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Extended Applicability of Classical Phenolphthalein: Color Changing Polymeric Materials Derived from pH-Sensitive Acrylated Phenolphthalein Derivatives

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Supporting Information

ABSTRACT: Polymerizable phenolphthalein derivatives with pH-sensitive properties were synthesized in the course of electrophilic aromatic substitution reactions. N-(2-hydroxy-5-(1-(4-hydroxyphenyl)-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzyl)acrylamide (3) and N,N'-(((3-oxo-1,3-dihydroisobenzofuran-1,1-diyl)bis(2hydroxy-5,1-phenylene))bis(methylene))diacrylamide (4) were obtained andcharacterized. Copolymerization of 3 and 4 with acrylic acid (5a), <math>N-(isopropyl)acrylamide (5b), and N,N-dimethylacrylamide (5c) enabled the synthesis of color switchable materials. Thereby, water-soluble pH sensitive linear polymers 6 and 7 were prepared using monomer 3. Additionally, cross-linked polymers 8 were prepared successfully by copolymerization of 4 and 5c. These pH-sensitive polymers form hydrogels in aqueous solution. Linear viscoelastic behavior depending on the concentration of the cross-linker was observed.



■ INTRODUCTION

Triphenylmethane dyes are important substances for analytical purposes since many decades. For example, thymol blue, bromphenol blue, phenol red, and bromocresol blue are used as indicators in titrimetic determinations of vitamin B_1 .¹ Some transition metal complexes formed with ethyl violet can be used to detect traces of arsenic ions in water.² Malachit green exhibits fungicidal effects, but due to its cytotoxic properties, it is not used in pharmaceuticals. The compound is applied as an acid—base indicator like many other triphenylmethane dyes.³ Some of the most important triphenylmethane dyes are represented by crystal violet and phenolph-thalein.⁴

Phenolphthalein was discovered by Adolph von Baeyer et al. in 1871 while heating a mixture of phthalic anhydride, phenol and sulfuric acid. Baeyer also observed the molecule's indicative properties.⁵ It appears colorless in neutral solution whereas it is colored pink in basic medium. The perceived color change is caused by a structural change in basic medium. Namely, this structural change is the opening of the lactone ring which is induced by the deprotonation of the phenolic hydroxyl groups. The formation of this quinoid structure of the molecule requires a change in the hybridization of the central carbon atom. This results in an increasing delocalization of the π -system although the molecule is still not completely planar but propeller-like.⁶

Because of its indicative properties, phenolphthalein was added to wines in Hungary in the 1930s in order to indicate contaminations with basic additives. This enabled the detection of laxative effects caused by phenolphthalein. During succeeding years, the dye became one of the most important synthetic laxatives, which can be considered to be due to its low toxicity toward the kidneys and its low price.^{7,8}

Nowadays, it is known that phenolphthalein possesses some carcinogenic effects.⁹ Thus, it is not used for medical applications anymore, but it is still an important indicator dye.

Principally, a polymer-bound phenolphthalein can be considered being nontoxic or at least less toxic than free phenolphthalein. Thus, the development of polymerizable phenolphthalein derivatives is of great interest. In addition to that, cross-linked phenolphthalein-containing polymers can be reused for many times. Accordingly, they represent favorable alternatives for phenolphthalein in many applications, e.g., in industrial processes and in chemistry classes in schools. In order to conserve the molecule's indicative properties the modification with polymerizable groups has to proceed at the aromatic rings and cannot take place at the phenolic hydroxyl groups. Recently, the synthesis of microporous pH-switchable networks based on phenolphthalein-derivatives was published by Antonietti et al. For this purpose, 3',3",5',5"-tetrabromophenolphthalein and 1,4-diethynylbenzene were subjected to a Sonogashira-cross-coupling reaction. The resulting polymers can be used for the adsorption of gases or as photoinitiators in order to start free radical polymerizations.¹⁰ But due to the fact that those polymers are not water-soluble they cannot be used as indicative devices in aqueous solution.

In the past, some dyes were covalently emplaced into copolymers but to the best of our knowledge, pH-sensitive polymers bearing covalently attached phenolphthalein derivatives have not been described so far.^{11,12}

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Scheme 1. Synthesis of Monomer 3 and Bifunctional Cross-Linker 4



In this paper, we wish to present our results about syntheses of hydrolytically stable new polymerizable phenolphthalein derivatives, which were subsequently applied in the synthesis of various linear and cross-linked polymers.

RESULTS AND DISCUSSION

The first aim of this work was to synthesize acrylated and therefore polymerizable phenolphthalein derivatives. It was of great interest to conserve the molecule's indicative properties, thus, an etherification involving the phenolic hydroxyl groups was not an option. Instead, the modification was performed selectively in the *ortho*-position to the phenolic hydroxyl groups. In order to attach a polymerizable group, N-(hydroxymethyl)-acrylamide (2) and phenolphthalein (1) were condensed under acid conditions. Therefore, the reaction was carried out in trifluoroacetic acid as solvent.

