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Tetrahedron Letters 49 (2008) 3652–3655
Tetrahedron Letters

Selective recognition of fumarate from maleate with a gold nanoparticle-based colorimetric sensing system

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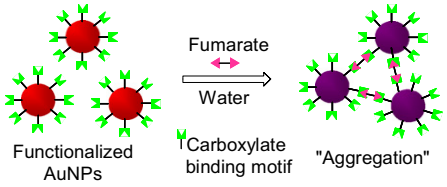
Received 25 February 2008; revised 25 March 2008; accepted 31 March 2008
Available online 8 April 2008

Abstract

A colorimetric sensing system of gold nanoparticles functionalized with carboxylate-binding units of *o*-(trifluoroacetyl)carboxanilide is described, which selectively recognizes a *trans*-dicarboxylate (fumarate) from its cis-isomer (maleate) and several dicarboxylates through inter-particle cross-linking, resulting in an apparent color change from red to purple.

Keywords: *o*-(Trifluoroacetyl)carboxanilides; Gold nanoparticles; Colorimetric sensing; Fumarate; Dicarboxylates

Design and synthesis of functionalized gold nanoparticles (AuNPs) are of current interest due to its potential applications as a colorimetric sensing system for chemical and biological sciences.[1] The visual sensing ability of AuNPs relies on the changes in color, arising from the surface plasmon resonance phenomenon,[2] from red to blue through analyte triggered aggregation.[1h–j,2] The importance of the anions in a wide range of biological and chemical processes[3] has fostered the development of sensing systems, which can selectively recognize and sense specific anion through macroscopic physical response.[1c,l,4] Recently, considerable efforts have been made in the development of selective sensing systems for carboxylates and dicarboxylates anions, which are present in a variety of biomolecules.[4c,m–p] Although AuNP-based optical sensing systems have been extensively utilized for the detection of biological macromolecules such as DNA and proteins,[1o,5] there are only a few AuNP-based systems for biologically important small molecular anions.[1c,n,l,4b,d–h] For the last few years our research has been directed toward the utilization of a novel anion recognition motif, *o*-(trifluoroacetyl)carboxanilide (TFACA),[6] which shows significant binding affinity toward carboxylates[6c,e] to a practically useful level. TFACAs are neutral yet recognize anions by forming a reversible covalent adduct, which properties seem to be useful for the development of a nanoparticle-based sensing system. We report herein the synthesis of a TFACA derivative of thioctic acid (**1**), which can be attached on AuNP surface to produce a novel optical sensing system **2** that operates in aqueous media. The sensing ability was investigated by UV–vis titration for several dicarboxylates. Noticeably this system shows sensitivity selective to the analytes that can bind to the TFACA binding motif on AuNPs in the inter-particle way (Scheme 1). Hence, a *trans*-dicarboxylate such as fumarate, one of the key components generated in the Krebs cycle,[7] can be sensed readily over its cis-isomer, maleate. Selective



Scheme 1. Schematic diagram for the aggregation of functionalized AuNPs by molecular recognition event.

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0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.03.142

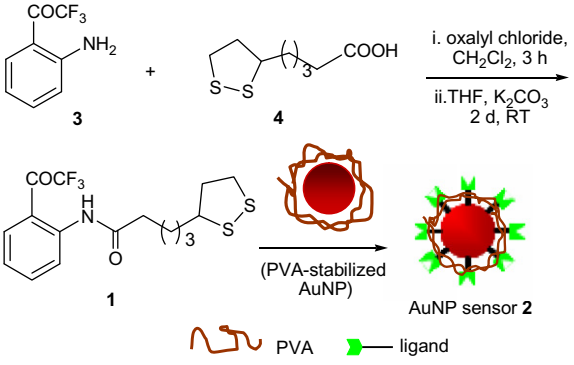
sensing of cis/trans-geometrical isomers is rather challenging, and, to the best of our knowledge, only a handful of examples are known so far.[4n,8] Also, AuNP-based sensing of dicarboxylates has not been reported yet.

