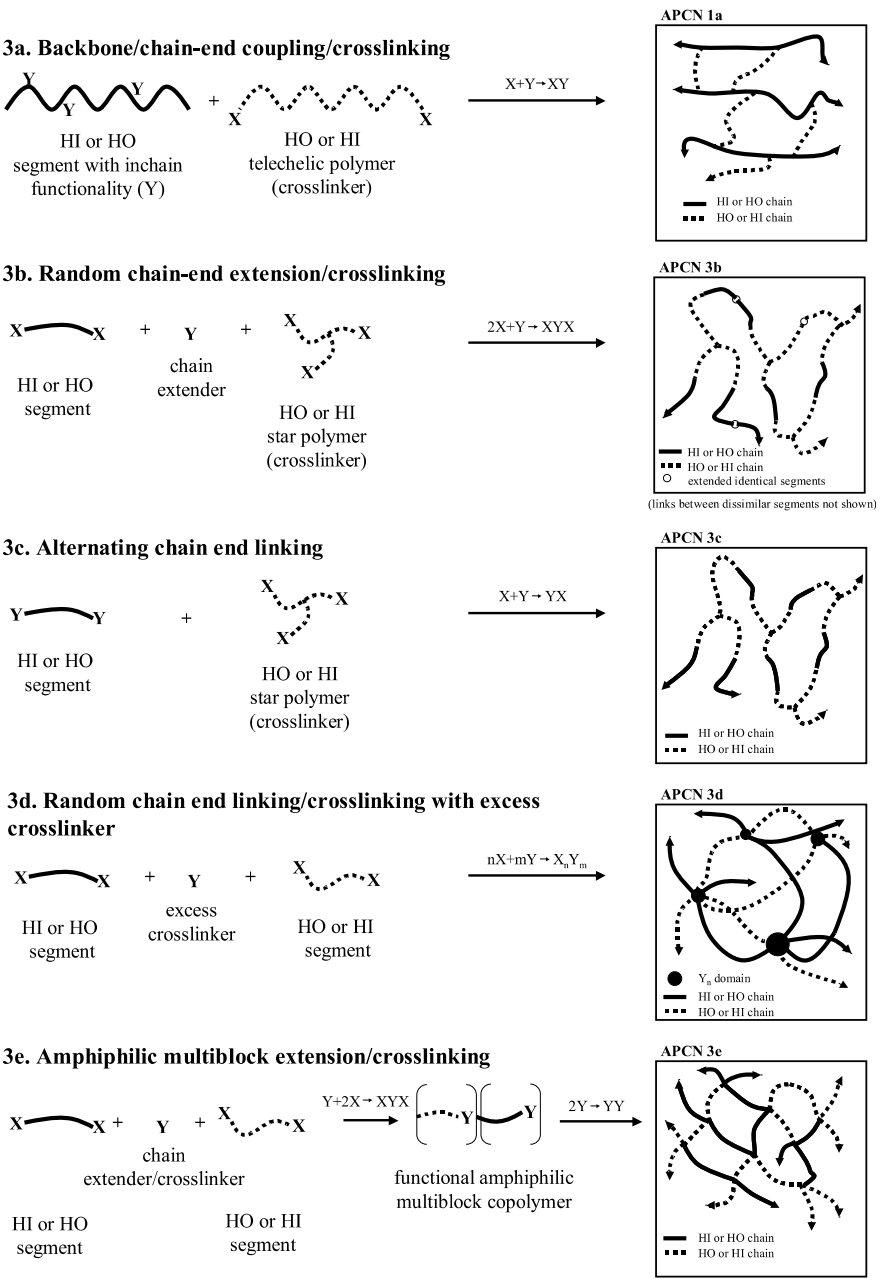


Fig. 3 (*continued*)

of the macrocrosslinker can be precisely controlled by independent synthesis. The MW of the random main chain produced by the free radical copolymerization (and crosslinked by the preformed macrocrosslinker), is controlled by the kinetics of the copolymerization and can be calculated; for example, $M_{c,HI}$ (the MW of the HI segment between the crosslinking sites) of the PDMAAm segment in PDMAAm-*l*-PIB (where *l*= linked by) obtained by the copolymerization/crosslinking of DMAAm+MA-PIB-MA, is calculated by:

$$M_{c,HI} = \frac{W_a M_n}{2W_{PIB}}$$

where W_a is the weight fraction of the HI segment, M_n is the number average molecular weight of the PIB, and W_{PIB} is the weight fraction of PIB.

