Reversible Binding of Gold Nanoparticles to Polymeric Solid Supports

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Gold nanoparticles (NPs) are essential components in the design of various functional systems of nanometer dimensions. Their properties are determined by their size and the chemical composition of their capping layer. We have recently presented a scheme for controlled modification of Au NP capping layers by reversible binding to a polymeric solid support via boronic acid chemistry. Octanethiol-stabilized Au NPs were bound reversibly to a polymeric resin derivatized with boronic acid groups. Specially synthesized bifunctional linker molecules carrying a diol on one end and a thiol on the other were bound to the boronic moieties on the resin via the diol group, enabling attachment of Au NPs to the linker-loaded resin through the thiol moiety of the linkers. The resin-bound NPs could be released back to solution by cleaving the boronate ester between the resin and the linker, leaving one (or a few) linker molecule(s) on the NPs. The released NPs retained their properties (optical, solubility) and could be rebound to boronic resins through the linker molecules on their surface. This process of reversible NP binding to a polymeric solid support is studied here in detail. Several boronic-modified resins and linker molecules were prepared and investigated. The chemical conditions for cleavage of the boronate ester were found to be different for NP-free and NP-loaded resins, varying with the type of diol on the linker molecules. Reversible NP binding to high-surface-area solid supports may be useful for preparative reactions on NPs, including controlled NP modification, design of synthetic schemes for modification of NPs under protected conditions, and prevention of NP−NP interactions during chemical manipulation.

Introduction

Nanoparticles (NPs) comprising various metals or semiconductors have been the subject of high interest in the past decade due to their special properties, deriving primarily from electronic confinement effects and high surface-to-volume ratio.[1,2] These lead to a myriad of actual and anticipated applications in areas such as biological markers,[3,4] dyes,[5] optical and electronic sensors,[6−8] platforms for drug delivery,[9,10] building blocks for electronic devices,[11,12] and others. Most of these applications require careful design of individual NPs as well as of NP assemblies. The basic precondition for achieving these goals is control over the NP properties, which are determined by the NP composition, dimensions, and stabilizing layer.

We have recently introduced an effective approach to controlled NP manipulation via reversible binding to a polymeric solid support.[13] Binding of molecules to high-surface-area solid supports has been widely used in organic synthesis and in affinity chromatography, to achieve isolation and separation of molecules through selective binding. Reversible binding of NPs to solid supports has been reported,[14−16] including reversible binding of Au NPs to agarose beads through DNA interactions and their release by heat treatment.[17]

In our scheme,[13] reversible binding of Au NPs to the resin is achieved via boronic acid chemistry. Boronic acids are

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known to bind reversibly to *cis*-1,2 diols, 1,3-diols, and diethanolamines.[18−20] This property was exploited for binding and detection of carbohydrates and demonstrated by, for example, Shinkai's group[21−26] as well as others.[27−36] Recently, this property was used for controlling free insulin.[37] Resins functionalized with diethanolamine,[38] 1,3-diols,[39,40] and catechol[41] were prepared and their binding properties to boronic acids studied. Resins carrying boronic moieties have been described in the literature and were used as diol binders[42] and as imprinted matrixes for carbohydrates[43] and other diols.[44] Studies of boronic acids and boronate esters on surfaces are also found in the literature.[45−48] Of special interest is the work of Whitesides' group where boronic acid monolayers on Au were produced and their esters with various diols studied.[49]

Our preparative method for reversible binding and controlled modification of NPs[13] is studied here in detail via binding of hydrophobic, octanethiol-stabilized Au NPs to boronic-acid-bearing polymeric supports based on modified Merrifield resins. NP binding is achieved through custom-synthesized bifunctional linker molecules, while NP release occurs via cleavage of the boronic acid ester. The linker molecules (one or a few) remain on the released NPs, embedded in the octanethiol capping layer, thus showing no apparent change in the NP properties. The NP binding is stable, and following binding to the polymeric support, the NP-loaded matrix can be dried and stored with no apparent change in the system reversibility.

Use of boronic acid chemistry provides two major elements, i.e., reversibility and mild reaction conditions. Applying a solid support scheme to preparative-scale reversible binding of NPs under mild conditions may provide new routes to separation of NPs based on functional groups in the capping layer, as well as enable carrying out sequences of reactions on immobilized NPs under protected conditions, followed by release of the modified NPs to the solution for further use. Although various NP functionalization methods have been reported (e.g., incubation with functional thiols), NP manipulation on solid support provides the unique feature of separation of the functionalized NPs from unreacted ones.

Results and Discussion

Methodology. Figure 1 shows schematically the approach to reversible binding of Au NPs. The hydrophobic NPs, stabilized with a monolayer of octanethiol molecules, dissolve in nonpolar organic solvents. The solid support is a cross-linked Merrifield resin derivatized with boronic acid groups, followed by treatment with special linker molecules bearing a thiol moiety on one end and capable of binding to the resin via a diol group on the other end. The linker-derivatized resin is treated with the Au NPs, which bind to the thiol groups on the linker molecules. Excess, unbound NPs are washed away. For the reverse process the NP-loaded resin is treated with a specific reagent which cleaves the boronate ester between the linker and the resin, releasing the NPs back to solution. This scheme enables convenient reversible binding of NPs to a high-surface-area solid support. The released NPs are similar to the original ones, with one (possibly a few) linker molecule(s) in their octanethiol capping layer.

Materials. Au NPs stabilized with octanethiol were prepared according to the procedure described by Brust et al.[50] Figure 2 shows a TEM image of the NPs and a size histogram, showing an average diameter of ca. 1.8 nm. These hydrophobic NPs can be dissolved in hexane, toluene, $CHCl_3$, and THF to give clear solutions. They aggregate in methanol, DMF, and acetonitrile. The NP solutions are stable when stored under dark refrigerated conditions. Stock solutions of the NPs were kept in heptane, the latter chosen due to its chemical inertness and better stability to air and light than solvents such as $CHCl_3$. The heptane could be evaporated and the NPs redissolved in other solvents. The NPs are also stable to mild acidic or basic conditions. This extended

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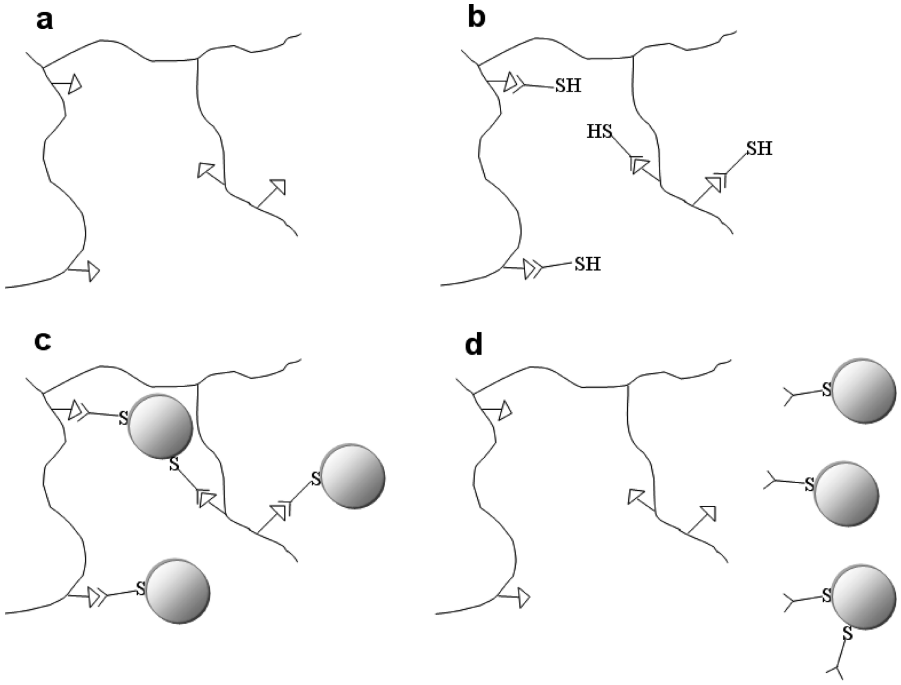

Figure 1. General scheme for reversible binding of NPs to polymer solid supports. A cross-linked polymer with appropriate functional groups (a) is treated with thiol (or disulfide) functionalized linker molecules capable of binding to the polymer, and excess linker is washed away (b). The linker-loaded polymer is treated with Au NPs stabilized with a monolayer of octanethiol (capping monolayer not shown). The NPs bind to the thiol moieties of the linkers. Excess NPs are washed away (c). A specific reagent which cleaves the bond between the polymer and the linker is introduced, thus releasing the NPs back to solution, carrying the linker molecule(s) in their capping layer (d).

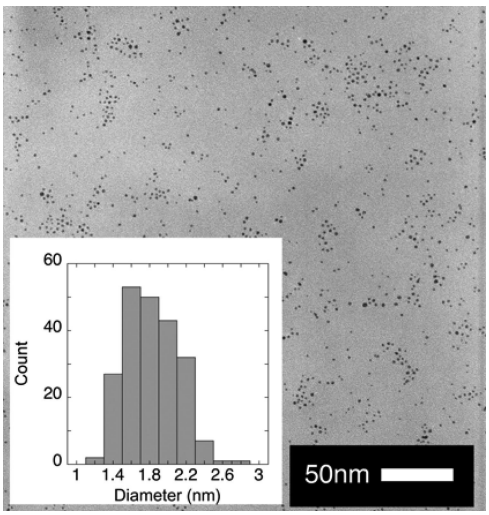

Figure 2. TEM image of gold NPs stabilized with octanethiol. Inset: Size histogram.

stability enables performance of multiple manipulations on the Au NPs.

Figure 3 shows schematically the synthesis of two types of resins carrying boronic moieties. Commercially available Merrifield resin **1** cross-linked with 2% divinylbenzene (DVB) was reacted with sodium 4-bromophenolate in dimethylformamide (DMF) to afford the bromophenoxy derivative **2**. Reaction with butyllithium in THF followed by treatment with triisopropylborate yielded the aromatic boronic acid resin **3**. Resin **5**, bearing aliphatic boronic moieties, was synthesized by reacting Merrifield resin **1** with sodium allyl alcoholate in DMF. The allyl derivative product **4** was reacted with excess borohydride to yield the aliphatic boronic product **5**. The presence of boronic moieties on the resins was confirmed by treating the resin with alizarin in basic conditions. Alizarin forms an orange ester with boronic acids, which emits orange fluorescence upon excitation with long-wave UV light. Treatment of the boronic derivatized resin beads with alizarin produced orange fluorescent beads. Resins **3** and **5** swell in toluene, $CHCl_3$, tetrahydrofuran (THF), and DMF.

