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β-Biguanidinium-cyclodextrin: a supramolecular mimic of mitochondrial ADP/ATP carrier protein

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ABSTRACT

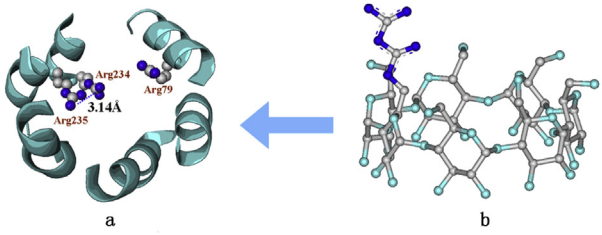
We reported a novel mono-β-cyclodextrin derivative, mono-6-deoxy-6-biguanidino-β-cyclodextrin (**β-biGCD**), which was investigated as a mimic of ADP/ATP carrier (AAC). Its affinity toward AMP, ADP, and ATP was evaluated by means of isothermal titration calorimetry (ITC). The association constants (K_a) of **β-biGCD** binding to AMP, ADP, and ATP were determined to be $(1.07\pm0.04)\times10^6$, $(5.86\pm0.02)\times10^6$, and $(4.33\pm0.06)\times10^6$ L mol^{-1}, respectively, which were 100-fold higher than mono-guanidino-β-cyclodextrin (ca. 10^4 L mol^{-1}). UV spectroscopic titrations further confirmed the above results. The interaction between **β-biGCD** and nucleotides was probed by docking simulation. These results reveal that the biguanidinium moiety mimics the arginine residues of mitochondrial AAC protein.

1. Introduction

Special attention has been long drawn to artificial enzyme studies. It is believed that the chemical enzyme mimic can provide valuable insight into the binding and catalytic mechanisms of enzymes.[1–8] Intensive studies on enzymes have revealed that the positively-charged arginine residues, the guanidiniums, play a central role in binding anionic groups of substrates. An interesting example is the mitochondrial ADP/ATP carrier (AAC), which transports ATP and ADP between mitochondrial matrix and cytoplasm.[9–13]

AAC protein has a funnel cavity with a maximum diameter of 20 Å and a depth of 30 Å, and a channel of length 20 Å and diameter 8 Å. A cationic cluster consisting of five arginine (Arg79, Arg137, Arg234, Arg235, Arg279) residues is located at the AAC surface close to the cavity bottom. As shown in Scheme 1, Arg79, Arg234, and Arg235 of AAC locate closely, between which the shortest distance is 3.14 Å.[14]

β-Cyclodextrin derivatives carrying mono-guanidino groups have been reported to mimic the function of mitochondrial ADP/ATP carrier.[15–17] The β-CD cavity size (ca. 7.8 Å) was close to that of natural ADP/ATP carrier. In this work, we designed and synthesized a β-CD derivative with a biguanidino group, mono-6-deoxy-6-biguanidino-β-cyclodextrin (**β-biGCD**), based on our previous works.[18–28] The properties of this **β-biGCD** as well as its binding to ADP/ATP have been investigated and compared with those of the mono-β-GCDs. The results showed that the modification with a biguanidino group lead to the much higher affinity, which represents an effective approach to construct a supramolecular mimic of AAC protein.



Scheme 1. (a) A representation of the mitochondrial ADP/ATP carrier protein (PDB: 1OKC) and (b) its mimic of **β-biGCD** showing the biguanidinium arm calculated by molecular docking combined with SYSBL 7.3. The AAC protein showed a cationic cluster consists of three arginines (Arg79, Arg234, Arg235) orienting toward the interior in the crystal structure of ADP/ATP carrier cavity. Arg groups were shown as ball and stick.

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2. Results and discussion

2.1. Association constants determined from ITC

ITC was particularly useful in the study of β-CDs inclusion compounds, by which the value of stoichiometry *N*, the enthalpy of association Δ*H*, the entropy of association Δ*S*, and the association constant K_a can be evaluated.[34,35,38,39] These parameters are crucial not only for understanding the physical processes at the molecular level but also for analyzing association reactions in various biochemical processes. In this study, the ITC was utilized to quantify the affinity between AMP/ADP/ATP and **β-biGCD**/**β-GCD**.

