residual electron density, 2.19/−2.18 e Å^{-3}.Compound **1** has crystallographic $C_i(\bar{1})$ site symmetry such that the asymmetric part of the crystal structure consists of 1/2 of a neutral cluster and one solvated acetone molecule; b) **2**·2 Me_2CO: monoclinic; $P2_1/n$; $a = 17.517(1)$, $b = 24.471(2)$, $c = 24.216(2)$ Å, $\beta = 106.233(1)°$, $V = 9966.5(13)$ Å^3; $Z = 2$, $\rho_{calcd} = 2.878$ Mg m^{-3}. $Mo_{K\alpha}$ data collected at 173(2) K with SMART CCD 1000 area detector diffractometer by 0.3ω scans over 2θ range 2.9–56.6°; empirical absorption correction (SADABS) applied ($\mu(Mo_{K\alpha}) = 4.900$ mm^{-1}; max./min. transmission, 0.758/0.374). Anisotropic refinement (1044 parameters; 74 restraints) on 24577 independent reflections converged at $\omega R_2(F^2) = 0.158$ with $R_1(F) = 0.052$ for $I > 2\sigma(I)$; GOF (on F^2) = 0.99; max./min. residual electron density, 2.13/−2.56 e Å^{-3}. Compound **2** has crystallographic $C_i(\bar{1})$ site symmetry such that the asymmetric part of the crystal structure consists of 1/2 of a neutral molecule and one solvated acetone molecule. CCDC-195160 (**1**) and -195161 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[16] Observed electron counts of 372, 648, and 290 electrons were obtained for **1**, **2**, and **3**, respectively. Application of the Mingos electron-counting model[17] for a close-packed metal cluster gives rise to the following predicted electron counts: namely, 290 electrons (i.e., 12 × 18(surface) + 18(interior) + 4 × 14(wingtip)) for **3** and 378 electrons (i.e., 12 × 24(surface) + 34(two interior) + 4 × 14(wingtip)) for **1**. The highly condensed geometry of **2** prevents a reliable predicted electron count.

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[19] In sharp contrast, corresponding mean radial Pd(i)–Pd(s_1) separations found in face-condensed icosahedral-based Pd-core geometries of high-nuclearity palladium carbonyl trimethylphosphine clusters are approximately 0.14 Å shorter than the mean tangential intrashell Pd(s_1)–Pd(s_1) separations (that is, 2.73 (av) versus 2.87 Å (av)).[9c] This large difference is ascribed to geometrically imposed radial compressions in icosahedral-based polyhedra. The close agreement of the mean Pd–Pd separations determined for the radial and tangential (intrashell) connectivities in **1**, **2**, and **3** point to the absence of geometrical distortions in the metal-core geometries of cuboctahedral-based systems.

Chemical Adaptor Systems

A Chemical Adaptor System Designed To Link a Tumor-Targeting Device with a Prodrug and an Enzymatic Trigger**

*Anna Gopin, Neta Pessah, Marina Shamis, Christoph Rader, and Doron Shabat**

Selective chemotherapy remains a key issue for successful treatment in cancer therapy. Prolonged administration of effective concentrations of chemotherapeutic agents is usually not possible because of dose-limiting systemic toxicities. Furthermore, strong side effects involving nonmalignant tissues are often observed. Therefore, much effort has been devoted to the development of new drug delivery systems that mediate drug release selectively at the tumor site. One way to achieve such selectivity is to activate a prodrug specifically by a confined enzymatic activity. In this concept, the enzyme is either expressed by the tumor cells, or brought to the tumor by a targeting moiety such as a monoclonal antibody.[1] The prodrug is converted to an active drug by the local or localized enzyme at the tumor site, thereby minimizing nonspecific toxicity to other tissues.

Here we present a new concept that combines a tumor-targeting device, a prodrug, and a prodrug activation trigger in a single entity. We designed a generic module or chemical adaptor that is based on three chemical functionalities as shown in Figure 1. The first functionality is attached to an active drug and**,** thereby, masks it to yield a prodrug. The second functionality is linked to a targeting moiety, which is responsible for guiding the prodrug to the tumor site, and the third functionality is attached to an enzyme substrate. When the corresponding enzyme cleaves the substrate, it triggers a spontaneous reaction that releases the active drug from the targeting moiety. As a result, prodrug activation will preferentially occur at the tumor site.