Table 2
APCN syntheses by free radical copolymerization of HI and HO monomers with opposite-philic macrocrosslinkers

Monomers	Macrocrosslinkers	References
HI	**HO**	
DMAEMA, DMAAm, HEMA, SEMA	MA-PIB-PIB, star-PIB $(MA)_3$, star-PIB$(MA)_8$	Kennedy [6,7,21–26,34–43,49–62,119]
EtA, HEMA, MAAc, DMAEMA, DMAAm	MA-PIB-MA	Ivan [71–75]
	MA-PDMS-MA	
HEA, AAc	MA-PDMS-MA	Tiller [30–33,76]
AAm, MAAc, AAc, NIPAM	MA-PTHF-MA	Peng [77–82]
HEMA, NIPAM, PVCL, BA	MA-PTHF-MA, Comb-PTHF $(MA)_n$ MA-PODVE-MA MA-PMVE-MA	Goethals-Du Prez [48,83–94]
HEMA	MA-PεCL-MA MA-P(D,L)LA-MA	Jerome [27]
HEMA	MA-PPO-MA	Matsumoto [95–97]
GMA	MA-PBMA-MA	Rimmer [98,99]
HO	**HI**	
MMA, NBMA, TBMA	MA-PEG-MA	Lutz [100,101]
BzMA, St	MA-PEG-MA	Matsumoto [97,102–106]
MMA, BMA, BA	MA-PEG-MA	Goethals-Du Prez [48,107–110]
	A-PROx-A MA-PDXL-MA	

Among the disadvantages of thermally induced free radical polymerizations are the numerous unavoidable side reactions that accompany these techniques, and the less than quantitative incorporation of the bifunctional crosslinker. If, for whatever reason, only one of the functional groups of the bifunctional macrocrosslinker undergoes copolymerization (and the probability for this to occur is non-negligible), a useless dangling chain will arise that does not contribute to load bearing. To overcome this disadvantage, terminally functionalized 3–8-arm star [51] or multifunctional [91] crosslinkers have been employed.

5.1.2. Photoinitiation

Photochemical or photoinitiated free radical copolymerizations are eminently useful for the synthesis of APCNs. This technique has been thoroughly investigated and exploited by scientists in the hugely successful contact lens industry for the manufacture of extended-wear soft contact lenses. The vast majority of APCNs described (or disclosed in patents) by these scientists are amphiphilic block copolymers comprising PDMS and various HI segments (typically PDMAAm of PNVP) fitted with methacrylate end groups or, to a lesser extent, vinyl carbonate termini suitable for photocrosslinking (see entry 1a. in Table 3). For example, Balafilcon A of Bausch and Lomb, approved by the Federal Drug Administration for six-nights extended-wear soft contact lens use, is prepared by photo-copolymerizing/-crosslinking of hydrophilic monomers (NVP, DMAAm, etc.) and TRIS (tris(trimethylsiloxy)silyl propyl methacrylate) with HO vinyl carbonate (CH_2=CH–O–CO–O–) telechelic PDMS macrocrosslinker [11–13]. The PNVP provides the HI phase, and the PDMS the HO phase. The presence of the large TRIS substituent in the APCN provides additional oxyphilicity. Similarly, Lotrafilcon A, an extended-wear soft contact lens material of CIBA Vision, is an APCN prepared by photo-crosslinking/-copolymerizing DMA and TRIS with MA-telechelic macrocrosslinker containing polysiloxane and fluorosiloxane segments [8,19,63]. Phase cocontinuity of the products is essential as the lens must permit the rapid and simultaneous permeation of aqueous solutions and HO oxygen, and is the key issue for on-eye mobility of the lens.

Tiller and coworkers used photoinitiation to synthesize APCNs designed for antimicrobial thin film coatings [30,31] and devices for the protection of enzymes [32,33]. They photo-copolymerized [30,31] (protected) AAc or HEA plus MA-PDMS-MA, and obtained APCNs containing PAAc or PHEA main chains crosslinked by PDMS. Phase cocontinuity was demonstrated by atomic force microscopy. The networks rapidly imbibed the antimicrobial agent cetyltrimethylammonium chloride and released it over a period of 3 weeks. The protection and delayed release of horseradish peroxidase by sequestering the enzyme in designed APCNs was demonstrated.

