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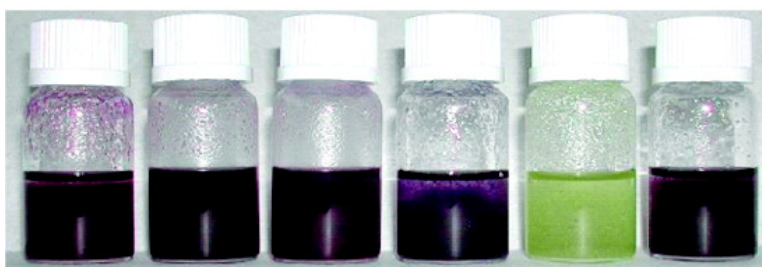
A Sensitive Colorimetric Method for the Study of Polystyrene Merrifield Resins and Chloromethylated Macroporous Monolithic Polymers

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*Same Merrifield resin,
different reaction conditions*



NBP screening test: no Cl  *remaining*

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A Sensitive Colorimetric Method for the Study of Polystyrene Merrifield Resins and Chloromethylated Macroporous Monolithic Polymers

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Reactive polymers have attracted great interest due to their application for the development of supported reagents and catalysts and for the parallel synthesis of chemical libraries.¹ One basic limitation in this area of work is the proper monitoring of the progress of the solid-phase supported reactions.^{2,3} Colorimetric methods are growing in popularity since they are fast and do not require expensive instrumentation. In recent years, we have been involved in the preparation of polymer-supported enantioselective catalysts.⁴ In this context, chloromethylated resins (either gel-type or macroporous) are the most useful starting materials. Current analytical methods for evaluation of the presence of chloromethyl groups range from elemental analysis (EA) (nitrogen analysis on the resin or Cl analysis on the solution after treatment with an amine) to spectroscopic FT-IR, FT-Raman methods.^{4c} Nevertheless, EA is very often subjected to significant inaccuracies, in particular for low Cl contents,⁵ and requires methodologies not directly available at many laboratories, and this limits its use for the day-to-day monitoring of the progress of solid-phase supported reactions. On the other hand, FT-Raman and, in particular, FT-IR methods can be subjected to a number of different interferences, depending on the functional unit being introduced and considering both the accessible and the nonaccessible chloromethyl groups, and this can be important for monolithic materials.⁶ Thus, the development of a fast methodology to properly monitor the presence of chloromethyl groups is highly desirable in this field. In this work, we describe a colorimetric methodology based on the reaction of 4-(4-nitrobenzyl)pyridine (NBP) for the detection of chloromethyl groups in polystyrene-based resins. Due to the increasing importance for applications in catalysis and separations of highly cross-linked macroporous monolithic resins,⁷ we have also extended the application of our colorimetric method for the analysis of this kind of materials.

NBP has been used in the field of medicinal chemistry to detect alkylating agents due to its high nucleophilicity and the further development of an optical signal at ~ 540 nm.⁸ NBP has been also used for the detection of alcohol groups bonded to a resin⁹ as well as to the monitoring of solid-phase oligosaccharide synthesis.¹⁰ For the classical Merrifield

Table 1. Polymers Used in This Study

sample	resin type	cross-linking degree (%) ^b	loading ^c (mmol Cl/g)	porogenic mixture ^d
1	PS ^a	1	0	
2	Merrifield	1	0.83	
3	Merrifield	1	1.19	
4	Merrifield	1	4	
5	PS monolith	50	0	5.0:1.0
6	CM ^e monolith	50	3.2	5.0:1.0

^a PS = polystyrene. ^b Molar content of divinylbenzene in a mixture with styrene. ^c Nominal content of Cl. ^d 1-dodecanol/toluene (only applicable to monoliths). ^e CM = chloromethylated.

