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COMMUNICATION

Stevens rearrangement as a tool for the structural modification of polyaminopolycarboxylic ligands†

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Polyaminopolycarboxylic acids are a well known class of ligands employed for metal ion complexation. Despite the large commercial availability, reports of their use as substrates for direct structural modifications are rare. Herein we report a simple and efficient protocol for the preparation of substituted polyaminopolycarboxylic ligands relying on a one-pot *N*-alkylation–Stevens rearrangement cascade.

Polyaminopolycarboxylic ligands are the best known chelating agents for metal ions.[1] The importance of EDTA (1,2-**e**thylene**d**iamine-*N*,*N*,*N*′,*N*′-**t**etraacetic **a**cid) in analytical chemistry is overwhelming[2] and its large scale use in detergent formulation and other applications leads to a worldwide market of several thousands of tons (worldwide use 200 000 tons per year in 2000).[3] Other well known representatives of this class of compounds are NTA (**n**itrilo**t**riacetic **a**cid), EGTA (**e**thylene-**g**lycol-*O*,*O*′-bis(2-aminoethyl)-*N*,*N*,*N*′,*N*′-**t**etraacetic **a**cid), DTPA (**d**iethylene**t**riamine-*N*,*N*,*N*′,*N*″,*N*″-**p**entaacetic **a**cid) and macrocyclic derivatives such as DOTA (1,4,7,10-tetraazacyclo**do**decane-1,4,7,10-**t**etra**a**cetic acid).

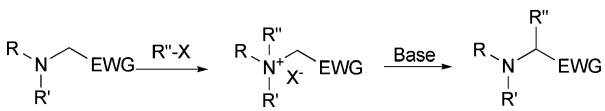
Despite the importance of the cited compounds, the literature reports only few examples of direct modification of these molecules.[4,5] Although a large number of derivatives have been prepared for different applications, their synthesis always relied on the assembly of structural frameworks. For example, the carboxymethyl groups are introduced on a prebuilt backbone in the last step of the synthesis[6–8] or, alternatively, suitably functionalized/protected carboxymethyl groups are linked on available simple polyamines,[9,10] or preformed synthons are assembled together to give the final ligand.[11,12]

The large scale and cost-effective availability of the cited ligands makes them suitable candidates as starting materials for modified and/or functionalized polyaminopolycarboxylic derivatives.

Long term involvement in the preparation of metal complexes for diagnostic applications[13] prompted us to explore novel protocols for the preparation of modified ligands starting from commercially available polyaminopolycarboxylic ligands. This goal is particularly impelling as recent molecular imaging applications require tailor-made chelates whose structure has to be finely tuned in order to attain a high and selective responsivity to a specific biological or physicochemical parameter.[14]

Polyaminopolycarboxylic ligands nearly always embody carboxylic groups and tertiary amines. Both of these groups cannot be used for structural modification or functionalization without reducing the overall denticity of the ligand itself and this restricts the potential modification sites to the molecule backbone carbon atoms or to the methylene groups between the carboxylic acid and the tertiary amine (α-carbon atoms). We choose the latter sites because: (i) α-carbon atoms are "activated" towards different chemical transformations by the concomitant proximity of two functional groups and (ii) α-carbon atoms are represented in the majority of polyaminocarboxylic ligands allowing their functionalization to be applied to a wider array of substrates.

We chose to focus on an old and well known reaction used to insert an alkyl residue on tertiary amines: the Stevens rearrangement (Scheme 1).[15]



Scheme 1

This reaction is a two step protocol involving a preliminary *N*-alkylation of the tertiary amine followed by base-induced migration of an alkyl group on an activated α-position. The Stevens reaction was recently reviewed[16] and although its mechanism is not yet entirely clarified, much evidence points toward a radical pathway for the key migration step.[17]

Particularly interesting is a procedure, employing DBU–K_2CO_3 in DMF, which performs the alkylation step and the base-induced migration at the same time.[18] Polyaminopolycarboxylic ligands are well suited substrates for this reaction, as the methylene α to carboxylic groups represents an "activated" position with respect to the base induced [1,2]-shift, allowing the latter to occur easily and regioselectively, as demonstrated by applications reported on amino acid derivatives.[19]

Nevertheless, in our hands the application of such conditions to a model polyaminopolyester, such as EDTA-*t*Bu_4 (**1**), failed to give significant yields of the expected products and led to the isolation of *N*-alkylated DBU. We decided to modify the reaction