5.2. Ionic sequential living polymerizations

Among the numerous ionic living polymerization methods that could be used for the synthesis of sequential amphiphilic copolymers, only group transfer polymerization (GTP) has been systematically exploited for the synthesis of APCNs. Patrickios' group made significant advances to the field of APCNs by the use of GTP. These investigators first produced amphiphilic block copolymers by sequential GTP, and, after the blocks had reached desirable lengths, crosslinked them by adding conventional small crosslinkers to the living GPT system. The

versatility of the GTP technique was exploited by the synthesis of a great variety of multiblocks, and crosslinking to various topologies [65–70]. Group 2 in Fig. 3 outlines one of the simplest possibilities of this strategy.

The great advantage of this methodology is that the lengths of both the HI and HO prepolymers can be precisely controlled by the use of the living GTP technique. After the addition of the crosslinker to the living block copolymer, gelation proceeds randomly and networks with random mesh-sizes arise. In this respect, our conclusions differ from those of Patrickios et al. who claim to have obtained model networks with uniform mesh sizes. The lasting merit of Patrickios is the demonstration of the utility of GTP for synthesis of a large variety of (meth)acrylate-based APCNs with diverse architectures (for a compilation of this work up to 2003, see Ref. [68]).

5.3. Chemical combination of HI and HO prepolymers

A plausible strategy for the synthesis of APCNs is the chemical combination of HI and HO prepolymers. Many investigators have implemented this strategy by functionalizing HI or HO prepolymers, dissolving them in common good solvents, and combining them by crosslinking to networks. Group 3 in Fig. 3 summarizes and outlines the strategies explored by various investigators. The pioneering German investigators produced PBd-*l*-PEG by this route (Group 3a in Fig. 3; see also Fig. 2, Section 4). Due to the high ene reactivity of the 1,2,4-triazole-3,5-dione termini of the PEG crosslinker with the unsaturations in PBd, crosslinking of PBd could be carried out by simply contacting the two prepolymers in the common solvent THF, and addition of catalyst (a potential contaminant) was unnecessary [5].

Rimmer and coworkers crosslinked PEG-co-acetylenedicarboxylate with furane-telechelic PBMA [111]. The macrocrosslinker (F-PBMA-F) was prepared by constructive degradation and subsequent chain end modifications. Crosslinking occurred by a Diels-Alder reaction of the furane endgroups and the acetylenedicarboxylate unit in the PEG. A significant amount of sol formed due to phase separation during crosslinking in the dry state.

A very similar strategy was used by Japanese investigators who crosslinked butyl rubber by PEG [112–114]. Thus, commercial bromobutyl rubber and HO-PEG-OH (Mw 1000–10,000) were dissolved in toluene and crosslinking was effected by the addition of tBuOK. Phase cocontinuity in the amphiphilic thermoplastic elastomer was demonstrated by swelling in THF, dioxane and cyclohexane solvents. The same group also prepared butyl rubber modified with D-maltose, and this amphiphilic thermoplastic elastomer also exhibited good mechanical properties. Films of the product swelled in toluene (solvent for butyl rubber, non-solvent for the maltose derivative), and dimethylsoulfoxide (solvent for the maltose derivative, non-solvent for butyl rubber).

Goethals and coworkers synthesized APCNs of PTHF and poly(propylene imine) segments [115]. The conetwork consisted of dendritic hydrophilic poly (propylene imine) domains connected by PTHF chains. A similar APCN was synthesized by Wooley and coworkers by crosslinking a hyperbranched fluoropolymer with amino telechelic PEG [45–47]. The hyperbranched fluoropolymer became the HO domain of the network.

Erdodi and Ivan prepared APCNs by crosslinking linear PEG with three-arm star PIB segments both fitted with isocyante termini [116,117]. The syntheses were carried out by reacting mixtures of HO-PEG-OH and hydroxyl-tritelechelic 3-arm PIB stars ($PIB(OH)_3$) with diisocyanatohexane or, alternatively, by combining NCO-ditelechelic PEG with $PIB(OH)_3$ in toluene solution. The former procedure was claimed to yield random PEG/PIB APCNs, while the alternative route gave segmented alternating PEG/PIB APCNs. These two methods are symbolized by Group 3b and 3c in Fig. 3.