Figure 4 shows schematically the synthesis of the three bifunctional linker molecules having a diol at one end and a sulfur-based group at the other end. 3-Mercaptopropionic acid was acetylated and the acetyl derivative **8** was coupled with dopamine to yield the thioacetylated catechol linker **9**. Catechol-disulfide linker **10** was prepared by coupling dopamine to thioctic acid. Linker **13**, containing a xanthate tail, was prepared by reacting the acetonide **11** with 1,6-dibromohexane followed by deprotection to obtain bromide **12**. The latter compound was treated with potassium ethylxanthate in acetone to yield the linker molecule **13**. In linkers **9** and **13** the thiol is protected due to instability of the free thiol moieties.

Attempts to deprotect the acetylated linker **9** resulted in an unstable molecule which tended to form sticky precipitates. The thioctic linker **10** was also unstable on storage, forming solids which could not be redissolved in $CHCl_3$. Mass spectra of the compound detected the presence of a derivative with additional oxygen, apparently on one of the sulfur atoms. The five-membered ring in such a product may open and react with other molecules to form polymers. It is well-known that while thioctic acid is stable, many of its derivatives are not.[51] Because of the instability of this linker, it was used only in the initial experiments.

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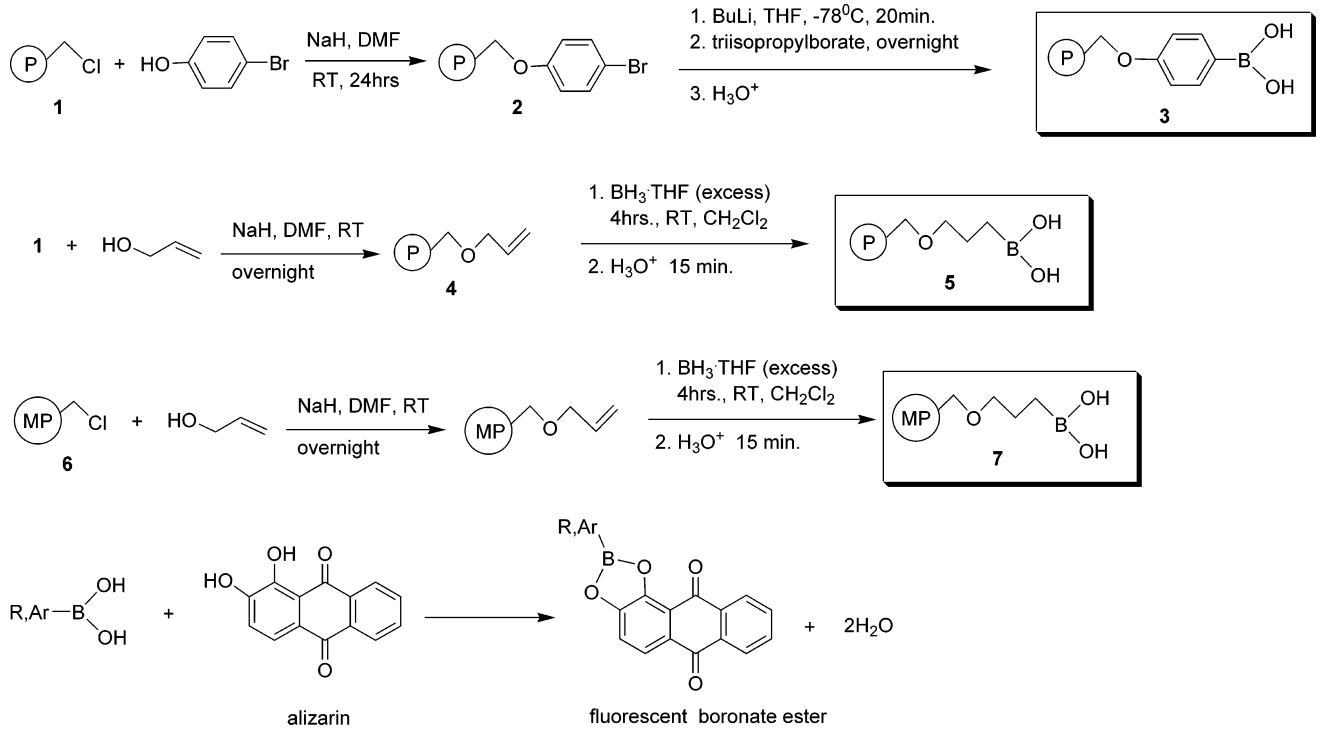

Figure 3. Synthesis of the aromatic boronic acid resin **3**, aliphatic boronic acid resin **5** and the macroporous aliphatic resin **7**. Also shown is the reaction of boronic resins with alizarin.

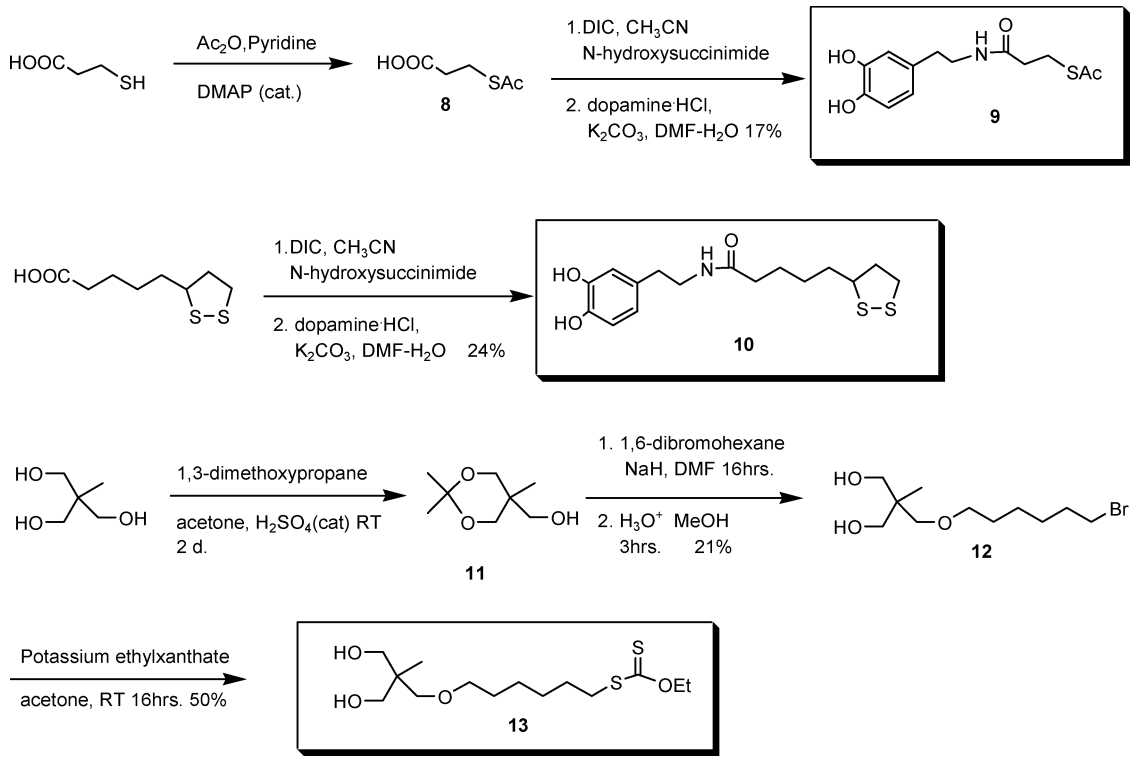

Figure 4. Synthesis of the three linker molecules, bearing catechol groups (**9** and **10**) and 1,3-diol (**13**).

Deprotection of the xanthate group in linker **13** resulted in a compound which immediately oxidized to the disulfide. Therefore, linkers **9** and **13** in $CHCl_3$ were deprotected in situ by using *N*,*N*-dimethylaminopyridine (DMAP) and *n*-butylamine in DMF as a cosolvent. The practice of deprotecting thiols in situ as done in this work was reported previously, under somewhat different conditions.[52]

Binding of Diols to Boronic Resins 3 and 5. To characterize the binding of the linkers to the boronic acid resins **3** and **5**, two linker analogues carrying a dye probe were prepared, as shown schematically in Figure 5. Dopamine was reacted with 2,4-dinitrofluorobenzene to afford the catechol analogue **14**. The analogue **17** was prepared by reacting acetonide **11** with Boc-protected 3-bromo-aminopropane **15**. The protected adduct **16** was then deprotected,

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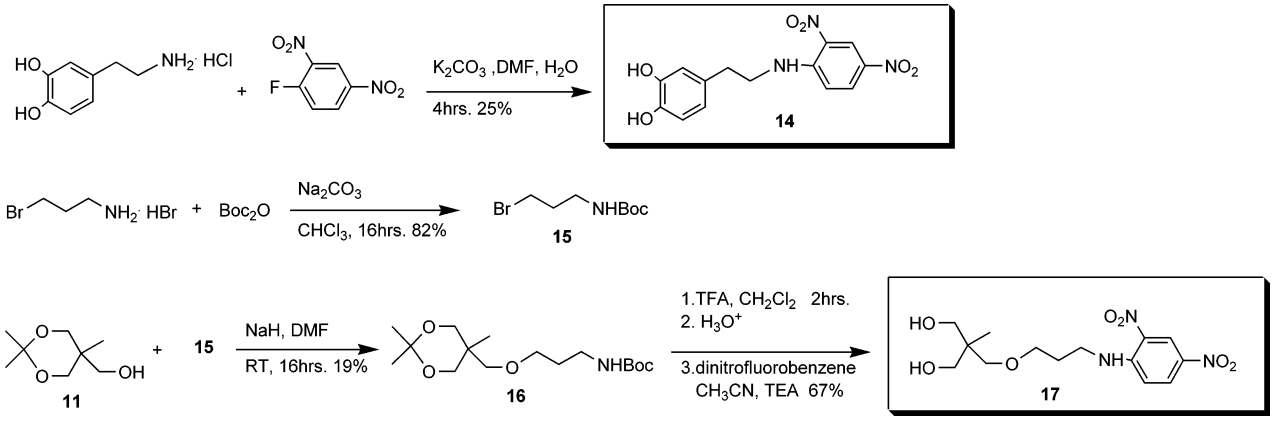

Figure 5. Synthesis of the linker analogues **14** and **17**.