The central core of our chemical adaptor (Scheme 1) is based on 4-hydroxymandelic acid, which is commercially available and has three functional groups suitable for linkage. Group **I** is a carboxylic acid that is conjugated to a targeting moiety through an amide bond. The drug is linked through the benzyl alcohol group **II**, and the enzyme substrate is attached through the phenol group **III** by a carbamate bond.

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

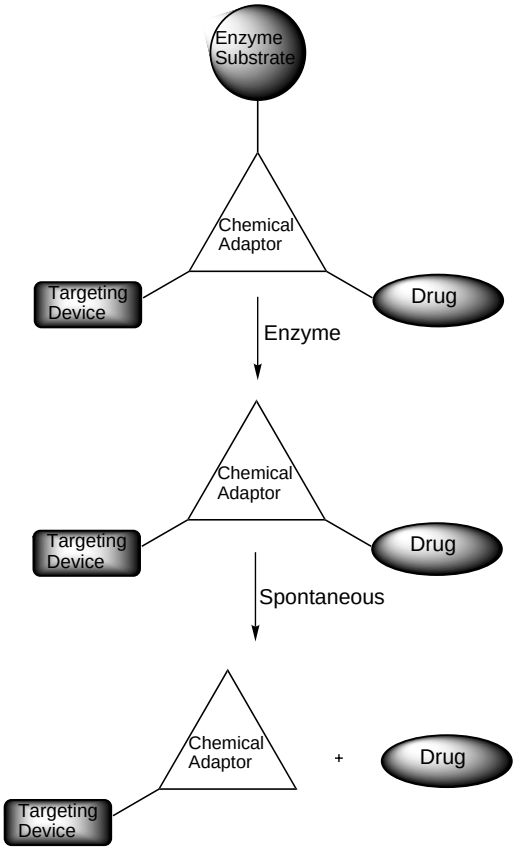
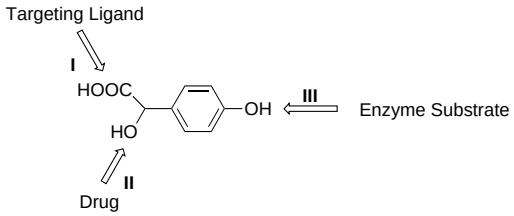


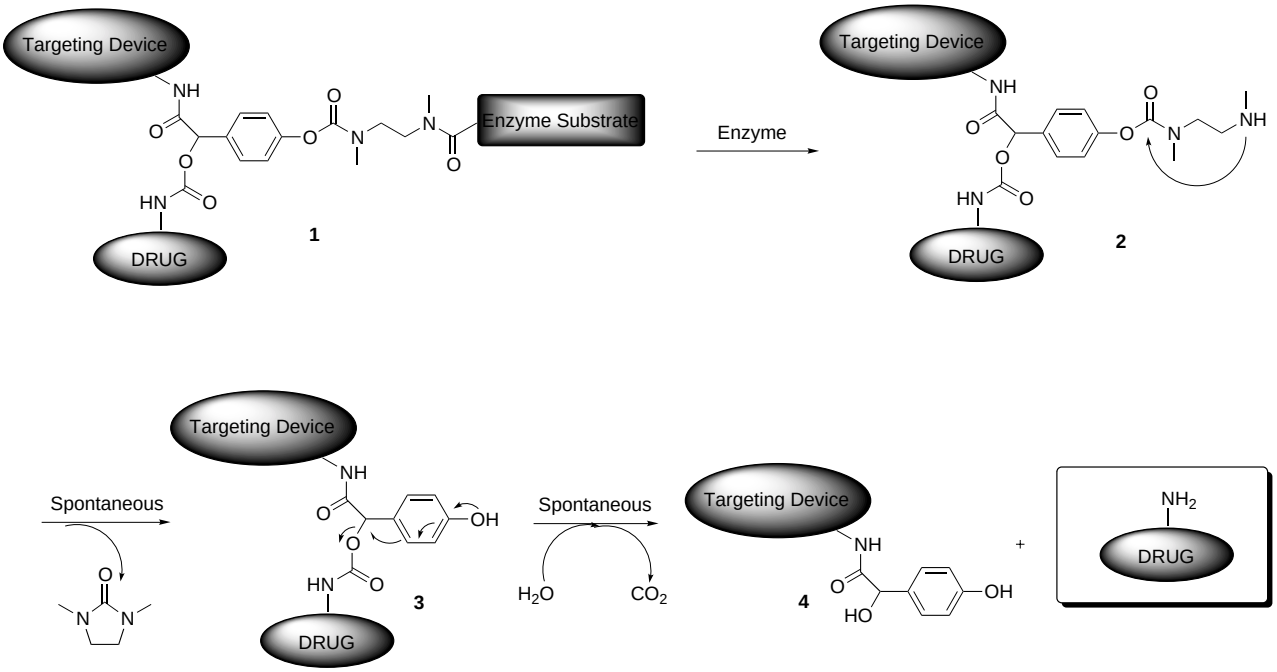
Figure 1. 4-Hydroxymandelic acid, the central core of the **c**hemical adaptor system.