As shown in Fig. 1, an exothermic signal was observed after each injection of ATP stock solution, which symbolizes the non-covalent interactions between ATP and **β-biGCD**. The association constants K_a for ATP to **β-GCD** and **β-biGCD** were found to be $(1.25\pm0.02)\times10^4$ L mol^{-1} and $(4.33\pm0.06)\times10^6$ L mol^{-1} from these ITC data, and the corresponding associating enthalpy Δ*H* were −532.8 cal mol^{-1} and −892.0 cal mol^{-1}, respectively. All evaluated parameter values are listed in Table 1. It is evident that the **β-biGCD** exhibited about 100 times higher affinity than **β-GCD**, which is comparable with that of crude AAC. Particularly, the ADP association constant of **β-biGCD** was the largest amongst those compounds that mimic the mitochondrial ADP/ATP carrier reported so far. This result suggests there is indeed strong interactions between the biguanidinium and the negatively charged phosphate chains of ADP/ATP.

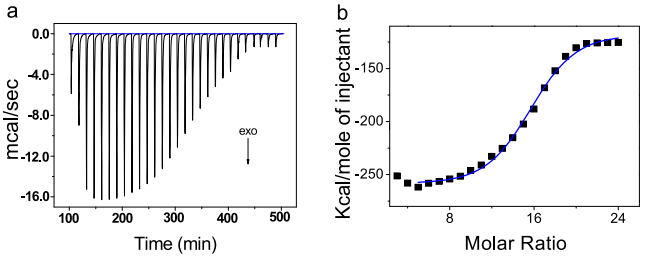


Fig. 1. (a) ITC results of adding ATP to **β-biGCD** solutions; (b) the integration of the heat signals of the microcalorimetric titration and the fitted curve. Injections of 10 μL of ATP solution in 50 mM Tris–HCl buffer at 0.1 M $NaClO_4$, pH 7.00, and 298±0.1 K ([ATP]=0.80 mM, [**β-biGCD**]=0.05 mM).

Table 1
Thermodynamic parameters for the interactions of the hosts, **β-GCD**, and **β-biGCD**, and the guests, AMP, ADP, and ATP, determined from ITC studies

		β-GCD	β-biGCD
AMP	K_a (L mol^{-1})	$(1.02\pm0.01)\times10^4$	$(1.07\pm0.04)\times10^6$
	Δ*G* (cal/mol)	−332.3±6.5	−537.2±70.2
	Δ*H* (cal/mol)	−320.6±7.3	−476.0±71.0
	Δ*S* (e.u)	0.49±0.02	2.43±0.02
	N	3.77	3.85
ADP	K_a (L mol^{-1})	$(3.03\pm0.02)\times10^4$	$(5.86\pm0.02)\times10^6$
	Δ*G* (cal/mol)	−575.2±11.0	−1158.0±116.0
	Δ*H* (cal/mol)	−435.2±12.0	−936.0±117.0
	Δ*S* (e.u)	5.60±0.05	8.97±0.03
	N	3.86	4.20
ATP	K_a (L mol^{-1})	$(1.25\pm0.02)\times10^4$	$(4.33\pm0.06)\times10^6$
	Δ*G* (cal/mol)	−572.8±6.0	−1043.5±60.5
	Δ*H* (cal/mol)	−532.8±6.4	−892.0±61.0
	Δ*S* (e.u)	1.60±0.01	6.42±0.01
	N	3.54	4.01

The association constant (K_a) and standard enthalpic (Δ*H*) of inclusion compounds were measured in 50 mM Tris–HCl buffer at 0.1 M $NaClO_4$, pH 7.00, and 298±0.1 K.