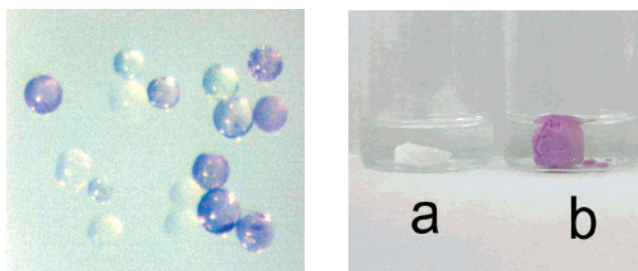


Figure 1. Pictures of samples treated with NBP. Left: mixture of beads (200–400 mesh) of lowly cross-linking polymers **1** (colorless) and **3** (blue) at the optical microscope. Right: (a) monolithic **5** (white) and (b) **6** (violet).

resin, consisting of low cross-linked (1–2%) chloromethylated polystyrene, no such a visual test has been described in detail.¹¹

When samples of commercial Merrifield resins **2–4** (see Table 1 for studied polymers) were immersed in a solution of NBP in $\text{CH}_2\text{Cl}_2/\text{DMF}$ with 5% triethylamine (TEA), the polymers developed a color ranging from pink to violet, depending on the loading of the resin. This observation can be rationalized as the result of the nucleophilic substitution of chlorine and subsequent deprotonation of the pyridinium moiety by the base, leading to the highly conjugated product shown in Scheme 1.¹²

A control experiment was performed with a 50/50 mixture of beads of simple polystyrene **1** and resin **3**. Microscopic analysis of the mixture showed the existence of blue and colorless beads clearly differentiated (Figure 1, left). To determine the minimum amount detectable by the naked eye, mixtures of resins **1** and **3** were prepared and submitted to the test. A mixture composed of 1 part of resin **3** and 99 parts of resin **1** could still be distinguished optically from a sample of pure **1**. Accordingly, the detection limit can be established approximately in 12 μmol of Cl/g of resin.

The test is also valid for macroporous polymers. Thus, samples of **5** (control prepared by polymerization of styrene (VB) and divinylbenzene (DVB)) and **6** (prepared by polymerization of VB, DVB and chloromethylstyrene) were submitted for the NBP test. In the former case, no coloration was observed, whereas in the latter, the resin turned to violet (Figure 1, right). An important difference was found between gel-type and macroporous resins. Whereas for the com-

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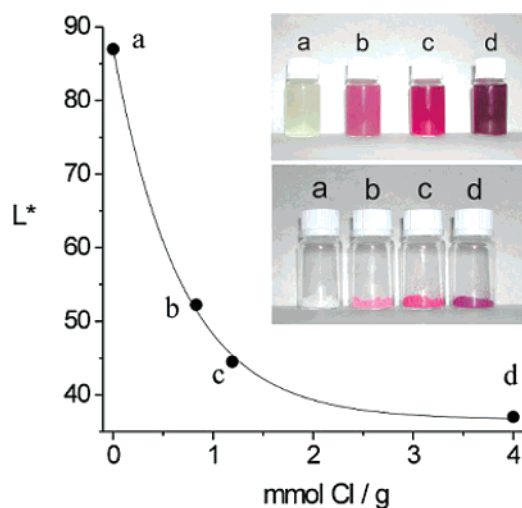


Figure 2. Correlation between samples of different Cl content and their colorimetric parameter L^* (of dry samples) after treatment with NBP/base (see note 13). Top picture: samples in suspension. Bottom picture: dry samples. Loading: (a) 0, (b) 0.83, (c) 1.19, (d) 4 mmol Cl/g resin.

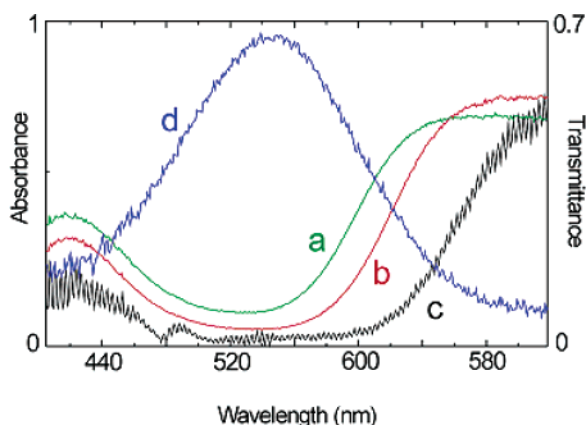


Figure 3. Diffuse reflectance spectra (right axis) of dry resins **2** (curve a), **3** (curve b), and **4** (curve c). For comparison, also shown is the absorption spectrum (left axis) of NBP in CH_2Cl_2 (5% TEA) in the presence of an excess of benzyl bromide (curve d).