Scheme 1. General design of the chemical adaptor system. Cleavage of the enzyme substrate generates an intermediate that spontaneously rearranges to release the drug from the targeting device.

Scheme 2 illustrates the release mechanism of the drug. Cleaving the enzyme substrate generates a free amine group (**2**) that spontaneously cyclizes to form a dimethyl urea derivative and phenol **3**. The latter undergoes spontaneous rearrangement to give a quinone methide intermediate (trapped by water to give benzyl alcohol **4**), which releases the drug in the form of carbamic acid, which then decarboxylates spontaneously, yielding the active drug.

The design of our generic module allows us to potentially link any targeting device to a variety of drugs and to release them with any enzyme by using the corresponding substrate as a trigger. As proof of the concept, we designed a pilot system for which we chose catalytic antibody 38C2 as the cleaving enzyme.[2] Antibody 38C2 catalyzes a sequence of retro-aldol retro-Michael reactions, using substrates that are not recognized by human enzymes, and thus, are ideal triggers for selective prodrug activation. Antibody 38C2 has proven its ability to catalyze the retro-aldol reactions with a broad range of substrates[3] and recently was conjugated to an *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer for tumor targeting.[4] Furthermore, antibody 38C2 has demon-



Scheme 2. General mechanism of drug release starting with specific enzymatic cleavage.

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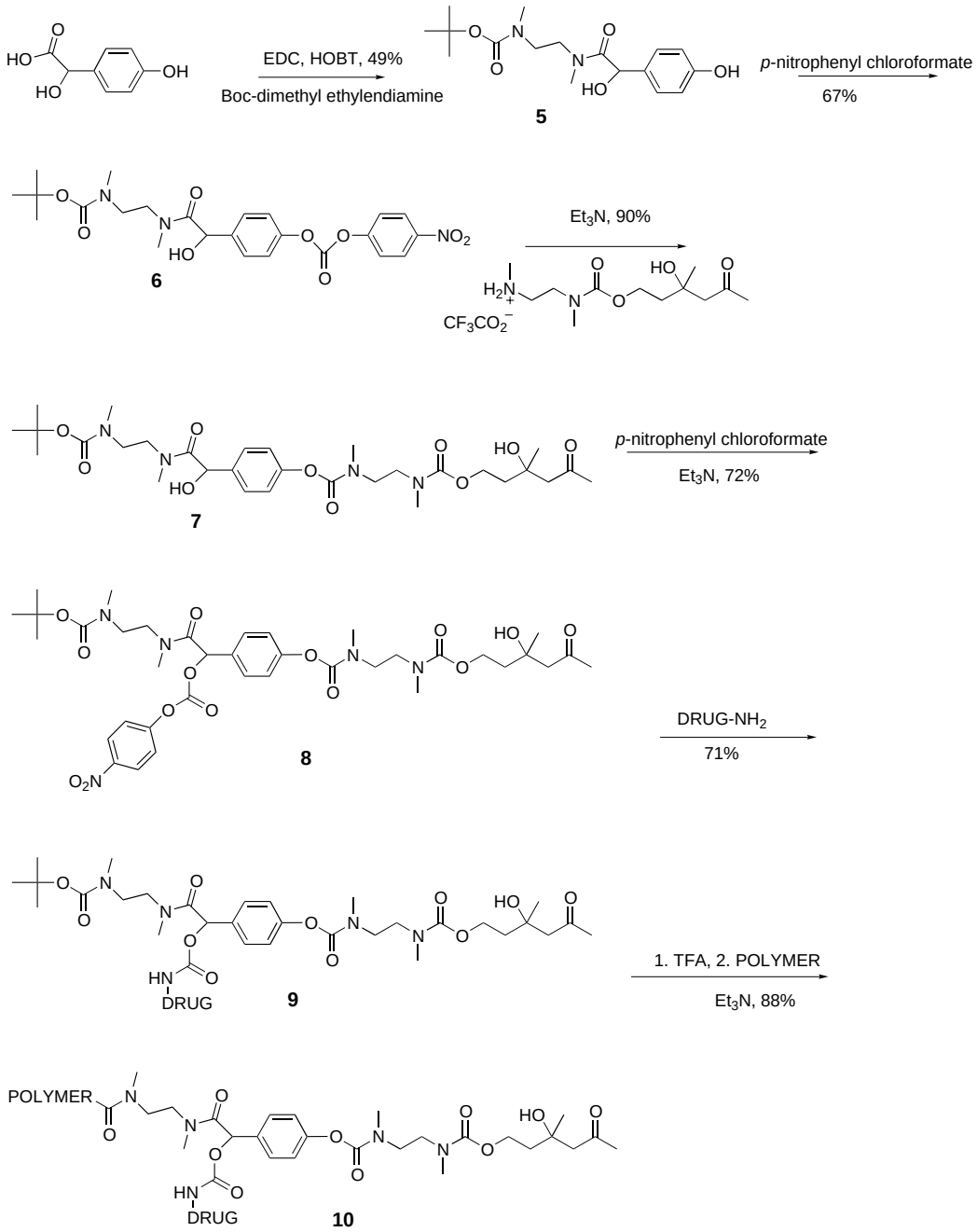
strated its efficacy in activating several prodrugs in vitro and in vivo.[5] A dramatic 75% decrease in subcutaneous (s.c.) tumor size has been observed in mice that received an intratumoral injection of antibody 38C2 and systemic treatments with an etoposide prodrug.[6]