AuNPs with an average diameter of about 13 nm were capped with the TFACA derivative **1** and then stabilized with poly(vinyl alcohol) (PVA)[1d,9] to give the sensing complex **2** (Scheme 2). The functional unit **1** was prepared by the condensation reaction of 2-(trifluoroacetyl)aniline (**3**) and thioctic acid (**4**) as its acid chloride.[10] The AuNPs used were obtained from the chemical reduction of tetrachloroauric acid ($HAuCl_4$) by sodium citrate.[5c,d]

For the functionalization of AuNPs, 80 μL of 2.0 mM solution of **1** in acetonitrile was added to an aqueous solution of the PVA-stabilized AuNPs (~3 nM, 20 mL) and stirred for 12 h at room temperature.[11] The solution was directly used for the sensing study.

The resulting sensing system was characterized by TEM and FT-IR spectroscopy. The TEM image shows that the average diameter of the particles is about 13 nm and remains almost in the same size after the functionalization. A comparison of FT-IR spectra taken for the AuNP solutions before and after functionalization with the TFACA derivative **1** showed the characteristic peaks for C–H stretching peaks at 2865 and 2929 cm^{-1} and a C=O stretching peak at 1675 cm^{-1}, which supports that **1** is attached on the surface of AuNP.

The anion sensing properties of the TFACA-functionalized AuNPs were investigated by UV–vis titrations with aqueous solutions of various di- and mono-carboxylate anions such as fumarate, maleate, oxalate, malonate, succinate, glutarate, propanoate, and 4-pentenoate as their sodium salts. UV–vis spectra were recorded by using 2.0 mL of the functionalized AuNP solution of **2** and adding an analyte solution (0.1 M aqueous sodium salt) into it (Fig. 1).[12] The aggregation of nanoparticles by the molecular recognition event in the inter-particle way was not fast under the conditions, giving a complete color change after 10 min; therefore, the spectrum was measured after 10 min of each addition. In the case of fumarate the spectrum shifted from 520 nm to 550 nm (Fig. 1a), indicating a color change due to the aggregation of AuNPs. Under higher



Scheme 2. Synthesis of the functionalized AuNP **2**.

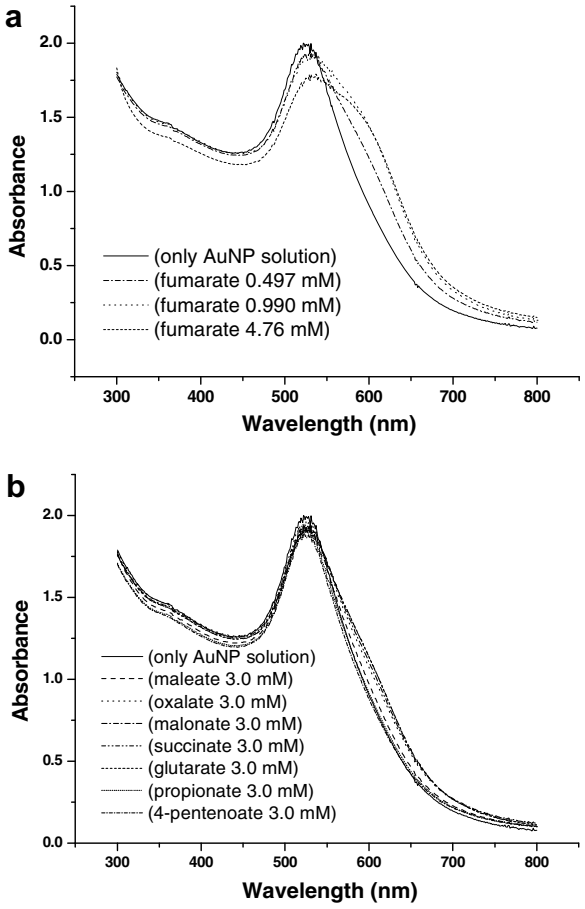


Fig. 1. Changes in the UV–vis spectra of **2** upon addition of (a) fumarate (10, 20, and 100 μL of 0.1 M aqueous sodium salt, respectively); (b) other di- and mono-carboxylate anions such as maleate, oxalate, malonate, succinate, glutarate, propionate, and 4-pentenoate (60 μL of 0.1 M aqueous sodium salt).

concentration of fumarate, the color of the particle solution became more intense and the peak of the UV–vis spectra showed more red-shift. But in case of other analytes, the system shows little spectral changes even at the higher concentration of 3.0 mM (Fig. 1b).