Table 1. Bleeding Experiments with Different Combinations of Resin/Analogue/Solvent

analogue loaded	**14**	**14**	**14**	**14**	**17**	**17**	**17**	**17**
resin type	**3**	**3**	**5**	**5**	**3**	**3**	**5**	**5**
solvent	$CHCl_3$	THF	$CHCl_3$	THF	$CHCl_3$	THF	$CHCl_3$	THF
amount of resin (mg)	4.9	5.4	4.6	4.8	4.5	4.6	5.1	5.2
	Amount of Analogue Released (mmol)							
treatment at time after loading								
wash after 30 min	0.083	0.156	0.103	0.140	0.012	0.017	0.037	0.036
wash after 1.5 h	0.080	0.083	0.081	0.117	0.008	0.018	0.029	0.035
wash after 23 h	0.067	0.029	0.144	0.042	0.036	0.516	0.194	0.467
removal of remaining analogue with acidic THF	0.032	0.003	0.008	0.001	1.345	0.700	0.422	0.151
total (mmol) ±10%	0.26	0.27	0.34	0.30	1.40	1.25	0.68	0.69

and reaction with 2,4-dinitrofluorobenzene afforded the 1,3-diol analogue **17**. The two analogue compounds show an intense yellow color with a high extinction coefficient (ϵ = 18000 M^{-1} cm^{-1} at 350 nm). The intense absorbance enables convenient monitoring of the binding and release of the linker analogues to/from boronic resins, both qualitatively (yellow coloration of the resin upon linker binding) and quantitatively, by measuring changes in the absorbance of the solution.

Binding experiments with the linker analogues were aimed at (i) optimizing the conditions for binding and removal of different types of diols to/from the boronic resins; (ii) testing the stability of the boronate esters; and (iii) quantifying the amount of boronic acid moieties on the resins. The experiments produced the following observations:

1. Although both analogues **14** and **17** were bound to the boronic resin in basic solution (see Experimental Section), the catechol analogue **14** requires basic conditions for binding whereas the 1,3-diol analogue **17** does not require addition of a base. This is in agreement with the behavior of alizarin, which contains a catechol group, and also requires basic conditions (see Experimental Section).

2. Both analogues could be removed from the resin by exposure to another diol (see below) in $CHCl_3$ or THF, aqueous acetic acid in THF, or diethanolamine solution in THF. The time needed for complete removal was less than 10 min.

3. Under experimental conditions similar to those used in NP binding experiments (see below), a tendency of the linker analogues to bleed from the resins into solution was observed.

The analogue binding results are different from those reported for binding of boronic acids to 1,3-diols on resins;[39] contrary to the literature data, no reflux was needed here for the binding.

The bleeding behavior of the resins was studied in detail. Table 1 shows the results obtained in bleeding experiments carried out with the aromatic boronic resin **3** and aliphatic boronic resin **5**. Analogue loading was carried out by treating the resins with either analogue **14** or **17** and *n*-butylamine in $CHCl_3$ for 15 min. The excess diol was washed away and the resin was then treated with 1 mL of solvent, either $CHCl_3$ or THF. After 30 min the solvent was discharged and collected and another 1 mL of solvent was introduced to the resin. The procedure was repeated twice, at times indicated in Table 1. After the last solvent collection (23 h) the remaining linker on the resin was removed with aqueous acetic acid in THF. The concentration of dye in each aliquot was measured by UV−vis spectroscopy. The following conclusions are drawn from the data in Table 1: (i) Bleeding is significantly higher in THF than in $CHCl_3$, as evident when the amount of dye remaining on the resins after 23 h is compared. (ii) Aromatic resin **3** binds the diol molecules much more strongly than the aliphatic resin **5**. (iii) The 1,3-diol model **17** binds more strongly to the resins than the catechol model **14**.

It is assumed that the bleeding is due to hydrolysis induced by residual water, which is consistent with the much higher solubility of water in THF than in $CHCl_3$. The THF was distilled from sodium, but it absorbs water readily from air. The experimental setup, identical to that used for NP binding experiments (see below), was closed but not airtight, hence the presence of residual water. It can therefore be concluded that use of $CHCl_3$ as a solvent is preferred over THF to minimize bleeding. However, certain bleeding of linker molecules into solution can be expected during experiments

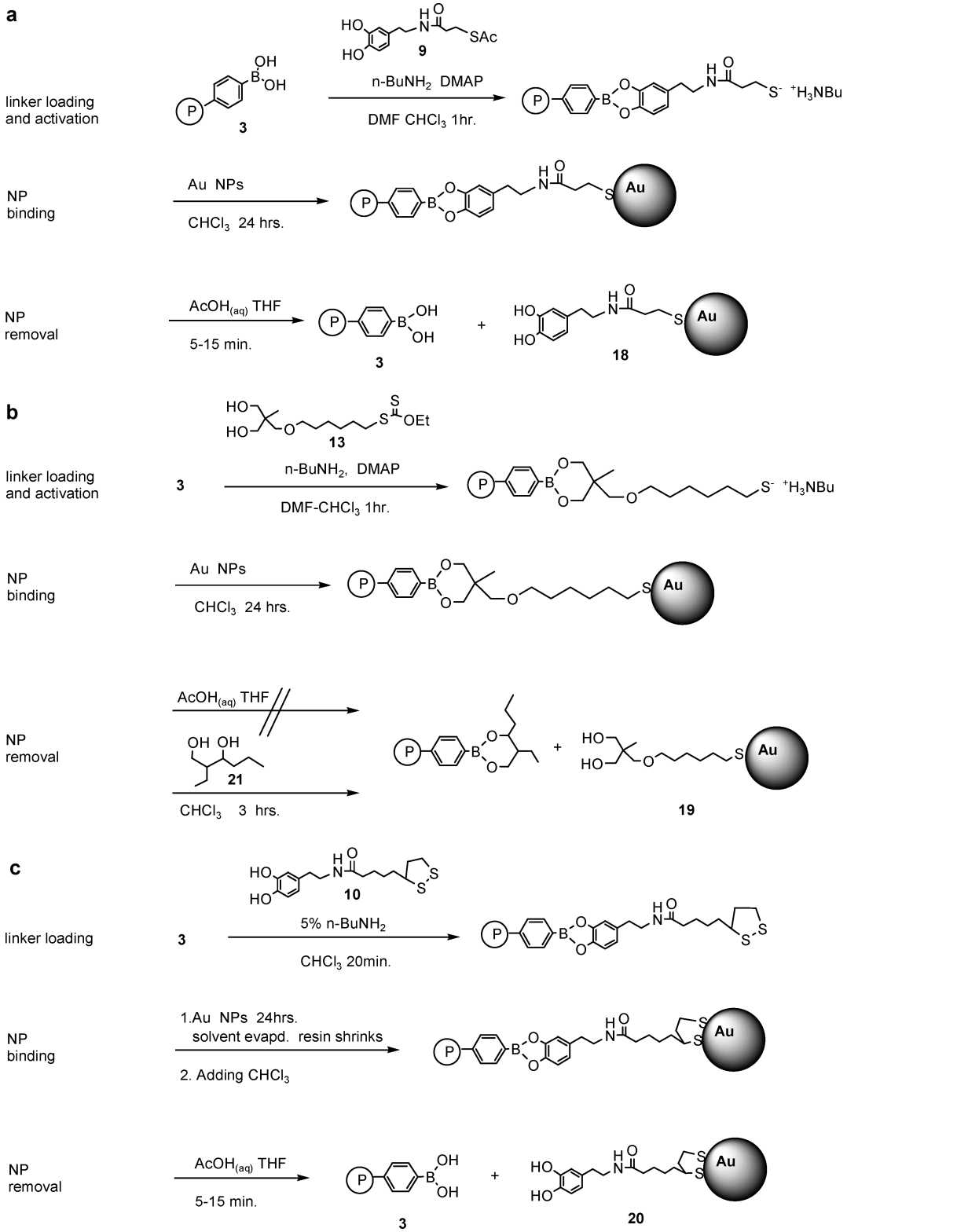

Figure 6. (a)−(c) Reversible binding of gold NPs to aromatic boronic resin **3** using linkers **9**, **13**, and **10**, respectively. The octanethiol capping monolayer on the NPs is not shown.

with NPs even in $CHCl_3$. Note that this may lower the probability of finding a single linker molecule per released NP (Figure 1), as linkers bleeding from the resin may bind to NPs on the resin.

From the results with linker analogue **17** in $CHCl_3$ (Table 1) the amount of boronic moieties on resins **3** and **5** can be estimated as 0.31 and 0.13 μmol/mg, respectively, assuming quantitative binding of the analogue to the resins. This is of interest with respect to the NP binding experiments discussed below. In the latter experiments ca. 5 mg of resin was used; the concentration of the NPs in solution was on the order of μM. The amount of NPs in 1 mL of solution was, therefore, on the order of nanomoles.

Reversible Binding of NPs to Aromatic Resin 3 Using the Three Linkers. The three linkers (Figure 4) were investigated for their ability to reversibly bind Au NPs to

resin **3**. Figure 6 presents schematically the experiments carried out with the three linkers. The protected linkers **9** and **13** (Figure 6a, b) were activated in situ: The linker solution in $CHCl_3$ was mixed with DMAP, DMF, and *n*-butylamine, and the mixture was added to the white, unloaded resin. After 1 h the resin was washed with $CHCl_3$, followed by addition of the NPs (brown colloid solution). After ca. 16 h the resins appeared brown. The excess NPs were washed with $CHCl_3$, leaving a brown, NP-loaded resin. Removal of the bound NPs from the resin, in the case of linker **9**, was achieved using aqueous acetic acid (0.2%) in THF for 5−15 min, leaving a white resin in a brown solution. In the case of linker **13**, acidic THF solution failed to remove the NPs; they could be removed by treatment with a solution of another diol, such as 2-ethyl-1,3-hexanediol (**21**) for ca. 3 h. Cleaning of the released NPs was achieved by evaporating the solvent with a stream of nitrogen and then adding methanol. The NPs aggregated while the impurities dissolved in the methanol. After centrifugation, the methanol was discarded and pure methanol was introduced. This step was repeated three times. Following the cleaning steps, the NPs were redissolved in THF or $CHCl_3$.

With the thioctic linker **10** negligible binding of NPs to resin **3** was observed. However, if the solvent was allowed to evaporate and the solid residue left overnight, addition of $CHCl_3$ showed a considerable amount of NPs bound on the resin, while unbound NPs dissolved back in the $CHCl_3$. The conditions (solvent, time) required to release the resin-bound NPs were the same as those used with linker **9**. The NPs could undergo the cleaning procedure with methanol described above and redissolve in THF. The inability of linker **10** to bind NPs according to the usual procedure is not yet understood.

It should be noted that the same experimental conditions were needed for removal of NPs bound through both catechol linkers **9** and **10**. This suggests that correlations can be found relating structure and performance in NP binding and release to/from boronic resins.

Blank experiments using resins without boronic groups, boronic resins without linkers, or boronic resins with protected linkers showed no binding of NPs. Furthermore, boronic resins without linker were suspended in a solution of NPs in $CHCl_3$ and the solvent was allowed to evaporate to dryness. After 24 h $CHCl_3$ was added again to the dark mass; the NPs dissolved completely, leaving the resin beads white.