As a targeting device we chose a polymer molecule for our pilot system. Water-soluble synthetic polymers such as HPMA copolymers are biocompatible, nonimmunogenic,[7] and nontoxic. Moreover, their in vivo distribution is well characterized[8] and they are known to accumulate selectively at tumor sites due to the enhanced permeability and retention (EPR) effect.[9] This effect occurs because of the difference between the vasculature physiology of solid tumors and normal tissues. Compared with the regular ordered vasculature of normal tissues, blood vessels in tumors are often highly abnormal. The growth of the tumor creates a constant need for the continuous supply of new blood vessels. This process, termed angiogenesis, often results in the construction of vessels with leaky walls, which allows enhanced permeability of macromolecules within the tumor. In addition, poor



Scheme 3. Synthesis of the chemical adaptor system using catalytic antibody 38C2 as the activating enzyme, an HPMA copolymer as a targeting device, and any drug with a functional amine group. EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, HOBT = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid.

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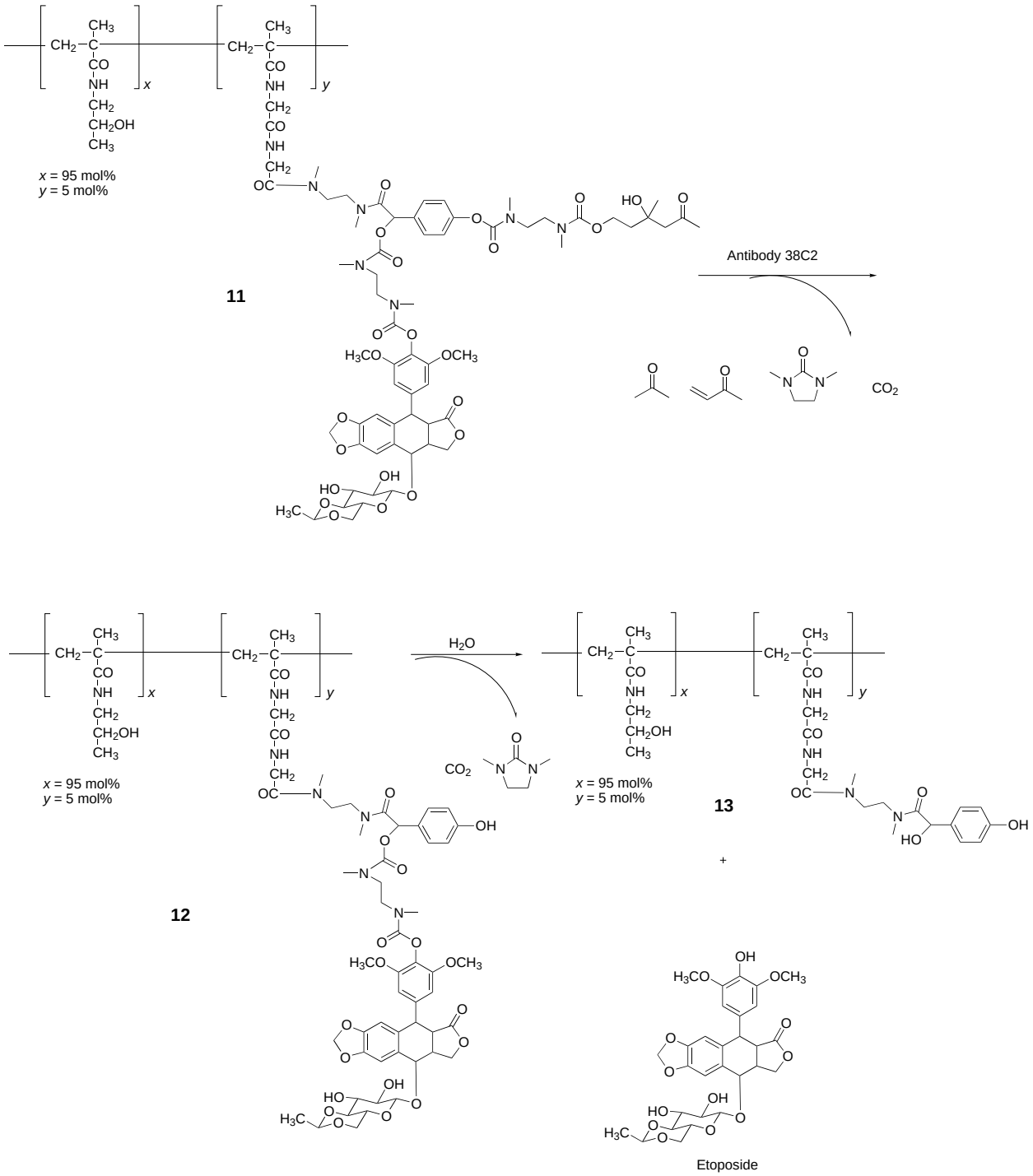
lymphatic drainage at the tumor site promotes accumulation of large molecules. Based on the tumor-targeting properties of molecules derivatized with HPMA copolymers, polymer-directed enzyme prodrug therapy (PDEPT) was developed by Duncan et al. as a novel approach toward selective chemotherapy.[10]