Fig. 2 shows the color changes after addition of different analytes (20 μL, 0.1 M) to the functionalized AuNPs solution (400 μL). The color changed from red to purple only in the case of fumarate. Whereas the other dicarboxylates do not show any color change. These results can be explained by assuming that selective aggregation of AuNPs through

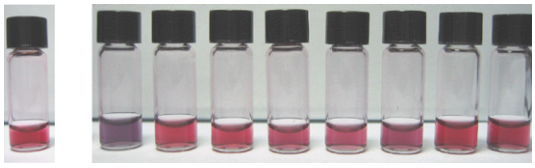


Fig. 2. Color changes of an aqueous solution of **2** (400 μL) upon addition of various analytes (as sodium salt, 20 μL, 0.1 M). From the left: without analyte, fumarate, maleate, oxalate, malonate, succinate, glutarate, propionate, and 4-pentenoic acid.

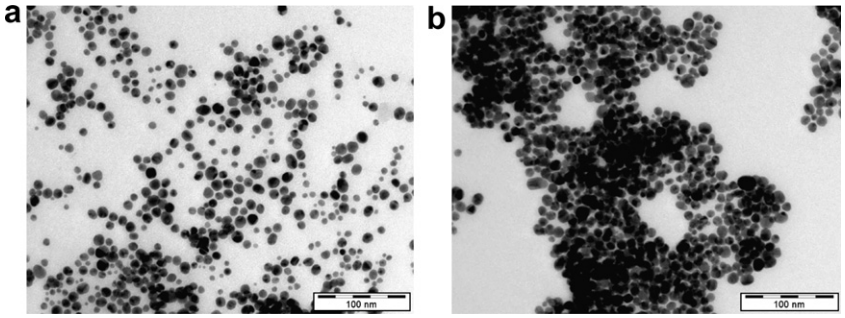


Fig. 3. TEM images of the TFACA-functionalized AuNPs **2**: (a) before and (b) after fumarate addition.

inter-particle cross-linking results from a molecular recognition event. The trans-isomer, fumarate, seems to provide a favorable geometry required for the inter-particle cross-linking of AuNPs. Obviously, the inter-particle cross-linking is not possible in the cases of monocarboxylates such as propionate and 4-pentenoic acid. Also, maleate, the cis-isomer of fumarate, is geometrically unfavorable to form the inter-particle cross-linking.

In the cases of other dicarboxylate analytes, their two carboxylate groups can add to the trifluoroacetyl binding sites on different AuNPs; however, under the sensing conditions, the inter-particle cross-linking seems to be unfavorable for the dicarboxylates that are conformationally flexible. In this case, rather than the inter-particle intra-particle cross-linking, that is, the molecular interaction between the two carboxylate functions of an analyte and two nearby trifluoroacetyl binding sites on the same nanoparticle seems to be favored. Therefore, the results suggest that analyte-triggered aggregation of AuNPs is a useful approach to selectively sense analytes containing the same functional groups but with different conformational flexibility. Our AuNP-based sensing system also shows that we can discriminate a trans-isomer, fumarate, from its cis-isomer, maleate, through geometry-driven inter-particle cross-linking.

Aggregation of the nanoparticles was confirmed by taking a TEM image of the resulting solution in the case of fumarate. An extensive aggregation change is shown after addition of the fumarate ion to the solution of AuNPs **2** (Fig. 3).

