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Inhibition and acceleration of deuterium exchange in amide-functionalized monolayer-protected gold clusters

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Hydrogen/deuterium exchange rates in amide-functionalized monolayer protected gold clusters (MPCs) are controlled by the radial nature of the surface, with inhibition and catalysis observed at different chain lengths.

Monolayer-protected metal clusters (MPCs) provide new materials for a variety of potential applications ranging from chemical catalysis to nanoelectronic and magnetic devices.[1] One of the key attributes of nanoparticles is their utility as scaffolds for receptors and molecular devices,[2] arising in part from their amenability to solution phase techniques, such as NMR and IR spectroscopies.[3] A second attribute of MPCs is the unique radial structure of the surrounding monolayer due to the faceted metal core, providing a scaffold that can be systematically fine-tuned in a radial/generational fashion.[4]

In recent studies, we have fabricated a series of amide-functionalized gold colloids in which the position of the amide moieties are systematically positioned at two carbon increments along the length of a hydrocarbon chain within the monolayer. Spectroscopic data on these systems show that *intra*molecular hydrogen bonding between adjacent amides substantially decreases with increasing distance from the particle surface.[4] This fine-tuning of non-covalent interactions mimics aspects of enzyme active site structure, making MPCs potential models for dynamic features of biocatalysis. To explore this possibility, we have examined hydrogen/deuterium (H/D) exchange in colloids **1**–**4** (Fig. 1) featuring 2.0 nm gold cores, produced as previously described[4] using the procedure developed by Brust and Schiffrin.[5]

Amide deuterium/hydrogen exchange rates of peptides are a sensitive probe for detecting changes in overall protein conformation and dynamics.[6] For instance, isotopic exchange rates are drastically reduced if the amide proton is involved in hydrogen bonding and/or if the amide proton is buried deep within the protein making it inaccessible to the solvent.[7] H/D exchange rates for colloids **1**–**4** and amide **5** were quantified by monitoring the disappearance of the amide NH resonance upon addition of a large excess of CD_3OD. As shown in Fig. 2, these exchange rates were first order in colloid. H/D exchange was quite rapid in the exposed amide of control **5**. As expected, as the amide became further buried within the monolayer, this exchange rate slowed dramatically, with isotopic exchange for MPCs **1** and **2** orders of magnitude slower than for colloids **3** and **4** (Table 1, column 1). This trend in exchange rates for MPCs **1**–**4** presumably arises from a combination of enhanced hydrogen-bond strength (a function of the proximity of the amide to the core) and solvent inaccessibility due to the length of alkyl chain shielding the amide within the monolayer.

To further explore the dynamics of H/D exchange within the monolayer, we examined the effect of added acid on the exchange process. When catalytic amounts of acid are added to peptide-based systems an increase in the observed rate of amide exchange typically results.[8] This increase in rate is not uniform for all the amide protons on the peptide but is strongly influenced by such factors as solvent accessibility and hydrogen bonding ability.

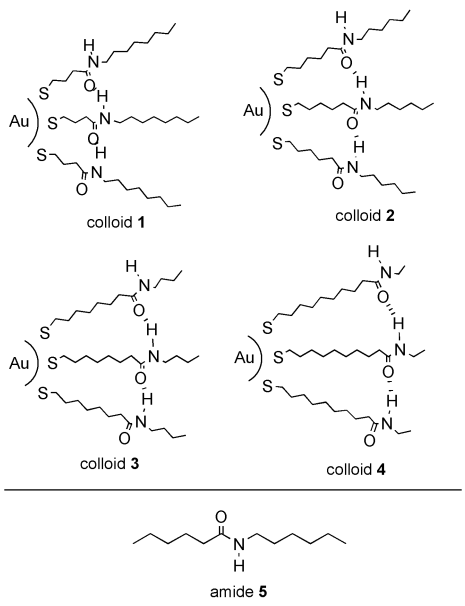

Fig. 1 Colloids **1**–**4** and amide **5**.

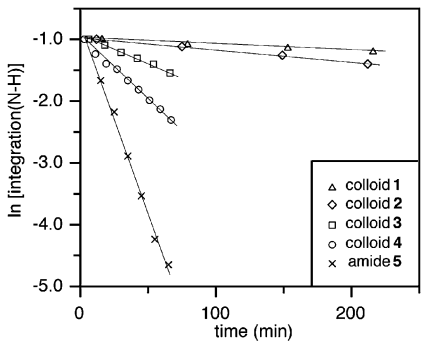

Fig. 2 Normalized first order kinetic plots for the isotopic exchange of the amide NH for colloids **1**–**4** and **5**. All experiments were performed in 10% CD_3OD–$CDCl_3$ ($CDCl_3$ was stored over K_2CO_3).