Gitsov and coworkers [118], more-or-less inadvertently, obtained complex APCNs by producing PEG bridges (via transesterification) between PSt-D moieties (where D = dendritic fragment of poly(benzyl ether)) surface-modified by—COOEt groups. The PEG content was varied between 52 and 75 wt%. Phase separation was demonstrated by identifying two T_g's and by solution studies using chloroform and water.

Kennedy et al. combined vinyl-telechelic PDMS and allyl-telechelic PEG by hydrosilation using pentamethylcyclopentasiloxane (D_5H), a novel multifunctional co-crosslinker [43,44,49,50]. The strategy is symbolized by Group 3d in Fig. 3. The synthesis involved the random co-hydrosilation/crosslinking of vinyl-ditelechelic PEG and vinyl-ditelechelic PDMS chains of various lengths by large amounts of D_5H in the presence of Karstedt's catalyst. Under the particular conditions developed (presence of moisture and oxygen) the D_5H co-crosslinker polycondenses and yields a new domain: polyD_5H (PD_5). The PD_5 phase serves three functions: it is a crosslinking site, a reinforcing filler, and it contributes to the oxygen

permeability of this tricomponent construct [50]. Group 3d in Fig. 3 outlines the structure of the ingredients involved and the microstructure of this APCN. Membranes containing about equal amounts of PEG, PDMS and PD_5 give rise to morphologies that allow the simultaneous permeation of water, heptane and oxygen via cocontinuous channels. The very low quantities of extractables indicated efficient crosslinking. The MW of the continuous PEG segments determines the pore dimensions of the channels through which water can