Etoposide was selected as the drug in our pilot system. It is a well-established anticancer drug, which was approved for clinical use by the FDA in the late 1970s, after it demonstrated efficacy in chemotherapy. Etoposide exhibits its antitumor activity by inhibition of enzymes that cut and pass double-stranded DNA called topoisomerase inhibitors.[11] The phenol group of etoposide was used to link it to the complex through a carbamate bond (see Scheme 4).

Starting from 4-hydroxymandelic acid, we built the complex as described in Scheme 3. In brief, 4-hydroxyman-



Scheme 4. Mechanism of etoposide drug release from the HPMA-copolymer, using catalytic antibody 38C2 as the triggering enzyme.

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delic acid was coupled with monoprotected Boc-dimethylethylenediamine in the presence of EDC and HOBT to give amide **5**. Selective acylation of the phenol group with *p*-nitrophenyl chloroformate afforded carbonate **6**, which was treated with antibody 38C2- substrate to give compound **7**. Acylation of the benzylic alcohol with *p*-nitrophenyl chloroformate gave carbonate **8**, which was treated with an amine drug to give compound **9**. The Boc protecting group was removed by TFA to give the corresponding amine salt, which was immediately coupled with the *p*-nitrophenyl ester of the HPMA copolymer to give the final complex **10**. The drug–polymer conjugate was purified by dialysis against water. By measuring its UV spectrum, the number of drug molecules attached to the HPMA copolymer was determined. Based on the etoposide chromophore, which has a λ_{max} value at 280 nm, we found that on average three molecules of the drug were linked to one molecule of the HPMA copolymer.