Figure 7 shows UV−vis spectra of the NPs at different stages of experiments using resin **3** loaded with linkers **9** and **13** (7a and 7b, respectively). Curves 1 present the spectra of a 1.5 mL solution of the NPs in $CHCl_3$ (0.1 mg/mL) as introduced into the syringe containing the resins. The spectra show the characteristic Au NP absorbance with a shoulder around 500 nm. Curves 2 show the spectra of the same 1.5 mL solution after 16 h with the resin. The decrease in the absorbance of the solution is an indication of NP binding to the resin. Curves 3 show the NP spectra after removal of the bound NPs from the resin using the appropriate removal solution (see above). Curves 4 show the spectra of 1 mL THF solution of the cleaned NPs (the spectrum is enhanced for clarity).

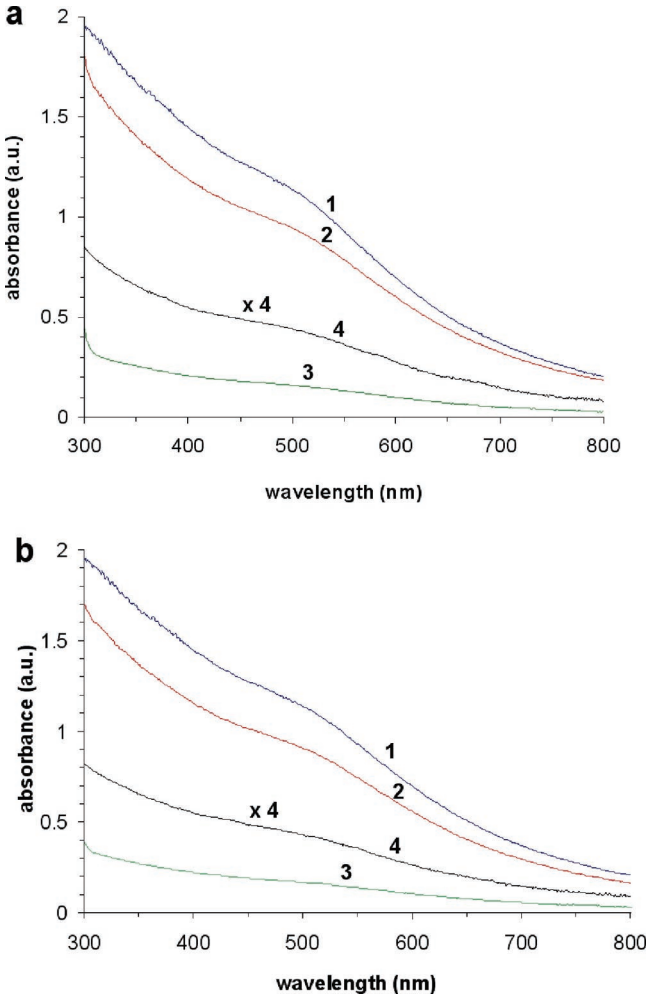

Figure 7. UV−vis spectra measured during NP reversible binding to aromatic resin **3** via linkers **9** (a) and **13** (b). (1) NP solution (1.5 mL), 0.1 mg/mL in $CHCl_3$. (2) The NP solution after 16 h with the resin. (3) NPs in 1 mL of appropriate removal solution after release from the resin. (4) The released NPs in 1 mL of THF after cleaning (spectrum enhanced ×4).

Table 2. Absorbance Data from Figure 7a and Corresponding Estimated NP Concentrations[a]

entry	measurement	abs. at 500 nm corrected to 1.5 mL	concentration (μM)
1	NPs at beginning	1.13	2.5
2	NPs after 16 h with the resin	0.94	2.1
3	difference	0.19	0.4
4	NPs in removal solution (% of initially adsorbed)	0.11 (55)	0.24
5	NPs in THF after cleaning (% of released)	0.07 (60)	0.15

[a] All absorbance values are corrected to 1.5 mL of solution. The amount of resin was 4.9 mg.

Table 2 summarizes the results of the experiment described in Figure 7a using linker **9**. The absorbance values are all corrected to 1.5 mL of solvent. The concentrations of the NP solutions were estimated from the size distribution, obtained by TEM imaging as in Figure 2 (for details see Experimental Section). The amount of NPs released from the resin is lower than the amount initially immobilized, as given by the absorbance difference in the binding solution. Since the resin appears white after treatment with the removal

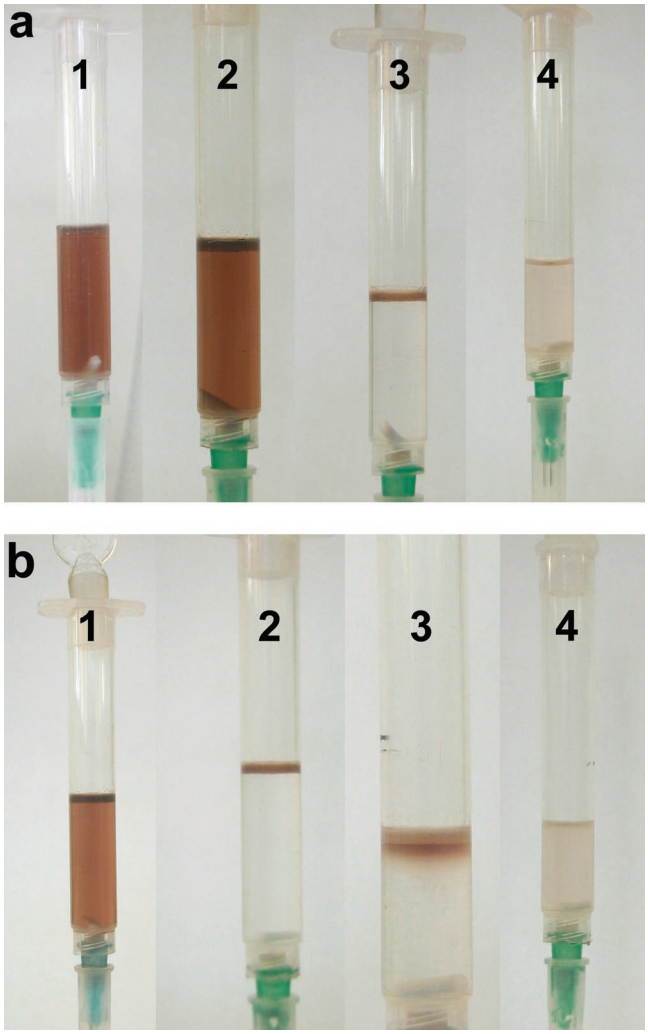

Figure 8. Pictures taken during NP reversible binding to resin **3** via linkers **9** (a) and **13** (b). Sequence a: (1) Resin (white) floats on $CHCl_3$ solution of the NPs. (2) After ca. 16 h the beads become brown due to NP binding. (3) Excess NPs were washed away with $CHCl_3$, leaving the brown resin beads in the syringe. (4) After acidic THF was applied for 15 min, the NPs were released from the resin. Sequence b: (1) NPs after 16 h with the resin. (2) Excess NPs were washed away with $CHCl_3$, leaving the brown resin beads in the syringe. (3) Resin after 1.5 h treatment with a solution of diol **21** in $CHCl_3$; a cloud of NPs was released from the beads. (4) After an additional 1.5 h the NP removal was complete.

solution, the possibility of irreversible binding can be excluded. It is therefore assumed that physically adsorbed NPs were removed during the washing step before introduction of the removal solution. As expected, the final cleaning step involves some loss of NPs. It is summarized that the amount of NPs chemically bound to the resin is relatively low in this case. The results calculated for linker **13** according to the spectra in Figure 7b are similar to the results with linker **9** (Table 2).

Figure 8 shows photographs taken at different stages of the experiments. The white resin floating on the $CHCl_3$ solution of the NPs gradually becomes brown as a result of NP binding. Washing away the excess NPs with $CHCl_3$ leaves the brown resin beads floating on $CHCl_3$. The NPs are then removed from the resin using the appropriate removal solution. In the case of linker **13** (Figure 8b) the NP removal is slower, and the brown cloud of NPs released from the resin into solution (while the resin becomes white) is clearly seen in Figure 8b (3).

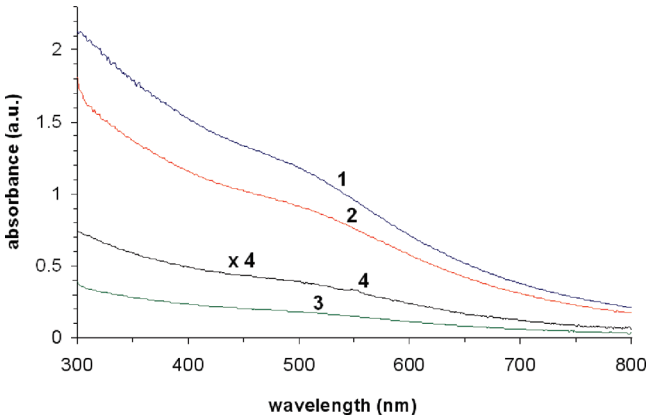

Figure 9. UV−vis spectra measured during reversible NP binding to aliphatic resin **5** via linker **9**. (1) NP solution (1.5 mL), 0.1 mg/mL in $CHCl_3$. (2) The NP solution after 16 h with the resin. (3) NPs in 1 mL of removal solution after release from the resin. (4) The released NPs in 1 mL of THF after cleaning (spectrum enhanced ×4).

Performance of Aliphatic Resin 5 vs Aromatic Resin 3. NP binding and release were also studied with the aliphatic resin **5** (Figure 3). Hence, the experiment described in Figures 6a, 7a, and 8a were also carried out with resin **5**. Figure 9 shows the results of a binding/release experiment carried out with resin **5** using linker **9**, analogous to the data in Figure 7a corresponding to resin **3**. The results are practically identical (within experimental error) to those obtained with the aromatic resin **3**. Experiments with resin **5** using linker **13** also gave similar results to those obtained with aromatic resin **3**.

Role of Resin Morphology. From the data in Figures 7 and 9 it can be seen that essentially the same results were obtained with different combinations of resins and linkers, although the amount of linker molecules present on the resin is quite different. It was already shown in Table 1 that bleeding of the linkers was highest when a catechol model was used with the aliphatic resin **3**, implying that the amount of linker molecules **9** on resin **3** was lower than in the other cases; the NP binding results, however, are similar (Figures 7 and 9). Experiments with 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB, Ellman's Reagent), a reagent specific to thiols, established the existence of nonactivated linker molecules on the resin, as well as activated linkers which did not bind any NPs. These observations support the notion that the limiting factor in NP binding is not the amount of active linkers present on the resin, but rather the morphology of the resin, which determines the accessibility of the binding sites to the NPs. Evidently, with the resins used, the fraction of sites capable of accommodating NPs is rather small compared to the total amounts of active linkers on the resin.