Interestingly, the competition between the inter- and intra-particle binding processes seems to be affected by the analyte concentration. When we increased the analyte concentration to a higher concentration (15 mM), the dicarboxylates such as malonate, succinate, and glutarate showed color changes in addition to fumarate, plausibly due to the inter-particle aggregation (Fig. 4). Under the higher concentration of analytes, we can expect that the probability of inter-particle cross-linking will increase and thus the nanoparticle aggregation seems to be effective as the sensing process. Under the condition the oxalate did not show any change, plausibly owing to its short distance between the dicarboxylate groups and/or its decreased binding affinity toward the trifluoroacetyl group. Both

Fig. 4. Color changes of an aqueous solution of **2** (400 μL) upon addition of a larger amount of analyte (as sodium salt, 70 μL, 0.1 M). From the left: fumarate, maleate, oxalate, malonate, succinate, glutarate, propionate, and 4-pentenoic acid.

are unfavorable factors for the effective inter-particle cross-linking. Surely, monocarboxylates did not show the aggregation behavior observed by the dicarboxylates even at the high concentration.

In conclusion, we have demonstrated that a TFACA-functionalized AuNP-based sensing system can differentiate geometrical isomers, such as fumarate, a *trans*-dicarboxylate, from its cis-isomer and also from conformationally flexible dicarboxylates, through analyte-triggered aggregation caused by inter-particle cross-linking. Current efforts are directed toward the structural modification of the binding sites and applications to other analytes.

Acknowledgments

This work was supported by grants from the Center for Integrated Molecular Systems (R11-2000-070-070010), Korea Health Industry Development Institute (A05-0426-B20616-05N1-00010A), and Korea Research Foundation Grant (MOEHRD, Basic Research Promotion Fund: KRF-2005-070-C00078).

References and notes

1. (a) Xu, X.; Han, M. S.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3468–3471; (b) Huang, C.-C.; Chang, H.-T. *Chem. Commun.* **2007**, 1215–1217; (c) Itoh, H.; Naka, K.; Chujo, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3026–3027; (d) Kim, Y.; Johnson, R. C.; Hupp, J. T. *Nano Lett.* **2001**, *1*, 165–167; (e) Lin, S.-Y.; Wu, S.-H.; Chen, C.-h. *Angew. Chem.* **2006**, *118*, 5070–5073; (f) Huang, C.-C.; Yang, Z.; Lee, K.-H.; Chang, H.-T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6824–6828; (g) Niemeyer, C. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4128–4158; (h) Shenhar, R.; Rotello, V. M. *Acc. Chem. Res.* **2003**, *36*, 549–561; (i) Daniel, M.-C.; Astruc, D. *Chem. Rev.* **2004**, *104*, 293–346; (j) Rosi, N. L.; Mirkin, C. A. *Chem. Rev.* **2005**, *105*, 1547–1562; (k) Liu, J.; Lu, Y. *Nat. Protoc.*

2006, *1*, 246–252; (l) Lee, K. Y.; Kim, D. W.; Heo, J.; Kim, J. S.; Yang, J.-K.; Cheong, G.-W.; Han, S. W. *Bull. Korean Chem. Soc.* **2006**, *27*, 2081–2083; (m) Ipe, B. I.; Yoosaf, K.; Thomas, K. G. *J. Am. Chem. Soc.* **2006**, *128*, 1907–1913; (n) Lin, S.-Y.; Chen, C.-h.; Lin, M.-C.; Hsu, H.-F. *Anal. Chem.* **2005**, *77*, 4821–4828; (o) Kim, J. H.; Estabrook, R. A.; Braun, G.; Lee, B. R.; Reich, N. O. *Chem. Commun.* **2007**, 4342–4344; (p) Lee, J.-S.; Han, M. S.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4093–4096; (q) Minami, K.; Kaneko, K.; Nagasaki, T.; Kubo, Y. *Tetrahedron Lett.* **2008**, *49*, 432–436.