Next we tested whether the etoposide drug can be released from complex **11** by the catalytic activity of antibody 38C2. According to our design, the drug should be spontaneously released after the generation of phenol **12** as illustrated in Scheme 4. We incubated complex **11** with catalytic antibody 38C2 in phosphate-buffered saline (PBS) (pH 7.4) at 37 °C and monitored the appearance of etoposide using an HPLC assay. As a positive control, we used a previously described etoposide prodrug[6] that is activated by antibody 38C2. As Figure 2 shows, etoposide was released by the catalytic activity of antibody 38C2 to form compound **13** and the free drug. The rate of drug release was similar to the activation rate of the known etoposide prodrug. No spontaneous etoposide release was observed in the absence of the antibody.

The general synthetic approach of introducing the drug in our chemical adaptor system as outlined in Scheme 3, involves a reaction between an amine group of the drug and a *p*-nitrophenyl carbonate of a hydroxybenzyl alcohol to form a carbamate linkage. This strategy is convenient when the drug has an available amine group such as in the case of doxorubicin. Drugs like etoposide, which have free hydroxy groups that need to be masked, are linked through an *N*,*N*-dimethylethylenediamine spacer, which spontaneously immolates to form a dimethyl urea derivative (see Scheme 4).

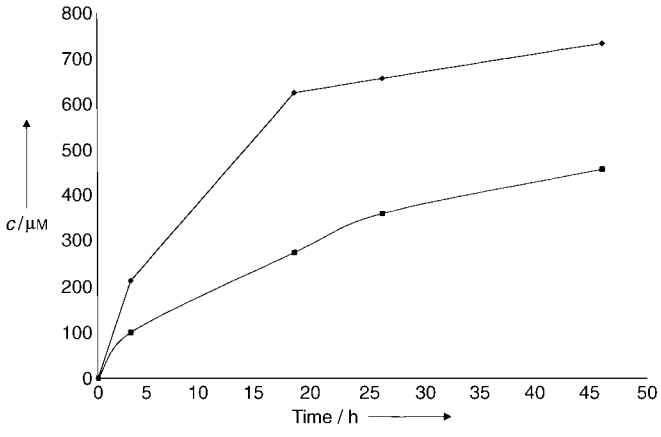

Figure 2. Determination of etoposide release from the HPMA copolymer versus drug formation from a known etoposide prodrug by catalytic antibody 38C2. ◆ Complex **11** (500 μM) with antibody 38C2 (66 μM) in PBS-7.4. ■ Etoposide prodrug (500 μM) with antibody 38C2 (66 μM) in PBS (pH 7.4). Reactions were incubated at 37 °C for the indicated time. The drug release concentration *c* was monitored by HPLC analysis.

A similar and elegant approach of enzymatic cleavage leading to a small-molecule release, was recently published by Waldmann et al.[12] An enzyme-labile linker group was attached to a solid support and a third functionality was used for solid-phase synthesis of a target molecule. The small molecule was detached from the polymeric support, starting by enzymatic cleavage, leading to generation of an intermediate that spontaneously released the product. In one example a quinone methide rearrangement was used to release the target molecule, similarly to our approach.[13] The intermediate was generated by enzymatic cleavage of an ester group, which would result in a high background if used for in vivo prodrug activation. Whereas ester functionalities are stable in organic solvents, they undergo rapid hydrolysis in aqueous solutions at physiological pH. In addition, endogenous enzymes with esterase activity further contribute to nonspecific prodrug activation. In view of these facts, we designed a chemical adaptor system that does not contain any ester linkages but utilizes rather stable amide and carbamate bonds.

In conclusion, we have developed a drug delivery system based on a chemical adaptor that provides a generic linkage of a drug with a targeting device in a manner suitable for triggering by defined enzymatic activity. The system is generic and can be applied to a variety of drugs, targeting devices, and enzymes by introducing the corresponding substrate as a trigger for drug release in the chemical adaptor. The chemical adaptor system was designed with stable chemical linkages to avoid nonspecific drug release in vivo. Proof of the concept was demonstrated by using etoposide as the drug, an HPMA copolymer as the targeting device, and catalytic antibody 38C2 as the triggering enzyme. Currently we are synthesizing a variety of chemical adaptor systems using different tumor-targeting devices, prodrugs, and enzymatic triggers. Two additional examples, comprising a penicillin amidase substrate as the enzymatic trigger and camptothecin as the anticancer drug, respectively, are described in the Supporting Information. In vivo studies aimed at testing our chemical adaptor concept for the selective targeting of tumors have been initiated.