2.2. Association constants determined from UV spectroscopic titration experiments

To further confirm the above results, UV spectroscopic titration experiment was also employed to probe the host–guest interactions.[32,40] The typical UV–vis spectral changes upon the addition of **β-biGCD** to ATP solutions are shown in Fig. 2, and the job plot results for the binding between **β-biGCD** and AMP, ADP or ATP indicates the 1:1 complexation stoichiometry (Fig. S9). The association constants of the inclusion compound were calculated via a modified Hilderbrand–Benesi equation:

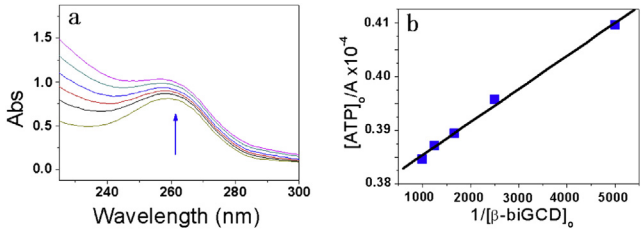


Fig. 2. (a) UV–vis absorption spectra of the mixture of ATP and (b) **β-biGCD** and the plots of absorbance $[G]_0$/A versus 1/$[$**β-biGCD**$]_0$ in the presence in 50 mM Tris–HCl buffer at 0.1 M $NaClO_4$, pH 7.00, and 298±0.1 K ([ATP]=0.10 mM, [**β-biGCD**]=0 mM, 0.20 mM, 0.40 mM, 0.60 mM, 0.80 mM, and 1.00 mM).

$$\frac{[G]_0}{A} = \frac{1}{K_a\varepsilon[\beta-CDs]_0} + \frac{1}{\varepsilon} \quad (3)$$

The association constants (K_a) of all CDs-nucleotide inclusion compounds are summarized in Table S2. The K_a values of **β-biGCD**-AMP/ADP/ATP inclusion compounds (K_a=1.38–1.68×10^6) were about two orders of magnitude higher than those of **β-GCD**-AMP/ADP/ATP (K_a=0.61–3.47×10^4) at pH=7.00, indicating a tighter binding ability of the host **β-biGCD**. By changing the buffered pH, the pH dependency of the binding constant was investigated. As a result, the K_a for **β-biGCD** with AMP, ADP, and ATP were found to be 1.41×10^6 L mol^{-1}, 1.66×10^6 L mol^{-1}, and 1.51×10^6 L mol^{-1} at pH 6.00, and the K_a for **β-biGCD** with AMP, ADP, and ATP were found to be 1.37×10^6 L mol^{-1}, 1.64×10^6 L mol^{-1}, and 1.48×10^6 L mol^{-1} at pH 7.90. These results indicates the binding of **β-biGCD** to AMP, ADP, and ATP was pH-independent in the tested pH range. This is probably due to the high pK_a of guanidinium, which comes around pH 12–13 under normal condition.

2.3. Interaction intermediates calculated by molecular docking simulation

The semiempirical calculations have been performed to investigate the interactions between **β-biGCD** and **β-GCD** and AMP/ADP/ATP, in which the associating affinities were evaluated using molecular docking (MD simulations) combined with SYSBL 7.3.[41–44] The molecular modeling results of **β-biGCD** inclusion compounds, i.e., **β-biGCD**-AMP, **β-biGCD**-ADP, **β-biGCD**-ATP, were shown in Fig. 3.

The calculating results demonstrated that **β-biGCD** was the most efficient receptor, especially to ADP, as was reflected in the non-covalent bond lengths. As shown in Fig. 3b, the distances between O2 atom of guest molecule and the central active N3 and N5 atoms of biguanidinium were about 2.68 Å and 2.81 Å, respectively, being comparable to the corresponding distances in AAC (2.63 Å).[14] Compared with **β-GCD**, **β-biGCD** can form more hydrogen bonds with guest molecules (The bond distances were: N5–O1, 2.68 Å; N5–O2, 3.32 Å; N5–O3, 3.40 Å; N3–O2, 2.81 Å; N3–O3, 3.26 Å, in which N3 and N5 were two central nitrogen atoms of