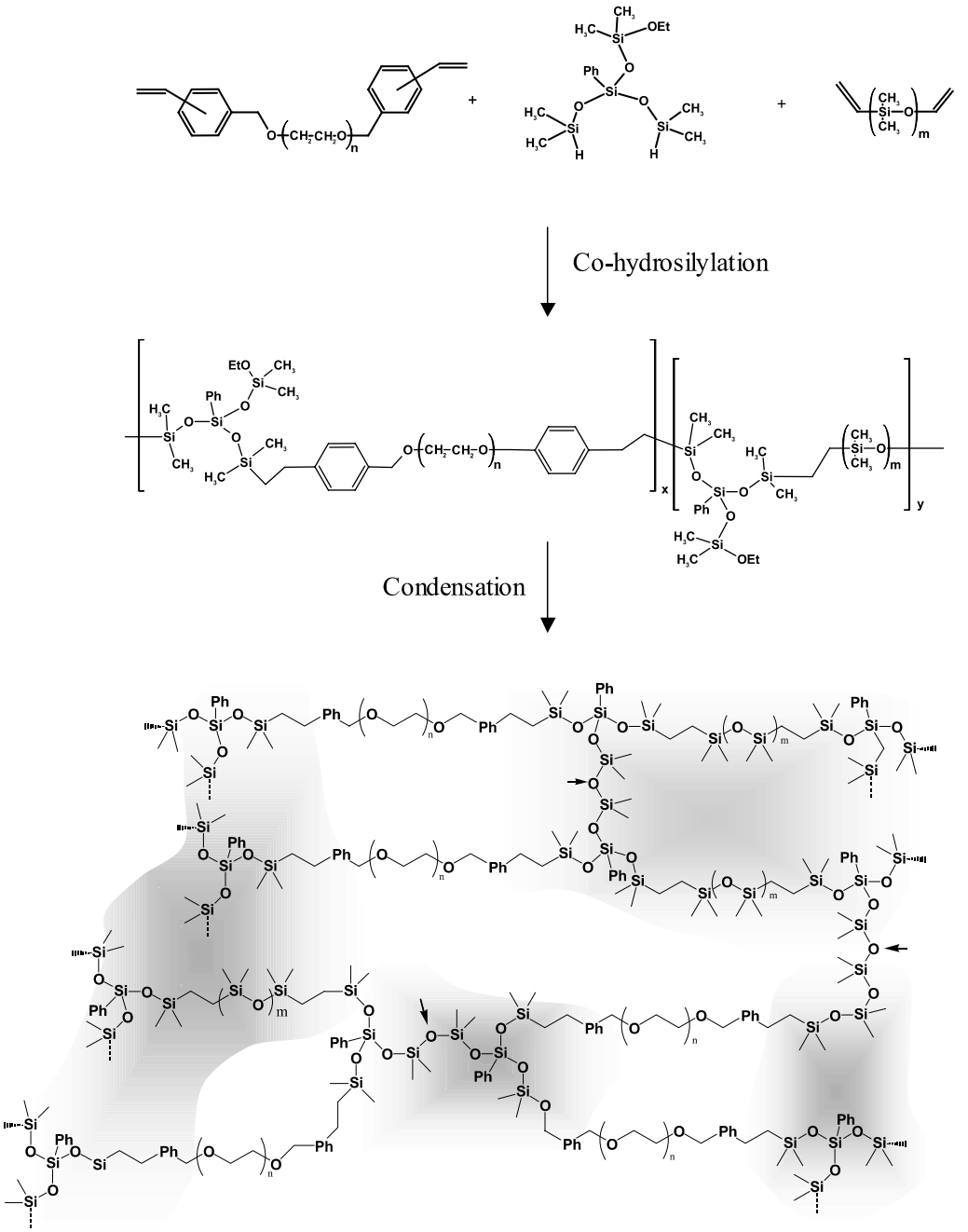


Fig. 4. Structures of PEG/Y/PDMS conetwork and starting materials. Arrows show newly formed oxygen bridges and shaded areas indicate cocontinuous hydrophobic domains.

permeate. The continuous PDMS domains ensure the rapid permeation of oxygen and provide for elasticity. The PD_5 domains provide crosslinking, reinforcement, and contribute to O_2 permeability. The mechanical properties (strength and elongation) of PEG/PD_5/PDMS conetworks can be controlled by overall network composition. Very similar syntheses were also carried out by the use of allyl-ditelechelic PIB as the HO constituent (Group 3d in Fig. 3) [55].

The latest strategy for the synthesis of APCNs is the crosslinking of linear amphiphilic multiblock copolymers (see Group 3e in Fig. 3) [7,119]. Erdodi and Kennedy prepared well-defined multiblocks comprising PEG and PDMS segments with an extender/crosslinker Y between the HI and HO polymer blocks: $(PEG\text{-}Y)_n(PDMS\text{-}Y)_m$. The multiblocks were prepared by random co-hydrosilation of styryl-telechelic PEG and vinyl-telechelic PDMS with a new extender/crosslinker $Y = SiPh(SiH)_2OEt$ in toluene common solvent. The Y unit fulfills two functions: first, it extends the two incompatible PEG and PDMS segments to a random multiblock copolymer and, subsequently, it crosslinks the multiblocks to APCNs. Fig. 4 helps to visualize the structure of the starting materials and the morphology of the conetwork formed.

This conetwork is ideal (the lengths of the PEG and PDMS segments are respectively identical), and tetrafunctional (exactly four segments emanate from every crosslink site). The great advantages of this synthesis method are simplicity, essentially quantitative conversions, and that the multiblock intermediate can be readily purified by extraction or precipitation (structurally similar diblocks or triblocks cannot be simply purified from contaminating starting materials because they form micelles both in HI and HO solvents). Further, the practicality of the process is greatly enhanced by separating the synthesis and crosslinking of the multi-diblock prepolymers; in this manner crosslinking can be carried out in neat (solventless) systems. The cocontinuity of the PEG and PDMS phases was demonstrated by equilibrium swelling experiments with water and *n*-heptane solvents. The overall composition of the conetworks was varied in the 16–40% PEG range and cocontinuity (bipercolation) appeared with ca. 12% PEG (by extrapolation). Both dry and water-swollen membranes were optically clear, indicating the presence of PEG and PDMS domains with dimensions well below the wavelength of visible light.

We conclude this section on syntheses by noting that APCNs in which HO chains are linked to HO chains and HI chains are linked to HI chains, and both HO and HI chains are linked to each other, have not yet been prepared.