mercial Merrifield resin, the color of the sample is stabilized after ~ 1 h, in the case of synthetic macroporous monoliths,

24 h is needed. This observation clearly reflects the kinetic differences found between gel-type and monolithic resins. Clearly, the present methodology can be applied in a time-resolved mode, monitoring the development of the visual signal, to improve overall reaction rates when the limiting step is the access of chemicals to the reactive sites of the matrix.¹³

Attempts to correlate the loading of functional resins with the visual appearance of the colored polymer were made. In this way, samples **2–4** and the control polystyrene **1** submitted to the NBP test were filtered and analyzed by means of diffuse reflectance spectroscopy. Figure 2 shows the color of the four samples, **1–4**, both in suspension (top) and after filtration (bottom). Measurements afforded the corresponding CIELab colorimetric parameters for every dry sample.¹⁴ An exponential relationship was found between the L^* parameter, which represents the lightness of the sample, and the nominal chlorine content. Those results suggest that this test is especially appropriate for quantitative analysis of samples with low loadings (< 1 mmol Cl/g). However, for those samples with high functionalization degrees, the color is too saturated and the L^* differences are not high enough to establish an accurate correlation. Nevertheless, the main value of this methodology focuses on the qualitative and semiquantitative rapid naked eye detection of full or incomplete loading of chloromethylated resins.

The diffuse reflectance spectra of the colored samples (Figure 3) allowed us to confirm that the species responsible for the colors (from pink to violet) is the same and has a maximum of light absorption at ~ 540 nm, in agreement with the value described in the literature,⁸ and with a control experiment carried out placing NBP in CH_2Cl_2 and 5% TEA in the presence of a great excess of benzyl bromide as alkylating agent.

The NBP test is especially useful to determine optimal reaction conditions for reactive polymers in a fast, low-cost way. Because of the high sensitivity of this method, it can be easily applied using a combinatorial approach. As an illustrative example, Figure 4 shows the results of the test for a few samples of a lowly cross-linked (**4**) and a highly

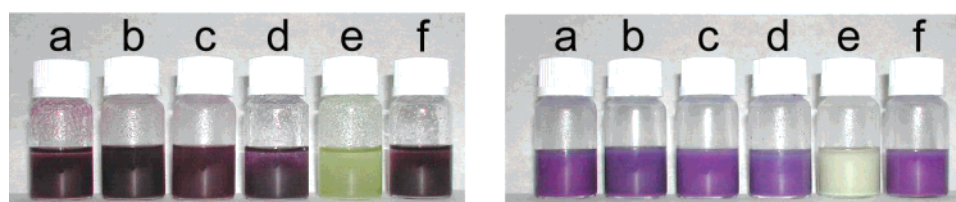
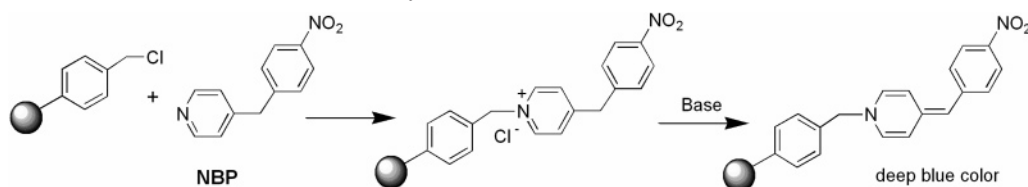


Figure 4. Example of fast assessment of reaction conditions in a model substitution reaction using Merrifield resin **4** (left) and monolithic polymer **6** (right). Each sample was treated with the NBP test (polymer in suspension) after reaction with pyridine (py) as model nucleophile under the following conditions: (a) control; (b) $\text{CH}_2\text{Cl}_2/\text{py}$ [9:1, v:v], 4 h, rt; (c) acetone/py [9:1, v:v], 4 h, rt; (d) toluene/py [1:1, v:v], 0.5 h 50 °C; (e) toluene/py [1:1, v:v], 1 h reflux; (f) $\text{CH}_2\text{Cl}_2/\text{py}$ [9:1, v:v], 1 h reflux.