2. Mulvaney, P. *Langmuir* **1996**, *12*, 788–800.
3. *Supramolecular Chemistry of Anions*; Bianchi, E., Bowman-James, K., García-España , E., Eds.; Wiley-VCH: New York, 1997.
4. (a) Martínez-Máñez , R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419–4476; (b) Aranzaes, J. R.; Belin, C.; Astruc, D. *Chem. Commun.* **2007**, 3456–3458; (c) Keaveney, C. M.; Leigh, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1222–1224; (d) Daniel, M.-C.; Aranzaes, J. R.; Nlate, S.; Astruc, D. *J. Inorg. Organomet. Polym. Mater.* **2005**, *15*, 107–119; (e) Watanabe, S.; Nakamura, T.; Tazume, Y.; Seguchi, H.; Yoshida, K. *Trans. Mater. Res. Soc. Jpn.* **2004**, *29*, 869–871; (f) Astruc, D.; Daniel, M.-C.; Ruiz, J. *Chem. Commun.* **2004**, 2637–2649; (g) Beer, P. D.; Cormode, D. P.; Davis, J. J. *Chem. Commun.* **2004**, 414–415; (h) Watanabe, S.; Sonobe, M.; Arai, M.; Tazume, Y.; Matsuo, T.; Nakamura, T.; Yoshida, K. *Chem. Commun.* **2002**, 2866–2867; (i) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 1; (j) Beer, P. D.; Gale, V. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (k) Beer, P. D.; Gale, P. A.; Chen, G. Z. *J. Chem. Soc., Dalton Trans.* **1999**, 1897–1910; (l) Valerio, C.; Fillaut, J. L.; Ruiz, J.; Guittard, J.; Blais, J. C.; Astruc, D. *J. Am. Chem. Soc.* **1997**, *119*, 2588–2589; (m) Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841–864. and references cited therein; (n) Costero, A. M.; Colera, M.; Gavina, P.; Gil, S. *Chem. Commun.* **2006**, 761–763; (o) Costero, A. M.; Gavina, P.; Rodriguez-Muniz, G. M.; Gil, S. . S. *Tetrahedron* **2006**, *62*, 8571–8577; (p) Costero, A. M.; Gavina, P.; Rodriguez-Muniz, G. M.; Gil, S. . S. *Tetrahedron* **2007**, *63*, 7899–7905.
5. (a) Mirkin, C. A.; Letsinger, R. L.; Mucic, R. C.; Storhoff, J. J. *Nature* **1996**, *382*, 607–609; (b) Elghanian, R.; Storhoff, J. J.; Mucic, R. C.; Letsinger, R. L.; Mirkin, C. A. *Science* **1997**, *277*, 1078–1080; (c) Storhoff, J. J.; Elghanian, R.; Mucic, R. C.; Mirkin, C. A.; Letsinger, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 1959–1964; (d) Demers, L. M.; Mirkin, C. A.; Mucic, R. C.; Reynolds, R. A., III; Letsinger, R. L.; Elghanian, R.; Viswanadham, G. *Anal. Chem.* **2000**, *72*, 5535–5541; (e) Taton, T. A.; Lu, G.; Mirkin, C. A. *J. Am. Chem. Soc.* **2001**, *123*, 5164–5165; (f) Otsuka, H.; Akiyama, Y.; Nagasaki, Y.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 8226–8230; (g) Hazarika, P.; Kukolka, F.; Niemeyer, C. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6827–6830.
6. (a) Kim, Y. K.; Lee, Y.-H.; Lee, H.-Y.; Kim, M.-K.; Cha, G. S.; Ahn, K. H. *Org. Lett.* **2003**, *5*, 4003–4006; (b) Chung, Y. M.; Raman, B.; Kim, D.-S.; Ahn, K. H. *Chem. Commun.* **2006**, 186–188; (c) Kim, D.-S.; Miyaji, H.; Chang, B.-Y.; Park, S.-M.; Ahn, K. H. *Chem. Commun.* **2006**, 3314–3316; (d) Miyaji, H.; Kim, D.-S.; Chang, B.-Y.; Park, E.; Park, S.-M.; Ahn, K. H. *Chem. Commun.* **2008**, 753–755; (e) Ryu, D.; Park, E.; Kim, D.-S.; Yan, S.; Lee, J. Y.; Chang, B.-Y.; Ahn, K. H. *J. Am. Chem. Soc.* **2008**, *130*, 2394–2395.
7. Baldwin, J. E.; Krebs, H. *Nature* **1981**, *291*, 381–382.