Efficiency of Various Reagents in NP Removal. When diol molecules are bound to the boronic resin, they can be released by using diethanolamine, aqueous acetic acid in THF, or a competing diol. The situation is different in the case of bound NPs. Experiments involving release of resin-bound NPs back to the solution revealed intriguing behavior. Diethanolamine solution, which effectively removes linker molecules, linker analogues, and other diol molecules bound to the resin, failed to release the linker-bound NPs in all cases. Acidic THF solution was very effective for NP

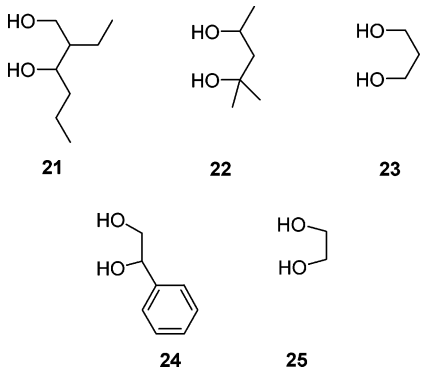

Figure 10. Diols tested for efficiency in the release of NPs bound via linker **13**.

Table 3. Absorbance at 500 nm of NPs Released from Resin 3 Treated with Various Reagents[a]

solvent	21	22	23	24	25	acidic THF
$CHCl_3$	0.16	0.14		0.04		
THF		0.12	0.05		0.00	0.00

[a] In all cases 1 mL of solution of the reagent was used. Treatment time was 95 min. The concentration of diol solutions was 0.15 M. Estimated error: ±10%.

removal in the case of catechol linkers **9** and **10**, requiring 5−15 min for NP release. With linker **13** the acidic THF solution was ineffective.

Use of another diol for transesterification of the linker boronate ester, thus releasing the NPs bound via linker **13**, was found to be effective. The diols used in this experiment are shown in Figure 10. NPs were bound through linker **13** to resin **3** and then treated with 0.15 M solutions of diols **21**−**25**. After 95 min the solution was transferred to a cuvette and a UV−vis spectrum was taken, from which the relative amount of NPs released to the solution was determined. The spectra were normalized to the weight of resin used in each experiment.

Table 3 shows the results obtained with the different diol reagents. The solvents used were $CHCl_3$ or THF, owing to the limited solubility of 1,3-propanediol **23** and ethylene glycol **25** in $CHCl_3$. 2-Methyl-2,4-pentanediol **22** was used in both solvents, to evaluate possible solvent effect. The amount of diol reagents was ca. 2 orders of magnitude higher than the amounts of boronate esters on the resin. Diols **21** and **22** were considerably more effective than diol **23,** the latter exhibiting slightly higher activity than diol **24**. Diol **25** showed no activity.

From Table 3 it is evident that the release efficiency of the different diols follows their ability to bind to boronic acid; i.e., 1,3-diols bind more effectively than 1,2-diols, while alkyl or phenyl side chains improve the binding. This order of efficiency was not observed when similar experiments were conducted on linker analogue **17**, which was released almost completely (93%) by diols **21**−**24** in 10 min. This can be explained by the hydrophobic nature of the octanethiol-capped NPs. In the absence of NPs the concentration of all diol reagents around the reaction center, i.e., the boronate ester, is high enough to promote effective substitution of the linker analogue with diols having different binding constants. The presence of the NPs introduces a hydrophobic environment in the vicinity of the boronate ester, resulting in lower concentrations of the reagents around the reaction center. This may explain the slow removal of NPs (a few hours), as well as the large difference in NP release efficiency of the different diol reagents.

Table 4. Results of Reversible Binding Experiments Carried Out with Macroporous Resin 7

linker	**9**	**13**
amount of resin **7** (mg)	3.5	3.3
treatment	abs. at 500 nm	
NP solution at beginning	1.16	1.16
NP solution after 16 h	0.55	0.61
Δ abs.	0.61	0.55
NPs released from resin (% from bound)	0.49 (81)	0.37 (68)
NPs after cleaning (% of released)	0.30 (61)	0.27 (71)

Table 5. Binding and Release of NPs 19 to/from Resin 3

	solution at beginning	solution after 12 h	Δ abs.	NPs released from resin
abs. at 500 nm	0.24	0.11	0.13	0.07

The hydrophobic effect of the bound NPs also explains the inefficiency of aqueous acid in THF to release NPs bound through linker **13**. The binding of boronic acid to catechol is known to be much weaker than the binding to 1,3-diols; hence, the low concentration of acid in the vicinity of the reaction center was enough to release NPs bound through catechol linkers **9** or **10**, but not to hydrolyze the ester with 1,3-diol linker **13**, the latter easily achieved in the absence of NPs. Diethanolamine solution, which effectively removes diol molecules bound to the resin, was ineffective with linker-bound NPs in all cases, which is similarly explained by hydrophobic exclusion. Moreover, diethanolamine binds to boronic moieties through a transannular coordinative bond, which is not favored in the hydrophobic environment of the NPs.

Treatments of Bound NPs with Solutions of Thiols. NPs bound to the resin were treated with solutions of other thiols such as octanethiol or octadecanethiol (10 mM, overnight). Although one may expect exchange of linker molecules with the dissolved thiol, resulting in removal of the NPs from the resin, no NP removal was observed. (The NPs could be removed by the usual cleavage of the boronate ester.) These experiments show that exchange of linker molecules by thiols in solution did not occur, indicating that place-exchange reactions on the bound NPs are confined to the NP surface exposed to the solvent.

Use of a Macroporous Resin. As discussed above, the performance of resins **3** and **5** is relatively modest in terms of the amount of NPs bound per unit weight of the resin. It was also shown that the morphology of the resin determines the accessibility of binding sites to the NPs. To tackle the performance issue, a different matrix was tested, i.e., the macroporous resin **7** (Figure 3) having much smaller average bead size of 35 μm and relatively high porosity, stabilized by a high degree of cross-linking.[13] This resin is based on macroporous Merrifield resin **6** modified similarly to the preparation of resin **5** (Figure 3). The aliphatic boronic macroporous resin thus obtained showed superior performance compared to that of resins **3** and **5**, as described below. A noted advantage of macroporous resins is that they can be utilized in a variety of solvents, as the pore system in

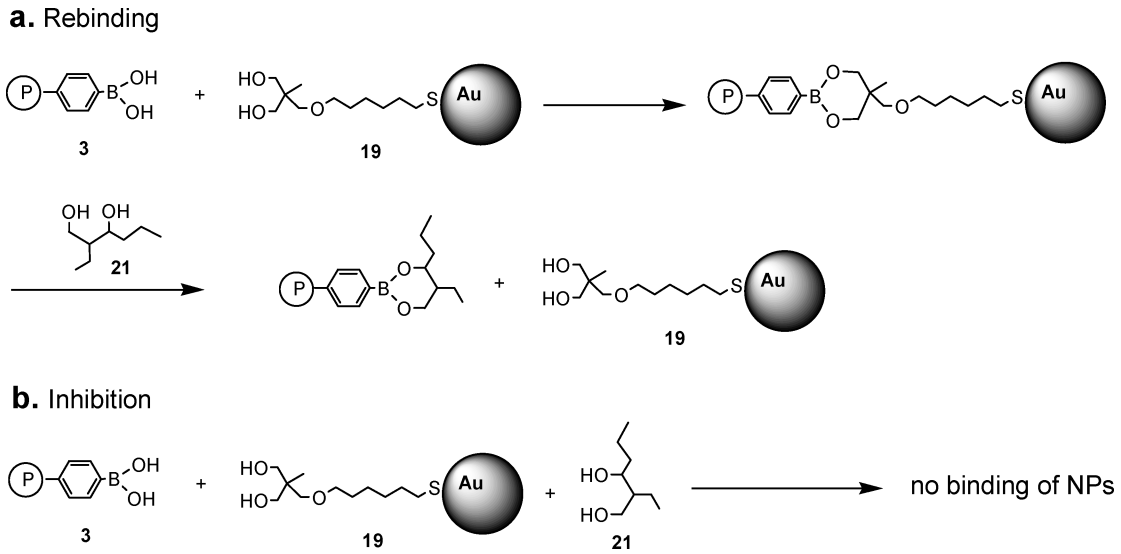

Figure 11. Second-cycle NP binding and release: (a) NPs **19** (released from resin **3**) are rebound by treatment with fresh resin **3** and can be released again using diol **21**. (b) When diol **21** is added to the initial mixture of NPs **19** and resin **3**, NP rebinding is totally inhibited.

these highly cross-linked matrixes is fixed and essentially no change in dimensions occurs upon solvation. Low cross-linked resins such as **3** and **5** can only be employed in certain solvents in which they swell (e.g., $CHCl_3$).[53]

Resin **7** was tested with linkers **9** and **13** following the respective protocols in Figure 6. Linker loading proceeds similarly to the loading of resins **3** and **5**. Table 4 shows NP binding/release results obtained with resin **7** and linkers **9** and **13**. Comparison with the data in Table 2 shows that resin **7** exhibits higher capacity for NPs than resins **3** and **5**. Moreover, most of the binding occurred in the first 2−3 h, rather than ca. 16 h in the case of resins **3** and **5**. Note that blank experiments where resin **7** was reacted with NPs without linkers, or NPs with linkers not activated by *n*-butylamine (Figure 6), showed no binding.

After NP binding, the resins could be washed, air-dried, and stored under ambient conditions for 1−2 weeks. The NPs could then be released back to solution by introduction of the solvent and the appropriate removal reagent.

The macroporous boronic resin **7** exhibits clear advantages over resins **3** and **5** in terms of NP binding capacity, binding kinetics, and solvent selection. The main advantage of resins **3** and **5** is that they are derived from resin **1**, which is readily available and can be modified in large quantities to the boronic products.

Second-Cycle NP Binding and Release. NPs **18**−**20** (Figure 6) released from the linker-modified resins with one (or a few) linker molecule(s) embedded in their octanethiol capping layer can be rebound to a fresh, unmodified boronic resin via reaction of the diol linker on the NPs with the boronic acid moieties on the resin. This process, presented by us before[13] using NPs **19** and boronic-modified macroporous resin **7**, is described here in detail for rebinding of NPs **19** to boronic resin **3**.