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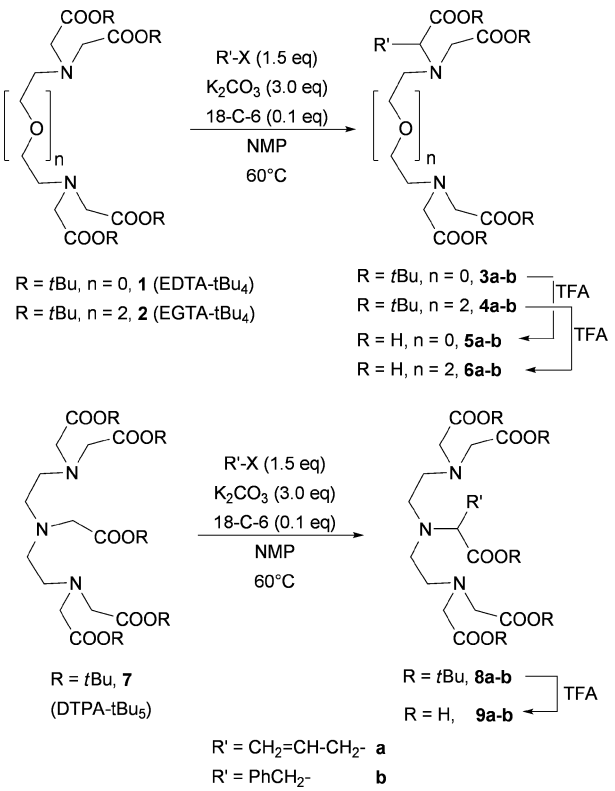
conditions, turning to a non-nitrogen base in order to avoid side reactions and selected the combination K_2CO_3–18-crown-6. Concurrently, DMF was substituted with *N*-methylpyrrolidone (NMP). Gratifyingly, the reaction worked well in these conditions and produced the expected alkylation–Stevens rearrangement products in fair to good yields. The optimal conditions were found to be 1.5 eq. alkyl halide, 3.0 eq. K_2CO_3, 0.1 eq. 18-crown-6 and moderate heating (60 °C). Higher temperatures induced degradation of the intermediate quaternary salt giving unsaturated by-products, likely from competing Hofmann elimination. On the other hand, at room temperature the reaction did not proceed beyond the quaternary salt stage. Higher amounts of the alkylation agents induced the formation of bis-alkylated species isolated during the purification. The optimized conditions were then applied to esters of common polyaminopolycarboxylic ligands (EDTA, EGTA and DTPA) and selected alkylating agents, such as allyl and benzyl bromides (Scheme 2).



Scheme 2

The corresponding results are summarized in Table 1. EDTA and EGTA esters are cleanly monoalkylated in one of the equivalent α-positions. DTPA gave the product resulting from alkylation of the α-position of the central arm, along with trace amounts of the other regioisomer. This regioselectivity may seem surprising, but could be explained by the greater basicity and nucleophilicity of the central nitrogen atom of diethylenetriamine and DTPA,[20] which is in this respect preferentially quaternized.

Table 1 Reaction yields

Substrate	Products[a]	
1	**3a** (65%)	**3b** (62%)
2	**4a** (70%)	**4b** (78%)
7	**8a** (62%)	**8b** (57%)

[a] Isolated yields.

Simple haloalkanes did not afford alkylated derivatives and the reaction seems to be limited to reactive halides, at least under these mild conditions. The products may be easily converted to the substituted free ligand by simple removal of *t*-butyl esters by standard treatment with neat trifluoroacetic acid, completing this alternative and short protocol to substituted ligands. Yields are in the range 57–78% for the tandem *N*-alkylation–Stevens rearrangement cascade, while the deprotection step is quantitative.

Conclusions

In conclusion we reported a novel synthetic access to substituted polyaminopolycarboxylic ligands, relying on a simple procedure involving a one-pot *N*-alkylation and Stevens rearrangement. This protocol avoids the use of strong bases and gives a shorter access to tailored ligands, paving the way to the wide variety of applications of their metal complexes, including their conjugation to biomolecules, macromolecules and surfaces. Efforts are ongoing to investigate further the protocol, optimizing yields and extending the array of ligands and alkylating agents involved.

Experimental

General

All chemicals were purchased from Sigma–Aldrich or from Alfa-Aesar and were used without purification unless otherwise stated.

NMR spectra were recorded on a JEOL ECP 300 (operating at 7.05 T). ESI mass spectra were recorded on ThermoFinnigan LCQDeca XP-Plus and melting points (uncorrected) with a Stuart Scientific SMP3 apparatus.

N-Alkylation–Stevens rearrangement – general procedure

To a solution of *t*-butyl polyaminopolycarboxylate (1 mmol) in NMP (10 mL) under dinitrogen atmosphere, K_2CO_3 (3 mmol), 18-crown-6 (0.1 mmol) and the corresponding alkyl bromide (1.5 mmol) were sequentially added. The mixture was vigorously stirred at 60 °C for 3 days. The inorganic salts were filtered off, diethyl ether (40 mL) was added to the filtrate and the organic layer was washed with water (3 × 50 mL). The organic layer was dried over sodium sulfate and evaporated. The crude product was purified by chromatography column.