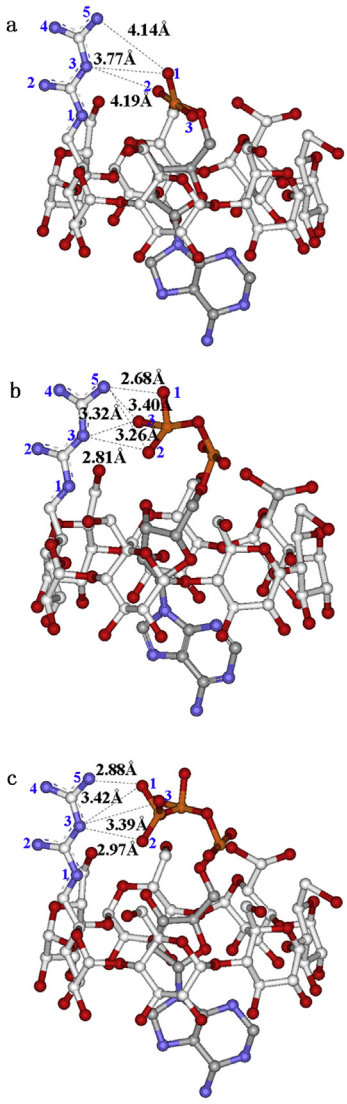


Fig. 3. Molecular modeling results of complexation. (a) **β-biGCD**-AMP; (b) **β-biGCD**-ADP; (c) **β-biGCD**-ATP. They were calculated using the molecular docking combined with SYSBL 7.3 methods, in which the color code scheme was: blue, nitrogen; metallic white, carbon; red, oxygen and orange, phosphorus. All hydrogen atoms were omitted for clarity.

biguanidinium while O1, O2, and O3 were three oxygen atoms of guest). The effects of positive charged arm as well as related interactions on the association constants can be seen clearly in **β-biGCD**-ADP inclusion compound, in which the active N3 and N5 atoms of the positive charged arm can strongly interact with ADP via five N–H···O hydrogen bonds. Therefore, the biguanidinium in **β-biGCD** may play the same role with that of Arg234 and Arg235 of AAC.

3. Conclusion

The **β-biGCD** carrying a cationic biguanidyl group, reported in this study, is an effective receptor of ADP and ATP. The recognition ability arises from the cavity accommodation and the hydrogen bonds and the electrostatic interactions between the biguanidyl group and the phosphates. This work represents an effective chemical approach to mimic the biological recognition of mitochondrial ADP/ATP carrier protein, which may implicate novel insights into the design of artificial enzyme.

4. Experimental section

4.1. Materials

Diisopropylethylamine (DIEA), 1*H*-pyrazole-1-carboxamidine hydrochloride (**L1**), and other reagents were purchased from Aldrich–Sigma and used as received. Reagent grade β-CD was recrystallized twice from H_2O and dried in vacuo for 12 h at 373 K prior to use. DMF were dried over CaH_2 for 2 days and subsequently distilled under reduced pressure prior to use. Milli-Q water was used in all physical measurements. 6-Monodeoxy-6-monoamino-β-cyclodextrin was prepared from 6-monodeoxy-6-monoazido-β-cyclodextrin according to the procedure reported by Jicsinszky[29] with a minor modification. 6-Mono(*p*-toluenesulfonyl)-β-cyclodextrin was prepared in dry pyridine solution rather than aqueous solution.[30,31] The purity of all synthesis products were confirmed by elemental analyses, ESI-MS, and NMR spectroscopy.

4.2. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA-500NB or Mercury plus 500 spectrometer. The elemental contents were analyzed by a Perkin–Elmer 240 elemental analyzer. ESI-MS spectra were obtained from a Thermo LCQ-DECA-XP spectrometer. UV–vis spectra were measured via a Varian Cary 300 UV–vis spectrophotometer equipped with a temperature controller (±0.1 K). The ITC was conducted using the VP isothermal titration microcalorimetry (MicrolCall®). Molecular simulation studies and the associating affinities were conducted using Molecular Docking 2.1 software combined with SYSBL 7.3.