6. Some conclusions in regard to the synthesis and topology of APCNs

6.1. Synthesis

As we pointed out at the beginning of Section 5, the key difficulty in the synthesis of APCNs is the crosslinking of thermodynamically incompatible HI and HO segments. To overcome this problem most investigators have employed a common good solvent in which all the starting ingredients are soluble and crosslinking proceeds in a seemingly homogeneous medium. This strategy, however, is beset by several limitations. First of all, cure versatility is limited to a few amphiphilic solvents (e.g. THF); further, crosslinking is slow and cumbersome; and last but not least, the common solvent strategy produces materials highly swollen in organic solvent(s). Obviously, such processes are unsuitable for the preparation of membranes for soft contact lenses and other biomaterials. This common-solvent handicap was avoided, for example, in the production of extended-wear soft contact lenses by employing low MW miscible staring materials and/or by varying the chemical nature of the starting ingredients; in other words developing conditions to avoid macroscopic phase separation during curing. However, the nature of the starting materials cannot be changed when only one specific polymer is able to provide the needed combination of properties for a particular application (e.g. PDMS for oxygen permeability in soft contact lenses).

Another strategy to prevent phase separation is to use large HO protecting groups, e.g. the trimethylsiloxane group, attached to HI monomers, e.g. MAAc, HEMA. After crosslinking, the HO protecting groups can be easily and quantitatively removed, and the APCN recovered. This laboratory strategy, however, is cumbersome, costly and monomer specific.

It has recently been demonstrated that phase separation during crosslinking can be avoided by the use of amphiphilic functional multiblocks [119]. Since in the starting amphiphilic multiblocks the amphiphilic segments are already covalently linked, macroscopic separation during crosslinking does not occur even in the absence of a common solvent. While the operational

Table 3
Topological classification of APCNs and molecular weight distribution of $M_{c,HI}$ and $M_{c,HO}$

Synthetic strategy	The philicity and nature of one component	j_{HI}	j_{HO}	$j_{HI/HO}$	MWD $M_{c,HI}$	MWD $M_{c,HO}$
1a	HO telechelic macromonomer	–	–	2/1	Gaussian	[a]
1b	HO telechelic 8-arm star	–	8	2/1	Gaussian	[a]
1c	HI comonomer	3	–	1/1	Gaussian	[a]
2	[b]	–	–	30–60/30–60	Broad	Broad
3a	HI telechelic macromonomer	–	–	2/1	[a]	Gaussian
3b	HO telechelic 3-arm star	–	3	1/1	Broad	[a]
3c	HO telechelic 3-arm star	–	3	1/1	[a]	[a]
3d	[b]	–	–	>10/>10	[a]	[a]
3e	[b]	4[c]	4[c]	1/3, 2/2, 3/1	[a]	[a]

[a] Philicities interchangeable.
[b] Present in low concentration.
[c] Reflects prepolymer MWD.

principle of this strategy has been documented (see Group 3e in Fig. 3), structural/morphological details of the APCNs prepared by this method are yet to be explored.

6.2. The influence of synthesis strategy on the structure and topology of APCNs

In Fig. 3, we identified and systematized the strategies documented to date for the synthesis of APCNs. The most important conclusions derivable from this compilation are that numerous strategies exist for the reliable synthesis of APCNs, and that the detailed structures and topologies of the individual networks produced by the different strategies are different.

We propose to describe the topological differences that exist between the various APCNs by the segment junction parameter j that indicates the number of segments emanating from common junctions. Depending on their location, we distinguish three such parameters; j_{HI} and j_{HO} for segment junctions in the HI and HO phases, respectively, and $j_{HI/HO}$ for segment junctions at the HI/HO interface; for example $j_{HI/HO}$ = 2/1 describes an interface junction point from which emanate 2 HI and 1 HO segments. The concentrations of the various junctions may be different in the conetwork. Columns 3–5 in Table 3 list segment junction parameters of APCNs obtained by the strategies classified in Fig. 3; for example, Strategy 1a, which involves the free radical copolymerization of HI monomers with a HO macrocrosslinker, is described by $j_{HI}=0$ and $j_{HO}=0$ (absence of junctions in the hydrophobic and hydrophilic domains), and $j_{HI/HO}=2/1$ indicating interface junctions of 2 HI and 1 HO segments. And the APCN formed by Strategy 3e, i.e. the strategy in which amphiphilic multiblocks containing crosslinking sites are crosslinked, is described by $j_{HI}=j_{HO}=4$ (these tetrafunctional junctions are, however, present in low concentration), and three $j_{HI/HO}$'s = 1/3, 2/2 and 3/1 (because the multiblock copolymer formation is random and produces three kinds of segment linkages).