Ligand deprotection – general procedure

The alkylated *t*-butyl polyaminopolycarboxylate (1 mmol) was dissolved in 5 mL of trifluoroacetic acid and the reaction was stirred overnight at rt. Volatiles were evaporated, the crude product was dissolved in 2 mL of MeOH and precipitated with diethyl ether (3 × 10 mL) to obtain the deprotected ligand.

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Notes and references

1 J. R. Hart, "Ethylenediaminetetraacetic Acid and Related Chelating Agents", in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2005.
2 D. C. Harris, *"Quantitative Chemical Analysis"*, ed. V. H. Freeman, 2010.
3 C. K. Schmidt, M. Fleig, F. Sacher and H. J. Brauch, *Environ. Pollut.*, 2004, **131**, 107.
4 J. F. W. Keana and J. S. Mann, *J. Org. Chem.*, 1990, **55**, 2868.
5 (*a*) H. Nemoto, J. Cai and J. Yamamoto, *Tetrahedron Lett.*, 1996, **37**, 539; (*b*) H. Nemoto, J. Cai, H. Nakamura, M. Fujiwara and J. Yamamoto, *J. Organomet. Chem.*, 1999, **581**, 170.
6 A. Warshawsky, J. Altman, N. Kahana, R. Arad-Yellin, A. Deshe, H. Hasson, N. Shoef and H. Gottlieb, *Synthesis*, 1989, 825.
7 C. F. Meares, M. J. McCall, D. T. Reardan, D. A. Gudwin, C. I. Diamanti and M. McTigue, *Anal. Biochem.*, 1984, **142**, 68.
8 A. Leonov, B. Voigt, F. Rodriguez-Castañeda, P. Sakhaii and C. Griesinger, *Chem.–Eur. J.*, 2005, **11**, 3342.
9 F. Uggeri, S. Aime, P. L. Anelli, M. Botta, M. Brocchetta, C. De Haën, G. Ermondi, M. Grandi and P. Paoli, *Inorg. Chem.*, 1995, **34**, 633.
10 S. G. Levy, V. Jacques, K. Li Zhou, S. Kalogeropoulos, K. Schumacher, J. C. Amedio, J. E. Scherer, S. R. Witowski, R. Lombardy and K. Koppetsch, *Org. Process Res. Dev.*, 2009, **13**, 535.
11 M. Stéphane, C. Pierre and T. Frédéric, *Synth. Commun.*, 2005, **35**, 2415.
12 P. L. Anelli, F. Fedeli, O. Gazzotti, L. Lattuada, G. Lux and F. Rebasti, *Bioconjugate Chem.*, 1999, **10**, 137.
13 (*a*) P. L. Anelli, L. Lattuada, V. Lorusso, G. Lux, A. Morisetti, P. Morosini, M. Serleti and F. Uggeri, *J. Med. Chem.*, 2004, **47**, 3629; (*b*) A. Barge, E. Cappelletti, G. Cravotto, A. Ferrigato, L. Lattuada, F. Marinoni and L. Tei, *Org. Biomol. Chem.*, 2009, **7**, 3810; (*c*) S. Aime, L. Calabi, C. Cavallotti, E. Gianolio, G. B. Giovenzana, P. Losi, A. Maiocchi, G. Palmisano and M. Sisti, *Inorg. Chem.*, 2004, **43**, 7588; (*d*) G. Gugliotta, M. Botta, G. B. Giovenzana and L. Tei, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3442.
14 (*a*) S. Achilefu, *Chem. Rev.*, 2010, **110**, 2575 (and whole thematic issue); (*b*) T. J. Meade and S. Aime, *Acc. Chem. Res.*, 2009, **42**, 821 (and whole thematic issue).
15 T. S. Stevens, E. M. Creighton, A. B. Gordon and M. MacNicol, *J. Chem. Soc.*, 1928, 3193.
16 (*a*) H. S. Pine, *Org. React.*, 1970, **18**, 403; (*b*) I. E. Markò in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming, G. Pattenden, Pergamon Press, Oxford 1991, vol. 3, 913–974; (*c*) J. A. Vanecko, H. Wan and F. G. West, *Tetrahedron*, 2006, **62**, 1043.
17 (*a*) D. Ollis, M. Rey, I. O. Sutherland and G. L. Closs, *J. Chem. Soc., Chem. Commun.*, 1975, 543; (*b*) Y. Maeda and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1491.
18 (*a*) I. Coldham, M. L. Middleton and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2951; (*b*) A. P. A. Arboré, D. J. Cane-Honeysett, I. Coldham and M. Middleton, *Synlett*, 2000, 236.
19 K. W. Glaeske and F. G. West, *Org. Lett.*, 1999, **1**, 31.
20 J. L. Sudmeier and C. N. Reilley, *Anal. Chem.*, 1964, **36**, 1698.