The following experiments were carried out with resin **3**: (i) In the experiment shown schematically in Figure 11a, NPs **19** were treated with a fresh portion of resin **3**. After 12 h NP binding to the resin was observed, indicated by the lower absorbance of the NP solution in $CHCl_3$ (Δ abs) and by the brown color developed in the resin beads. When the brown beads were washed and then treated with diol **21**, the NPs were released to the solution. (ii) An inhibition experiment was carried out, shown schematically in Figure 11b, where NPs **19** were mixed with resin **3** and diol **21**, resulting in no NP binding. (iii) A cross-experiment was demonstrated where NPs released from resin **7** were rebound to resin **5**. Note that blank experiments using NPs with no linker molecules in their octanethiol capping layer showed no NP binding to the resins.

Table 5 shows absorbance data of NP solutions during the various steps of second-cycle binding, corresponding to the experiment in Figure 11a. The absorbance data are normalized to the same volume of solution. The value corresponding to the amount of rebound NPs (Δ abs) is higher than the value corresponding to the amount of NPs recovered from the resin. This may be attributed to weakly bound NPs which were removed from the resin during the washing step.

The second-cycle binding (and release) experiments provide clear evidence for the transfer of linker molecules to the NPs following the first cycle of binding and release (Figure 6). They also demonstrate the virtue of boronic acid chemistry in providing reversibility. Moreover, they show that NPs of this type are stable enough to survive multiple treatments of binding, removal, and cleaning while maintaining their properties. In a more general view, the results imply that binding NPs to resins can be used for selective separation of NPs bearing specific groups showing affinity to the resin, even if these groups are present in a minute amount on the NP surface, possibly down to one molecule per NP.

Conclusions

We have demonstrated reversible binding of gold nanoparticles (NPs) to polymeric solid supports using boronic-acid-derivatized resins as the solid matrix. Use of boronic acid-diol chemistry affords reversibility and mild conditions, compatible with NP manipulation. Binding of the NPs to

(53) Sherrington, D. C. *Chem. Commun.* **1998**, 2275−2286.

the resin occurs via specially synthesized bifunctional linker molecules, which are transferred (one molecule or a few) to the NP capping layer upon release from the resin. The type of diol in the linker, determining the stability of the boronate ester between the linker and the resin, has a major influence on the NP release kinetics. This structure−activity relationship can be used for controlling the release by proper linker design. The conditions required for cleavage of the boronate esters were different when NPs were bound to the linkers, attributed to the effect of the hydrophobic stabilizing layer on the NPs on the permeability of various reagents. The latter was demonstrated by the difference in NP release efficiency of different diols. Understanding these processes may enable tailoring of the system properties and efficiency by the choice of resin, linker, and diol. The NP-bound resins are quite robust: they can be washed, air-dried, and stored and still release the NPs by addition of solvent and appropriate reagents.

The presence of one (possibly a few) linker molecule(s) on the NPs released from the linker-modified resin was demonstrated by second-cycle binding of the NPs to a fresh, unmodified boronic resin via the linker on the NP surface, and the rebound NPs could be released again. This approach can be used for separation and recovery of NPs based on specific affinity to resin groups.[13]

The resin morphology and swelling properties govern the accessibility of resin-bound linkers to the entering NPs, thus determining the maximum loading of the resin with NPs, the latter always lower than the amount of active linkers on the resin. In this respect the highly cross-linked macroporous resin used outperforms the 2% cross-linked resins; on the other hand, the latter are commercially available, are inexpensive, and can be used in large quantities for preparative-scale reactions.

The NP functionalization approach presented here is unique in providing inherent separation of functionalized NPs from unreacted ones. This scheme may also allow the following: single-molecule NP functionalization (using an appropriate resin); reactions on bound, isolated NPs; affinity separation of NP mixtures; and controlled release of NPs to solution. The solid support approach is therefore a clean, simple, preparative, and versatile tool for carrying out reactions on NP surfaces in a controlled manner.

Experimental Section

Materials and Methods. Unless otherwise stated, chemicals were analytical grade, purchased from Sigma-Aldrich, and used as received. Sodium hydride (Merck) was an 80% suspension in paraffin oil. Merrifield resin **1** was purchased from Fluka, product no. 63871, cross-linked with 2% DVB, bead size 200−400 mesh, loading ca. 0.7 mmol/g. Macroporous Merrifield resin **6**, bead size of 30 μm, 300 Å pores, loading ca. 1 mmol/g, was a kind gift from Dr. Andrew Coffee, Polymer Laboratories, UK. Octanetiol was distilled under reduced pressure. Solvents were purchased from Bio Lab, Israel. THF was distilled from sodium and benzophenone. $CHCl_3$, stabilized with amylene, was purified on basic alumina and stored in amber-colored bottles. DMF was dried on 4 Å molecular sieves. Column chromatography was carried out on silica gel 60, 200−400 mesh (Merck). TLC was performed on Merck silica 60 F_{254} plated aluminum. Spots were visualized by UV light or treatment with aqueous permanganate solution. Catechol derivatives were visualized by spraying the TLC plate with $FeCl_3$ solution in ethanol.

Analyses. ^{1}H NMR was carried out using a Bruker AMX-250 MHz instrument. UV−vis measurements were carried out with a Varian CARY 50 UV/vis spectrophotometer using a quartz cuvette with an optical path of 1 cm and width of 2 mm. TEM images were taken with a Philips CM120 instrument using 400 mesh copper grids coated with nitrocellulose followed by carbon evaporation. A drop of the NP solution was placed on the grid, followed by solvent evaporation at room temperature.

Gold Nanoparticles (NPs). Octanethiol-stabilized Au NPs were synthesized according to a literature procedure[50] as follows: Tetraoctylammonium bromide (375 mg) was dissolved in 20 mL of toluene. $HAuCl_4 \cdot 2H_2O$ (105 mg) in 5 mL of water was added. The chloroaurate was transferred to the toluene layer, coloring it orange. The toluene layer was separated and magnetically stirred vigorously. Octanethiol (46 μL) was added and the solution stirred for an additional 10 min. Freshly prepared solution of 129 mg of $NaBH_4$ in 6 mL of triply distilled water was added rapidly in one portion. The toluene layer became brown. After the solution was stirred for 3 h, the toluene layer was separated and evaporated to give a dark mass. Methanol (40 mL) was added and the dark mass formed black aggregates. The vessel was sonicated for 2 min in an ultrasonic bath, followed by centrifugation. The supernatant was washed, another portion of methanol was added, and the tube was again sonicated and centrifuged. This procedure was repeated two more times. Heptane (10 mL) was then added and the NPs dissolved almost immediately. The NPs were transferred to a weighed flask and the heptane was evaporated to dryness. The amount of NPs recovered was 42 mg. Heptane (42 mL) was added and the solution was kept in a refrigerator as a stock solution. Working solutions of 0.1 mg/mL were prepared by evaporating the heptane from an appropriate amount of stock solution and dissolving the NPs in the desired solvent.

The concentration of Au NP solutions was estimated by calculating the total weight of NPs shown in the histogram constructed from the TEM image in Figure 2, taking into account the different radii. This weight, calculated to be 1.4×10^{-14} mg, corresponds to the number of NPs (216) sampled to draw the histogram. Hence, a 1.0 mL solution of 0.1 mg of NPs contains $(0.1/1.4) \times 10^{14} \times 216$ NPs. This value corresponds to a NP concentration of ca. 2.5 μM. The measured absorbance of such a solution at 500 nm was 1.13 au.

Resin Washings after Synthetic Steps. The reaction content was transferred to a shaking flask composed of a glass cylinder, 9 cm long and 4 cm in diameter, equipped with a sintered glass and a tap at the lower end. The upper side of the flask was equipped with a neck ending with a ground glass opening through which the reaction contents were introduced. The liquid was vacuum-sucked through the tap, leaving the resin in the flask. Washing solvents were introduced (20 mL each), and the flask was closed and shaken for 5 min with each solvent. The solvent was discarded by vacuum suction through the tap and the process repeated with the other solvents.

Bromophenyl Ether Resin 2. *p*-Bromophenol (0.6 g, 3.5 mmol) was added to 0.1 g of NaH (80% suspension in paraffin oil, 3.3 mmol) in 10 mL of dry DMF. The reaction mixture was closed with a $CaCl_2$ tube and stirred until all the hydride dissolved and hydrogen evolution ceased. Then 1 g of resin **1** (0.7 mmol equivalents chloromethyl groups) was added and the $CaCl_2$ tube was replaced with a glass cap. The stirring rate was slowed in order to not damage the resin, and the reaction was allowed to proceed at room temperature for 24 h. The resin was then washed as

described above, using (in this order) H_2O ×3, DMF, THF, $CHCl_3$, THF, THF:(HCl, 1 M in water) 4:1 ×3, and THF ×3. The resin was dried under a stream of nitrogen and then in a vacuum.

Aromatic Boronic Resin 3. Resin **2** and a magnetic stirring bar were placed in a 25 mL round-bottomed flask, 10 mL of freshly distilled THF was added, and the flask was closed with a septum and immersed in an acetone-dry ice bath. Then 1.5 mL of *n*-butyllithium (1.6 M in hexane) was added through the septum using a syringe, and the reaction was left to stir slowly for 20 min. Triisopropylborate (2 mL) was added using a syringe and the reaction was left to stir overnight. The resin was washed as described above with the following solvents: THF, THF:MeOH 4:1 ×2, THF:(HCl, 0.5 M in water) 4:1 ×3, THF, MeOH ×2, MeOH:H_2O 1:1 ×3, THF ×3. The resin was dried under a nitrogen stream to afford white beads. Treatment of the resin with alizarin (see below) gave a positive reaction. Quantitative determination of the boronic moieties (see below) gave a loading of 0.4 ± 10% mmol/g.

Allyl Derivative 4. Allyl alcohol (0.7 mL, 10 mmol) was added to 0.32 g of NaH (80% suspension in paraffin oil, 10 mmol) in 20 mL of dry DMF. The flask was fitted with a $CaCl_2$ tube and allowed to stir until hydrogen evolution had ceased and the hydride dissolved. Then 1 g of Merrifield resin **1** was added, the flask was capped, stirring was slowed, and the reaction was left overnight. The resin was washed as described above, using (in this order) DMF, DMF:MeOH 1:1, H_2O ×2, DMF:H_2O 1:1, H_2O, DMF, $CHCl_3$, THF, and MeOH ×3.

Aliphatic Boronic Resin 5. To dry resin **4** in a 50 mL round-bottomed flask was added 10 mL of dichloromethane and 10 mL of BH_3·THF (1 M in THF). The flask was closed and the reaction left to stir slowly for 4 h at room temperature. The resin was washed as described above, using (in this order) MeOH ×2, H_2O ×2, THF, DMF, MeOH, $CHCl_3$, and MeOH ×3. The resin was obtained as white particles. Reaction with alizarin (see below) was positive. Quantitative determination of the boronic moieties on the resin (see below) gave a value of 0.2 ± 10% mmol/g.