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Light Harvesting with Gels

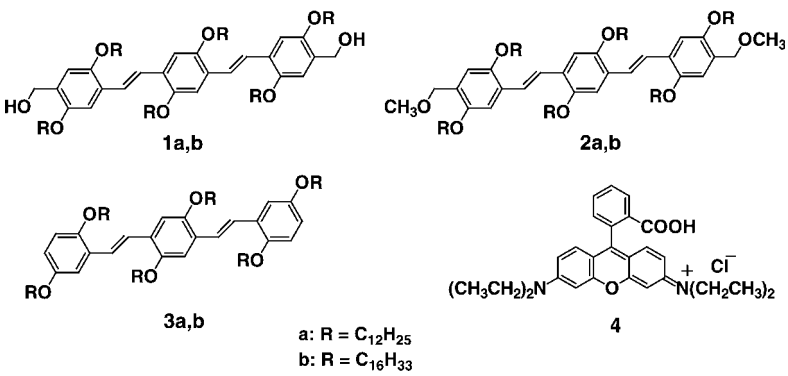
Gelation-Assisted Light Harvesting by Selective Energy Transfer from an Oligo(*p*-phenylenevinylene)-Based Self-Assembly to an Organic Dye**

Ayyappanpillai Ajayaghosh, Subi J. George, and Vakayil K. Praveen*

Dedicated to the memory of Darshan Ranganathan

Excitation energy transfer within and between molecular systems plays an important role in natural processes, such as photosynthesis. In this context, there has been widespread interest in mimicking the mechanism of solar-energy harvesting of natural photosynthesis with the aid of synthetic molecular systems. Apart from this, photoinduced energy transfer has become significant in the area of photovoltaics, organic light-emitting diodes, fluorescent labeling, and in a variety of photonic devices. In most of these cases, energy transfer is considerably influenced by the supramolecular ordering and spatial relationship of the donor and acceptor chromophores. Molecular architectures such as hydrogen-bonded systems,[1] dendrimers,[2] chromophore-linked polymers,[3] Langmuir–Blodgett films,[4] and self-assembled monolayers[5] are of extremely important in this context. Among a plethora of donor–acceptor systems investigated, energy and electron transfer from oligo(phenylenevinylene)s (OPVs) and poly(phenylenevinylene)s (PPVs) to acceptors, such as C_{60},[6] phenanthroline,[7] and doped organic dyes[8] have generated enormous interest because of their potential use in photovoltaic and light-emitting devices. From this view point, the recent reports by Meijer and coworkers on energy and electron transfer from OPV-functionalized dendrimers and supramolecular assemblies to various acceptors are of particular interest.[9] This situation has prompted us to investigate on the potential of OPV based organogels for the purpose of energy transfer and light harvesting.[10]

Small-molecule-based organogels have attracted much attention in recent years because of their interesting physical properties and architectural elegance.[11] However, organogels based on π-conjugated systems are relatively very few.[12] Recently, we have reported hydrogen-bond- and π-stack-induced supramolecular assembly of the OPV derivatives **1a**,**b**, which leads to the formation of entangled nanostructures, which induce gelation of hydrocarbon solvents.[13] The absorption and emission properties of **1a**,**b** showed dramatic changes during gelation, which is an indication of strong intermolecular π-electronic coupling of the ordered self-assembled OPV gel. Excitation of **1a**,**b** in cyclohexane at 380 and 470 nm revealed the emission corresponding to the monomeric species ($\lambda_{em} = 455$ and 483 nm, $\Phi_f = 0.40 \pm 0.01$ related to quinine sulfate, $\tau = 1.46$ ns; Figure 1, spectrum b) and self-assembled species ($\lambda_{em} = 525$ and 565 nm, $\Phi_f = 0.40 \pm 0.01$ related to Rhodamine 6G, $\tau = 1.62$ ns; Figure 1, spectrum c), which showed strong dependency on solvent polarity and temperature.



Herein we describe an interesting case of a thermoreversible fluorescence-resonance energy transfer (FRET) and light harvesting, exclusively from OPV based supramolecular gel nanostructures of **1a**,**b** to an organic dye. To study the feasibility of such an energy transfer, we chose Rhodamine B as the acceptor, the absorption ($\lambda_{max} = 555$ nm) of which

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