Scheme 1. Reaction between NBP and a Chloromethylated Resin



cross-linked polymer (6, in this case a pulverized sample) previously submitted to a model nucleophilic substitution as a benchmark reaction using different reaction conditions. Similar results can be obtained using other reactions reported for chloromethylated polymers.

For both kinds of resins, the variables considered were solvent, temperature, reaction time, and reactant concentration (see figure caption). As can be seen, the treatment with NBP helped to discard rapidly the reaction conditions that were not appropriate for this particular reaction (blue vials), allowing us then to continue the work with the positive conditions. With this positive/negative test, the research work, especially when trying to optimize a certain process depending on multiple parameters, is highly accelerated, since there is no need to analyze in detail with other techniques all the samples under study, but only those giving the expected results.

Analogously, a fast gathering of information about the accessibility or reactivity of resins can be achieved when the variables modified are those involved in the preparation of the reactive resin (such as monomer/cross-linker ratio, porogenic mixture, etc.), and hence, the decision-making process can be accelerated both in the laboratory and, especially, in industry, where time-consuming techniques are always undesirable.

In summary, results shown clearly reveal that the NBP test is ideally suited for the analysis of chloromethylated polymers either in gel-type (Merrifield) or monolithic resins (macroporous). This sensitive test can be applied both for the analysis of individual samples and in combinatorial approaches for the fast optimization of the preparation conditions for resins obtained by polymerization and that of reaction conditions for processes involving chloromethylated polymers. Additional work is being carried out in this line.

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Supporting Information Available. Experimental procedures and chemical characterization of polymers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (11) A brief suggestion on the potential use of the NBP for the analysis of halogenated resins is given in ref 3.
- (12) Preliminary results show that this method can also be applied to bromomethylated groups.
- (13) Results observed in monoliths reflect the sum of multiple variables, which are currently under more detailed investigation. The details about pore size and surface area of the samples are out of the scope of this report. An appropriate work will be presented in due course.
- (14) In the literature about colorimetric methods, it is usual to find vague descriptions of the sample colors (for instance “pale yellow”, “intense red”, etc). For the sake of reproducibility it would be more useful to describe colors according to a universally accepted code. In this sense, the CIE (L*, a*, b*) system is commonly used in many fields to characterize the color of solid samples, specially in analytical and food chemistry. The parameter L* characterizes the color intensity or brightness, being 0 the ideal black and 100 the ideal white. The value a* represents the red-green tendency and the parameter b* the yellow-blue tendency of tone. We have decided to provide the chromatic coordinates in this system (Supporting Information) since, in addition to being more objective, they can be measured very easily. In fact, there are small portable devices for the rapid assessment of color quality, mainly used in industry, that could also be useful in research in combination with the NBP test. More information about the CIELab system can be found in: Nassau, K. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 2000. Some examples of its utilization are (a) Castillejo, M.; Martín, M.; Ujia, M.; Silva, D.; Torres, R.; Manusaki, A.; Zafirooulos, V.; van den Brink, O. F.; Heeren, R. M. A.; Teule, R.; Silva, A.; Gouveia, H. *Anal. Chem.* **2002**, *74*, 4662–4671. (b) Lee, H. S. *J. Agric. Food. Chem.* **2000**, *48*, 1507–1511. (c) Karvinen, S. M. *Ind. Eng. Chem. Res.* **2003**, *42*, 1035–1043. (d) Thompson, B. C.; Schottland, P.; Zong, K.; Reynolds, J. R. *Chem. Mater.* **2000**, *12*, 1563–1571.