8. (a) Sancenón, F.; Martínez-Máñez , R.; Miranda, M. A.; Seguí , M.-J.; Soto, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 647–650; (b) Tseng, Y.-P.; Tu, G.-M.; Lin, C.-H.; Chang, C. T.; Lin, C.-Y.; Yen, Y.-P. *Org. Biomol. Chem.* **2007**, *5*, 3592–3598.
9. (a) Henglein, A. *Langmuir* **1999**, *15*, 6738–6744; (b) Jaiswal, J.; Gupta, S. K.; Kreuter, J. *J. Controlled Release* **2004**, *96*, 169–178.
10. Selected data for **1**: Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.9 (s, 1H), 8.86 (d, $J = 8.5$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.45 (t, $J = 7.4$ Hz, 1H), 7.22 (d, $J = 8.2$ Hz, 1H), 3.61 (d, $J = 6.39$ Hz, 1H), 3.23 (m, 2H), 2.52 (m, 3H), 1.97 (m, 1H), 1.86 (m, 4H), 1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 184.0, 183.5, 183.0 (q, $J = 34.2$ Hz), 172.8, 144.2, 138.4, 132.59, 132.54, 132.48, 132.42 (q, $J = 4.1$ Hz), 123.0, 119.1, 115.2, 111.4 (q, $J = 289.5$ Hz), 123.3, 121.9, 115.8, 56.9, 40.9, 39.17, 39.07 (d, 7.1 Hz), 35.3, 29.4, 25.7; ^{19}F (282 MHz, $CDCl_3$): δ 7.04; HRMS (FAB): calcd for $C_{16}H_{19}O_2NF_3S_2$ (M+H) 378.0810, found; 378.0805.
11. To a light-yellow solution of $HAuCl_4{\cdot}3H_2O$ (57 mg, 0.144 mmol) in deionized water (100 mL, purified by using a Milli-Q™ water purification system) under reflux was added quickly a solution of sodium citrate dihydrate (130 mg, 0.44 mmol) in deionized water (5 mL). The resulting solution became deep red within minutes, which was stirred for 30 min under reflux and then it was allowed to cool to room temperature. The reaction mixture was filtered through a cellulose nitrate membrane filter (pore size: 0.2 μm) to give a gold colloidal solution, which was diluted with deionized water (135 mL) and used for the next PVA-stabilization and TFACA-functionalization steps. To the diluted gold colloidal solution (20 mL) was added 40–80 μL of an aqueous solution of PVA (3.6 mg dissolved in 1.0 mL water; MW 9000–10,000) at room temperature. To this stabilized gold colloidal solution was added 80-μL of an acetonitrile solution of TFACA **2** (29 mg dissolved in 38 mL of acetonitrile) and the resulting mixture was stirred at room temperature for 12 h, which was used for the sensing experiments. Based on the literature data (Refs. 5c and 5d), the concentration of AuNPs in the colloidal solution is calculated to be ~3 nM. Omitting the PVA-stabilization step in the above resulted in an unstable gold colloidal solution, which turned blue during the TFACA-functionalization.
12. As the titration proceeds, the pH of the solution became a little basic (pH 7.8 when 20 μL of 0.10 M aqueous fumarate solution was added to 2.0 mL of the AuNP solution) because of added dicarboxylate anions; however, this direct sensing scheme is preferred over that of using a buffer solution. At lower pH such as pH 6, there was no color change for the given time because some of the dicarboxylate dianions become monocarboxylate, which is unable to cross-link the nanoparticles. In the case of a more basic solution such as at pH 8 (HEPES buffer), the color change took a longer time because the binding motif becomes more hydrated as the solution becomes basic (The TFACA binding motif is under equilibrium with its hydrated form in aqueous media). When necessary, it is recommended to use a buffer solution of neutral pH or slightly basic one (pH $\leqslant$ 8).