One-component networks and APCNs are fundamentally different: one-component networks contain only one M_c, while APCNs possess two: $M_{c,HI}$ and $M_{c,HO}$. The MWs and MWDs of the M_c's are critical for mechanical and other properties (permeability, etc.) of networks in general and for APCNs in particular. M_c's and junction concentrations can be controlled by selecting the MW of the prepolymers and/or by setting the relative concentrations of the starting materials. MWD of M_c's and segment junction parameters are characteristic of the synthetic method applied.

In Table 3, we indicate the MWDs of the $M_{c,HI}$ and $M_{c,HO}$'s produced by the various strategies summarized in Fig. 3. The MWD of M_c's can be controlled by the mechanism of the polymerizations used for the synthesis of APCNs, and by the mechanism of polymerizations used to prepare the macrocrosslinkers. For example, as shown in the first

three rows of Table 3 for Strategies 1a, 1b and 1c, $M_{c,HI}$ obtained by the free radical copolymerization of HI monomer with HO macrocrosslinker exhibits a Gaussian MWD, while $M_{c,HO}$ reflects the narrow (Poisson) MWD of the macrocrosslinker obtained by independent living synthesis. Strategy 2 (row 4 in Table 3) involves living GTP, and the APCNs prepared by this strategy are expected to exhibit a broad MWD for both $M_{c,HI}$ and $M_{c,HO}$ because the crosslinking by the bifunctional crosslinker is a random process (The dangling ends in this APCN of course have narrow MWD due to the living GTP used). Startegy 3b involves the use of narrow (Poisson) MWD prepolymers; however, random chain end coupling broadens the distribution of M_c's. This MWD broadening is avoided by the use of Strategy 3c. In Strategies 3d and 3e, the MWDs of $M_{c,HI}$ and $M_{c,HO}$ reflect those of the prepolymers.

In summary, we conclude that the synthesis strategy profoundly influences APCN microstructure and topology. The concentration and location of segment junctions, together with the MW (and MWD) of $M_{c,HI}$ and $M_{c,HO}$, determine crosslink densities and influence the physical/mechanical properties of APCNs. Since the crosslink density in one of the phases may be independent of that prevailing in the other phase, crosslink-density-dependent properties exhibited by one of the phases of an APCN may be independent of those exhibited by the other phase. Thus, ability to control the MW and MWD of $M_{c,HI}$ and $M_{c,HO}$, and the physical location of the segment junctions, enables the macromolecular engineer to design and prepare APCNs with desirable combinations of physical properties (i.e. mechanical, permeability, swelling).

7. A glimpse into the future

APCNs are products of modern macromolecular engineering, and as such, can be designed from the molecule up, for applications that can be defined in terms of material properties. APCNs are here to stay, and their scientific and technological significance can only increase in the years to come.

APCNs, in the form of extended-wear soft contact lenses, have reached the status of important commodities. Evidently, even such complex polymeric materials as APCNs can be produced efficiently and inexpensively.

While it is difficult to predict which among the many promising applications under investigations will next reach prominence, we are confident that the career of APCNs will continue unabated. It is not difficult to foresee that APCNs will be used as specialty hydrogels in applications where amphiphilicity is essential. The tip of the iceberg is visible in medical applications, which demand, in addition to amphiphilicity, biostability and biocompatibility, i.e. properties that can be readily engineered into an APCN system (see Section 3).

APCNs are stimuli (solvent) responsive smart networks; indeed their ability to undergo rapid and massive morphological rearrangement is a hallmark of these systems. It is theorized that the biocompatibility observed in several APCNs (PHEMA-*l*-PIB, PEG/PD_5/-PDMS, etc.) is due to such morphological rearrangement, which allows the system to adapt energetically favorable conformations in response to a medium of any polarity, including contact by amphiphilic proteins. We anticipate that APCNs that exhibit biocompatibility in combination with other desirable 'tunable' parameters (mechanical properties, diffusional characteristics) will find important niches in future applications.

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