Table 1 H/D exchange rates (k)[a] for colloids **1**–**4** and amide **5** with varying amounts of *p*-toluene sulfonic acid[b]

	Equivalents of acid added per amide			
	0.0	0.0015	0.003	0.0065
Colloid **1**	1.0	14.3	14.4	**15.7**[c]
Colloid **2**	2.3	21.8	**26.3**[c]	26.1
Colloid **3**	6.1	11.8	**44.8**[c]	20.4
Colloid **4**	12.4	**66.9**[c]	53.9	18.4
Amide **5**	33.2	29.9	30.2	34.3

[a] 10^{-3} min^{-1}. [b] A typical experiment consisted of dissolving the colloid (5.0 mg) in $CDCl_3$ (500 μL) in an NMR tube. CD_3OD (50 μL) was added to the tube followed by the acid (50 μL in $CDCl_3$) at the appropriate concentration. [c] Numbers in bold refer to the maximum rate of catalysis for each series of colloid.

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The exchange rate of the proton on amide **5** was essentially unaffected by addition of catalytic quantities of acid (Fig. 3). In contrast, colloids **3** and **4** exhibited quite dramatic increases in rate reaching levels of 7- and 5-fold faster respectively than without added acid. The maximum rate increase for these colloids is significantly higher than those observed for the "naked" control **5** under identical conditions.‡ The acid catalyzed rate enhancement observed for colloids **1** and **2** was even greater, reach limiting values of 16 and 11 fold faster respectively. The fact that the H/D exchange rate of MPCs **3** and **4** are faster than the totally unhindered amide **5**, indicates that the increase in rate is a result of site-specific catalysis, presumably provided by the hydrogen-bonding environment established at these positions within the monolayer.[9] This effect is also manifested in MPCs **1** and **2** which display even larger increases in their relative rates, however the observed rates are substantially attenuated by the solvent inaccessibility of the amides in these systems.

One notable aspect of the acid catalysis of H/D exchange in these MPC systems is the very low concentrations of acid required for maximal catalysis. This suggests that protonation occurs at vertices or other defect sites which activates a substantial portion of the monolayer structure. The origin of the varying degrees of rates observed is unknown, and is currently under investigation.

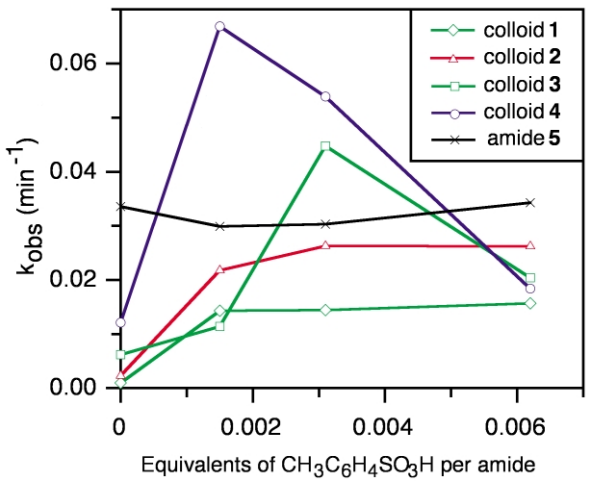

Fig. 3 Acid catalyzed rate constants determined from the disappearance of the amide NH for colloids **1**–**4** and amide **5** upon addition of catalytic amounts of *p*-toluene sulfonic acid.†All experiments were performed in 10% CD_3OD–$CDCl_3$ ($CDCl_3$ was stored over K_2CO_3).

In summary, we have demonstrated the efficient catalysis of hydrogen/deuterium exchange within the self-assembled monolayer of MPCs. The degree of catalysis was highly dependent upon the distance of the amide from the core, illustrating the utility of the radial structure of the MPC in controlling dynamic processes. Application of this capability to more complex examples of catalysis is currently underway, and will be reported in due course.

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Notes and references

† The equivalents of *p*-toluene sulfonic acid per amide were established from our previous TEM studies on these systems which showed an average core size of ~2.0 nm (ref. 4). It has been established that ~102 individual alkanethiol chains comprise a monolayer for particles of this size: A. Badia, L. Cuccia, L. Demers, F. Morin, B. R. Lennox, *J. Am. Chem. Soc.*, 1997, **119**, 2682.

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