Macroporous Boronic Resin 7. NaH (0.15 g, 80% suspension in paraffin oil) was weighed in a 25 mL round-bottomed flask. Then 12 mL of dry DMF was added, followed by the addition of 0.25 mL of allyl alcohol. The flask was capped with a $CaCl_2$ tube. After hydrogen evolution had ceased and the hydride was fully dissolved, 0.5 g of macroporous Merrifield resin **6** was introduced and the flask was left overnight with slow stirring. The reaction content was then transferred to a washing flask and washed with the following solvents: 1.5 mL of AcOH diluted with 60 mL of DMF, introduced in 3 × 20 mL portions, H_2O ×2, THF ×2, 0.5 mL of AcOH diluted with 20 mL of DMF, THF ×2, and $CHCl_3$ ×2. The resin was dried under a stream of nitrogen and left overnight in the washing flask. Then 20 mL of dichloromethane was added to the washing flask containing the dry resin, followed by 8 mL of BH_3·THF (1 M in THF). The flask was capped with a schliff and left with occasional shaking for 4 h. The resin was washed with the following solvents: 1 mL of AcOH diluted with 40 mL of DMF, introduced in 2 × 20 mL portions, H_2O ×2, THF ×3, THF:H_2O 1:1, MeOH:H_2O 1:3, and MeOH ×2. The resin was left to dry under a stream of nitrogen. It was positive to the alizarin test. Quantitative determination of the boronic moieties (see below) gave the value of 0.1 ± 10% mmol/g.

***S*-Acetylmercaptopropionic Acid (8).** To 1 g of 3-mercaptopropionic acid (9.4 mmol) were added 4 mL of pyridine and 3 mL of acetic anhydride and the reaction was left for 24 h at room temperature. The pyridine and most of the acetic anhydride were evaporated in vacuo. Then 1 mL of water was added and the reaction was left to stir for 30 min. The solvents were evaporated under reduced pressure, to afford compound **8** as a yellow oil which crystallized on cooling. ^{1}H NMR ($CDCl_3$): 3.11 (t, 2H, CH_2CO), 2.68 (t, 2H, CH_2S) 2.35 (s, 3H, CH_3).

***N*-(2-(3,4-Dihydroxyphenyl)ethyl)-2-thioacetylpropionamide (9).** One hundred milligrams of **8**, 62 mg of *N*-hydroxysuccinimide, and 124 μL of diisopropylcarbodiimide (DIC) were dissolved in 5 mL of acetonitrile. Urea precipitated after a few minutes. After 8 h, a solution of 100 mg of anhydrous K_2CO_3 was dissolved in 0.8 mL of water. A second solution of 128 mg of dopamine hydrochloride was prepared in 1.2 mL of DMF. The carbonate solution was added at once to the dopamine solution and the mixture was shaken briefly and immediately added to the reaction flask and left overnight. Water acidified to pH ∼ 5 with $NaHSO_4$ (10 mL) was added and the product was extracted with ethyl acetate (25 mL ×2) and dried with sodium sulfate. The ethyl acetate was concentrated and the urea was filtered. Further purification by column chromatography with ethyl acetate afforded 37 mg (17%) of **9** as colorless oil. ^{1}H NMR ($CDCl_3$): 6.95 (d, J = 8, 1H, CHC**H**COH), 6.73 (d, J = 2, 1H, COHC**H**C), 6.54 (dd, J = 8,2,1H, COHCHC**H**), 5.79 (t, 1H, NH), 3.46 (q, 2H, CH_2N), 3.08 (t, 2H, CH_2CO), 2.64 (t, 2H, CH_2S), 2.42 (t, 1H, C**H**$_2$$CH_2N$), 2.31 (s, 1H, CH_3). ESI-MS, *m*/*z*: 282.3 [M^- − H].

***N*-(2-(3,4-Dihydroxyphenyl)ethyl)-1,2-dithiolan-3-pentanamide (10).** One hundred thirty-eight milligrams of thioctic acid were reacted and worked up under the same conditions described for **9**. Column chromatography in ethyl acetate afforded 55 mg (24%) **10** as a yellow solid. ^{1}H NMR ($CDCl_3$): 6.77 (d, J = 8 Hz, 1H, CHC**H**COH), 6.71 (d, J = 2 Hz, 1H, COHC**H**C), 6.52 (dd, J = 8,2 Hz, 1H, CHC**H**C), 5.82 (t, 2H, NH), 3.46 (m, 3H, C**H**$_2$N + SC**H**), 3.10 (m, 2H, SCH_2), 2.66 (t, 2H, C**H**$_2$$CH_2N$), 2.41 (m, 1H, SCHC**H**H), 2.14 (t, 2**H**, CH_2CO), 1.83 (m, 1H, SCHCH**H**), 1.62 (m, 4H, C**H**$_2$$CH_2$C**H**$_2$), 1.36 (m, 2H, CH_2C**H**$_2$$CH_2$). ESI-MS, *m*/*z*: 340.3 [M^- − H]. On storage, compound **10** formed solids which failed to dissolve in $CHCl_3$. Mass spectra revealed the presence of a species with molecular weight 357. ESI-MS, *m*/*z*: 356.4 [M^- − H] corresponds to the addition of one oxygen atom to the molecule, presumably giving a sulfoxide.

2,2-Dimethyl-5-hydroxymethyl-5-methyl-1,3-dioxane (11). 1,1,1-Tris(hydroxymethyl)ethane (6 g) was dissolved in 40 mL of acetone and 5 mL of 3,3-dimethoxypropane. Then 0.2 mL of sulfuric acid was added and the reaction was left for 3 days. Evaporation of solvents and distillation under reduced pressure gave a colorless liquid. ^{1}H NMR ($CDCl_3$): 3.67−3.58 (m, 6H), 1.43 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 0.83 (s, 3H, CH_3).

2-(6-Bromo-hexyloxymethyl)-2-methyl-1,3-propanediol (12). Compound **11** (0.98 g, 6.12 mmol) was mixed with NaH (220 mg, 20% excess) in 25 mL of dry DMF. After complete dissolution of the hydride, 1,6-dibromohexane (1.9 mL, 2 equiv) was added and the reaction was left overnight. Then 70 mL water was added and the organic material was extracted in hexane (50 + 25 mL). Evaporation gave a liquid which consisted of the product and excess dibromohexane. A solution of 8 mL of methanol and 2 mL of 6 M HCl was added to the liquid and the mixture was left to stir for 3 h in order to hydrolyze the acetonide. A liquid insoluble in methanol was separated. The methanol was evaporated and the remaining liquid was washed with hexane (15 mL ×3) to remove the dibromohexane. The remaining liquid was evaporated, leaving a yellowish oil. Column chromatography with 7% methanol in ethyl acetate gave 370 mg (21%) of **12** as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.68 (dd, J = 19,11 Hz, 4H, C**HH**OH), 3.42 (m, 6H, C**H**$_2$OC**H**$_2$ + C**H**$_2$Br), 1.88 (m, 4H, C**H**$_2$$CH_2$Br + OH), 1.58 (quint, 2H, OCH_2C**H**$_2$), 1.42 (m, 4H, C**H**$_2$C**H**$_2$$CH_2$$CH_2$Br). ESI-MS, *m*/*z*: 305.5 [M + Na^+].

2-(6-Ethylxanthato-hexyloxymethyl)-2-methyl-1,3-propanediol (13). Compound **12** (0.12 g, 0.42 mmol) was dissolved in 15 mL of acetone. Potassium ethylxanthate (81 mg, 20% excess) was added and the reaction was left overnight. During that time KBr was precipitated. Most of the acetone was evaporated in vacuo, and 30 mL of ether was added. Filtration and evaporation yielded 145 mg of yellow oil. Column chromatography with $CHCl_3$ gave 70 mg (50%) of **13** as colorless oil. ^{1}H NMR ($CDCl_3$): 4.62 (q, 2H, OC**H**$_2$CH$_3$), 3.60 (dd, J = 31,12 Hz, 4H, C**HH**OH), 3.40 (t, 2H, OCH$_2$C**H**$_2$), 3.36 (s, 2H, CC**H**$_2$O), 3.08 (t, 2H, CH$_2$S), 1.66 (m, 2H, C**H**$_2$CH$_2$S), 1.56 (m, 2H, OCH$_2$C**H**$_2$), 1.43−1.33 (m, 7H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$S + OCH$_2$C**H**$_3$), 0.83 (s, 3H, CH$_3$). ESI-MS, *m*/*z*: 325.4 [M + Na$^+$].

4-[2-(2,4-Dinitro-phenylamino)-ethyl]-benzene-1,2-diol (14). 2,4-Dinitrofluorobenzene (70 mg, 0.37 mmol) was dissolved in 7 mL of acetonitrile. Dopamine hydrochloride (71 mg, 1 equiv) was dissolved in 0.7 mL of DMF and added to a solution of 0.1 g of anhydrous K_2CO_3 in 0.8 mL of water. The mixture was stirred briefly and added immediately to the 2,4-dinitrofluorobenzene solution. After 5 h the acetonitrile was evaporated and the organic material was extracted with 50 mL of ethyl acetate and washed with 15 mL of water acidified to pH ∼ 5 with $KHSO_4$. Column chromatography with $CHCl_3$−methanol afforded 30 mg (25%) of yellow powder. ^{1}H NMR (MeOH-d^4): 9.02 (d, J = 2 Hz, 1H, CNCHCN), 8.25 (dd, J = 8,2 Hz, 1H, CNO$_2$C**H**CH), 7.13 (dd, J = 8 Hz, 1H, C**H**CNH), 6.71 (m, 2H, COHC**H**C**H**), 6.62 (dd, J = 8,2 Hz, 1H, COHC**H**C), 3.69 (t, 2H, CH$_2$N), 2.90 (t, 2H, CH$_2$C). ESI-MS, *m*/*z*: 318.3 [M$^-$ − H], 637.6 [2M$^-$ − H].

***N*-Boc-1-amino-3-bromopropane (15).** 1-Amino-3-bromopropane hydrobromide (500 mg, 2.3 mmol) was dissolved in 10 mL of $CHCl_3$. A solution comprised of Na_2CO_3 (726 mg, 6.8 mmol) in 4 mL of water was added. Di-*tert*-butyl dicarbonate (500 mg, 2.3 mmol) was added and the mixture was left to stir overnight. The $CHCl_3$ layer was separated and washed with 10 mL ×2 of water acidified to pH ∼ 5 with $KHSO_4$. Drying on sodium sulfate and evaporation yielded 480 mg (82%) of **15** as a colorless oil sufficiently pure for the next step. ^{1}H NMR ($CDCl_3$): 4.6 (b, 1H, NH), 3.44 (t, 2H, CH$_2$Br), 3.28 (q, 2H, C**H**$_2$NH), 2.05 (quint, 2H, CH$_2$C**H**$_2$CH$_2$), 1.44 (s, 9H, t-Bu).