The monofunctional derivative *N*-(2-hydroxy-5-(1-(4-hydroxyphenyl)-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzyl)-acrylamide (3) was obtained using double molar excess of phenolphthalein.

Additionally, N,N'-((((3-oxo-1,3-dihydroisobenzofuran-1,1-diyl)bis(2-hydroxy-5,1-phenylene))-bis(methylene))diacrylamide (4) was prepared using concentrated sulfuric acid as solvent and catalyst and equimolar amounts of phenolphthalein and N-(hydroxymethyl)acrylamide (Scheme 1).

The UV/vis spectrum of phenolphthalein shows an absorption peak at 554 nm in basic medium. A weak bathochromic shift induced by the N-(methylene)acrylamide substituent takes place. Accordingly, the corresponding peak of 3 can be observed at 559 nm and at 564 nm for 4 (Figure 1).

Subsequently, linear copolymers were prepared by using monomer 3 and different acryloylic monomers (Scheme 2).

For the preparation of poly[(acrylic acid)-*co*-(3)] (6) acrylic acid (5a) and 1 mol % of 3 were used. A thin layer chromatography (TLC) was accomplished with a solution of the polymer. The non moving "polymer spot" ($R_f = 0$) could be detected by



Figure 1. UV/vis spectra of solutions ($c = 30 \ \mu$ M) of phenolphthalein 1, monomer 3, and cross-linker 4 recorded in basic aqueous solution (0,02 M NaOH).

use of an UV lamp. A spot of the free monomer **3** was not observed. If the TLC plate was fumigated with ammonia, the "polymer spot" turned from colorless to purple. Additionally, the covalent emplacement of monomer **3** was clearly proved by ¹H NMR spectroscopy. Besides demonstrating the polymer's indicative properties, these observations also clearly prove the desired covalent emplacement of monomer **3** into the polymer.

To obtain thermo- and pH-sensitive polymers poly[(N-(isopropyl)acrylamide)-co-(3)] (7) was synthesized with different amounts of monomer 3 and N-(isopropyl)acrylamide (5b).

As described above, the covalent emplacement of monomer **3** into the copolymer was proved by TLC and ¹H NMR spectroscopy.

Cross-linked copolymers poly[(N,N-dimethylacrylamide)-co-(4)] (8) were prepared by using phenolphthalein derivative 4 and *N*,*N*-dimethylacrylamide (**5c**) (Scheme 3).

Scheme 2. Synthesis of Linear Polymers 6 and 7







Figure 2. (a) Polymer 8 was placed in distilled water. In part a, due to the fact that the polymer's refractive index is very close to that of water, it is almost invisible. (b) NaOH solution was added and the polymer started to change its color. (c) if the pH value is higher than 10, the polymer is colored purple. (d) HCl is added, the polymer starts to turn colorless. (e) In neutral solution, the polymer is colorless and almost invisible again.

The covalent emplacement of cross-linking monomer 4 was demonstrated by the fact that the polymerization products were insoluble in any solvents. Instead, the formation of hydrogels could be observed in water. Additionally, the polymers were colored purple in basic medium whereas the solvent stayed colorless outside the network (Figure 2).

The polymers 8 were allowed to swell and the water content was determined by weighing. As expected, the lower the concentration of 4 was the more water was absorbed. Namely polymer 8a containing 0.5 mol % cross-linker exhibited a swelling degree of 7 whereas for polymer 8d, which contains 0,01 mol % cross-linker a swelling degree of 40 could be observed. When the polymers were subject to rheological investigations they showed linearly viscoelastic behavior. With increasing concentration of 4, a higher complex shear modulus was observed because of the higher degree of cross-linking. In the course of the rheological investigations, the linearly viscoelastic region was exceeded for the polymers 8c and 8d. In the case of polymer 8d even the tensile limit could be detected under the applied conditions as a consequence of the low concentration of cross-linker 4 (Figure 3).



Figure 3. Complex shear modulus of the polymers 8a-d depending on τ . (*) Tearing of the polymer was observed, therefore the investigation could not be completed.

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CONCLUSION

Polymerizable phenolphthalein acrylamide derivatives that still have indicative properties were synthesized for the first time from 1 and 2. Reaction of phenolphthalein (1) with hydroxymethyl acrylamide (2) in strong acids followed by column chromatography enabled the isolation of monomer 3 and the bifunctional cross-linker 4. With the exception of a weak bathochromic shift caused by this modification both compounds offer the same optical properties as native phenolphthalein.

Water-soluble and pH-sensitive polymers **6** and 7 could be prepared by the polymerization of **3** with hydrophilic monomers.

Copolymerization of 4 and *N*,*N*-dimethylacrylamide yielded cross-linked superabsorbent polymers 8. The swollen polymers show a refractive index very close to the refractive index of water which makes them appear almost invisible in neutral solution. In contrast to that, the polymers are colored purple in basic medium. Accordingly, the pH indicative properties of phenolphthalein could be conserved during the synthesis of several polymers.

ASSOCIATED CONTENT

S Supporting Information

Description of the syntheses and spectroscopic data of the obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ABBREVIATIONS

TLC, thin layer chromatography

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