2,2-Dimethyl-5-(*N*-Boc-3-aminopropyloxymethyl)-5-methyl-1,3-dioxane (16). Acetonide **11** (302 mg, 1.88 mmol) was dissolved in 10 mL of dry DMF. NaH (80% in paraffin oil, 70 mg, 1.2 equiv) was added. After all the hydride had dissolved and hydrogen evolution ceased, 480 mg of compound **15** (1.88 mmol) was added and the reaction was left overnight. The DMF was evaporated under reduced pressure. Then 12 mL of water was added and the product was extracted with 2 × 25 mL of ether and dried on sodium sulfate. Column chromatography with ethyl acetate−hexane gave 100 mg (19%) of **16** as colorless oil. ^{1}H NMR ($CDCl_3$): 3.70−3.50 (m, 6H, (CC**HH**OC) ×2 + CH$_2$C**H**$_2$O), 3.43 (s, 2H, OCH$_2$C), 3.23 (q, 2H, C**H**$_2$NH), 1.78 (quint, 2H, CH$_2$C**H**$_2$CH$_2$) 1.43 (m, 15H, (CH$_3$)$_2$ ketal + t-Bu), 0.86 (s, 3H, CH$_3$).

2-(3-(2,4-Dinitro-phenylamino)-propyloxymethyl)-2-methyl-1,3-propanediol (17). Compound **16** (100 mg, 0.3 mmol) was dissolved in 7.5 mL of dichloromethane and 2.5 mL of trifluoroacetic acid for 2 h. The content was evaporated to dryness and then treated with a mixture of 8 mL of methanol and 2 mL of 6 M HCl for 2 h. The solvent was evaporated to dryness. The solid was dissolved in a THF−methanol mixture, and 0.2 mL of triethylamine was added. The flask was cooled in an ice bath. 2,4-Dinitrofluorobenzene (56 mg, 0.3 mmol) in 1 mL of THF was added and the reaction was left at room temperature for 1.5 h. The solvent was evaporated and 5 mL of 5% methanol in ethyl acetate was added. Solid triethylammonium hydrochloride was filtered out and the rest was chromatographed using ethyl acetate−methanol to afford 80 mg (67%) of **17** as a yellow oil. ^{1}H NMR ($CDCl_3$): 9.14 (d, J = 2 Hz, 1H, CC**H**C), 8.69 (b, 1H, NH), 8.30 (dd, J = 8,2 Hz, 1H, NO$_2$CC**H**CH), 6.97 (d, J = 8 Hz, 1H, NHCC**H**), 3.71−3.78 (m, 10H, C**HH**OH, C**H**$_2$OC**H**$_2$, C**H**$_2$NH), 2.05 (m, 2H, CH$_2$C**H**$_2$CH$_2$), 0.85 (s, 3H, CH$_3$). ESI-MS, *m*/*z*: 342.4 [M$^-$ − H], 366.6 [M + Na$^+$].

Setup for Experiments with Resins. Experiments with the resins were carried out in 3 mL plastic syringes in which a porous plastic filter, cut from commercially available solid-phase reactors (Abimed, Germany), was fitted in the needle outlet. The syringes were closed with a glass cap. The needle outlet could be blocked by a cap made of a needle chopped and filled with squeezed Teflon tape. The reactors were washed with $CHCl_3$ and ethanol and were left filled with ethanol and then with $CHCl_3$ for 2 days in order to remove plastic impurities. In this setup the solid resin could be treated with various reagents, the needle cap then removed, and the liquid filtered out using a stream of nitrogen, leaving the resin in the syringe for collection or further treatment. A small Teflon-coated magnet was placed in the syringe for stirring.

Qualitative Determination of Boronic Moieties on the Resins. A sample of the resin was suspended in 1 mL of THF. Alizarin powder was added using a capillary, followed by 2 drops of triethylamine. Positive reaction gave orange beads which showed orange fluorescence upon excitation with 365 nm UV light.

Quantitative Determination of Boronic Moieties on the Resins. The following solutions were prepared: (i) A solution of linker analogue **17**: 10 mg of dye in 10 mL of $CHCl_3$. (ii) Removal solution: 0.3 g of diethanolamine in 25 mL of THF. (iii) Regenerating solution: A mixture of 7.5 mL of THF and 2.5 mL of water.

Procedure: Approximately 5 mg of the resin was accurately weighed in a syringe reactor and washed with 1 mL of regeneration solution, THF ×3, and $CHCl_3$ ×3. A solution of analogue **17** (1 mL) was then introduced and the resin was left for 10 min. The excess dye was washed away and the resin was washed with $CHCl_3$ ×5 and THF ×3; 1 mL of removal solution was then added. After 5 min, the solution was washed to a test tube and another 1 mL of removal solution was introduced to the syringe. After an additional 5 min the solution was washed and combined with the first portion (total of 2 mL). A sample of 0.06 mL was transferred to a cuvette and to this was added 1 mL of removal solution. The UV−vis spectrum was recorded vs removal solution as a background. Resin regeneration could be performed with regenerating solution followed by washing successively with THF ×3 and $CHCl_3$ ×3. The regenerated resin could be treated again with analogue **17**. The concentration of the boronic moieties was calculated from the absorbance at 350 nm, using an extinction coefficient of 18000 M^{-1} cm^{-1} (determined by measuring solutions of known concentrations).

Binding and Bleeding of Linker Analogues 14 and 17. A boronic resin (∼5 mg) was weighed in a syringe reactor and a stirring magnet was added. One milliliter of $CHCl_3$ was added, the syringe was capped at the needle outlet and the neck, and the resin was left to swell for 15 min with stirring. In an Eppendorf vial, 0.5 mL of solution of analogue **14** or **17** (1 mg/mL) and 0.5 mL of *n*-butylamine solution (10% v/v in $CHCl_3$) were mixed. The $CHCl_3$ in the syringe was washed away, the needle outlet capped, and the mixture in the vial introduced. The syringe was closed with a glass schliff and the resin allowed to stir for 15 min. During this time the dye analogue binds to the resin, coloring the beads yellow. The syringe was washed with 1 mL of $CHCl_3$ ×3 and then an additional last washing with 1 mL of $CHCl_3$ or THF, depending on the solvent to be tested. The needle outlet was capped and 1 mL of solvent

($CHCl_3$ or THF) was introduced. After 30 min the contents were washed to an Eppendorf vial and new 1 mL of solvent was introduced and the needle outlet capped. Then 0.5 mL of the washed solution in the Eppendorf was collected, added to 0.5 mL of the same solvent, and measured in the spectrophotometer in the wavelength range around 350 nm. The procedure was repeated 1 h later and again 21.5 h later. The resin was washed with 0.3 mL of THF and then with 1 mL of acidic removal solution. After 30 min the solution was washed to an Eppendorf and measured.

The acidic removal solution was prepared as follows: Glacial acetic acid (40 μL) was added to 1 mL of water. From this solution, 60 μL was added to 1 mL of THF.

Typical NP Binding Experiment. Boronic resin (~5 mg) was weighed in a syringe reactor and a stirring magnet was added. One milliliter of $CHCl_3$ was added, the syringe capped at the needle outlet and the neck, and the resin left to swell for 15 min with stirring. In a vial, 4.6 mg of DMAP was weighed followed by the addition of 0.5 mL of linker solution (1 mg/mL), 0.7 mL of DMF, and 60 μL of *n*-butylamine. The $CHCl_3$ was washed from the resin and the contents of the vial were poured onto the resin and left for 1 h with stirring. The resin was then washed with 5 × 1 mL of $CHCl_3$ and 1.5 mL of NP solution (0.1 mg/mL) was introduced. The resin was wiped from the walls and immersed in the $CHCl_3$. The $CHCl_3$ level was marked in order to correct for solvent loss by evaporation. After 16 h the resin became brown. The excess NPs were washed away, followed by washing of the resin with 3 × 1 mL of $CHCl_3$. The resin was kept in the solvent until NP release.

Release of NPs Bound via Linkers 9 or 10. The resin was washed with 1 mL of THF, the needle outlet was capped, and 1 mL of removal solution was introduced. Stirring was applied (optional). The brown color of the resin gradually faded as NPs were released to the solution. NP release was complete after 15 min.

Acidic removal solution was prepared as follows: Glacial acetic acid (40 μL) was added to 1 mL of water. From this solution, 60 μL was added to 1 mL of THF.

Release of NPs Bound via Linker 11. After washing the resin with $CHCl_3$, the needle outlet was capped and 1 mL of 0.15 M 2-ethyl-1,3-hexanediol (**21**) solution in $CHCl_3$ was introduced. NP release was complete in 3 h.

Cleaning of NPs Released from the Resins. A solution of NPs released from the resin was washed to an Eppendorf vial. The volatiles were evaporated with a stream of nitrogen. Acetonitrile (1 mL) was added and the vial centrifuged at 8000 rpm. The NPs were insoluble in acetonitrile and aggregated at the bottom. The liquid was discarded. This procedure was repeated three times. Traces of acetonitrile were evaporated with a stream of nitrogen. THF was added and the NPs dissolved again.

Testing the Release Efficiency of Diols. NPs were bound to 5 mg portions of resin **3** through linker **13** as described above. The excess NPs were washed away and the resin was washed with either $CHCl_3$ or THF, 1 mL ×4. A solution of 0.15 M diol in 1 mL of the desired solvent was introduced and stirring was applied. After 95 min the liquid was eluted to an Eppendorf vial and a UV−vis spectrum measured. The NP absorbance at 500 nm was used for comparison between the different diols (see Gold Nanoparticles section above).

Second Cycle Binding of NPs 19 to Resin 3. NPs **19** were prepared and cleaned as described above using 10 mg of resin **3**. The NPs were dissolved in 1 mL of $CHCl_3$ and their spectrum was recorded. Then 5 mg of resin **3** was weighed in a syringe reactor and soaked in $CHCl_3$ for 15 min. The $CHCl_3$ was washed away, the needle outlet was capped, and NPs **19** were introduced. The solvent level was marked in order to correct for solvent loss by evaporation, and the reaction was left overnight, during which the resin beads became brown. The spectrum of the solution was recorded and compared with the previous spectrum, measuring specifically the absorbance at 500 nm. The brown resin was treated with 0.5 mL of 0.15 M solution of 2-ethyl-1,3-hexanediol (**21**) in $CHCl_3$, resulting in NP release from the resin. The solvent was washed to an Eppendorf vial and the spectrum was recorded. Comparison with the previous spectra was carried out after correcting the absorbance at 500 nm to 1 mL of solution.

Binding of NPs to Macroporous Resin 7. Binding, release, and rebinding of NPs to/from resin **7** were carried out as described previously.[13]

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