4.3. UV spectroscopic titration experiments

UV–vis absorption spectra were recorded and monitored right after the nucleotides (AMP, ADP, ATP) and β-cyclodextrins (**β-GCD**, **β-biGCD**) were mixed in aqueous solutions of appropriate pH values. The calibration curve was obtained in 0.10 M Tris–HCl buffer (pH 7.00). 600 μL **β-GCD** or **β-biGCD** (0.10 mM, the guests) aqueous solution was added into the cell, in which 0.10 M sodium perchlorate solution was used to keep the ionic strength constant. All titrations were carried out at 298±0.1 K, and initiated by adding the aqueous titrant solutions (the nucleotides) to the titrand solution with a 0.20 mM increment. During the titrations, the guest concentrations were kept constant while the host concentrations were increased stepwise. To minimize the errors by the absorbance of the sample cell and solvent, each reaction was measured against a reference cell that was identical to the sample cell and contained the same buffer solutions. The maximum absorption peak of inclusion compounds of nucleotides with **β-biGCD** was at 259 nm and its absorption increased with increase of the host concentration. The raw titration data were fitted by a modified Hilderbrand–Benesi formula to evaluate the association constants of the inclusion compounds K_a.[26] The errors of K_a were estimated about 5%.

4.4. Isothermal titration calorimetry (ITC) experiments

The isothermal titration microcalorimetry was employed to characterize the complexation of β-cyclodextrins with AMP, ADP, and ATP. All experiments were carried out on the VP-ITC (MicrolCall®). There are usually many heat effects produced during the mixing process, therefore, careful preliminary controls are usually required in ITC experiments to unambiguously assign the observed heat effects. Specifically, the β-cyclodextrin derivatives were loaded into the 1.00 mL sample cell and nucleotide were loaded into the 250 μL syringe, respectively. 1.00 mL of Milli-Q water was loaded

into the reference cell. 0.80 mM solutions of AMP, ADP, and ATP were placed in a 250 μL continuously rotating (250 rpm) syringe. The concentrations of **β-GCD** and **β-biGCD** were 0.05 mM. The titrant and titrand concentrations were selected to ensure the criterion $10<K_a[M]_T<1000$, in which $[M]_T$ is the total concentration of host. The titration was conducted by adding 10 μL aliquots of the nucleotide solutions into the solutions of the β-cyclodextrin derivatives. The first 10 μL aliquot injection was ignored to eliminate the effect of solute diffusion across the syringe tip during the equilibration period.[33,34] Thereafter, the 10 μL aliquot of the nucleotide solutions was injected at an interval of 10 min. The signal (heat flow) produced during each injection leveled off when the guest became excessive. All titration experiments were carried out at 298±0.1 K.[35] The titration data were fitted with the Origin program provided by VP-ITC instrument, the fitting formula was shown as following equation:

$$Q=\frac{NM_t\Delta HV_0}{2}\left[1+\frac{X_t}{NM_t}+\frac{1}{NKM_t}-\sqrt{\left(1+\frac{X_t}{NM_t}+\frac{1}{NKM_t}\right)^2-\frac{4X_t}{NM_t}}\right] \quad (1)$$

The value of Q above can be calculated at the end of the injection and designated Q. V_0=active cell volume; M_t is bulk and free concentration of macromolecule in V_0; X_t is bulk and free concentration of ligand. Thus, the number of sites (N), the molar enthalpy changes (ΔH), and the inclusion compound association constants K_a were obtained from this fitting process, and ΔS was calculated based on the value of ΔH and K_a. The total heat produced during each injection was obtained by integrating heat flows over time. The calculated total heat (μcal) was plotted against the mole ratio of the titrant (guest) to the titrand (host). 'Exo' denoted the exothermic reaction.

The free energy (ΔG) of the binding reaction is determined via:

$$\Delta G = \Delta H - T\Delta S \quad (2)$$

in which ΔH and ΔS can be obtained from the fitting process of ITC data.

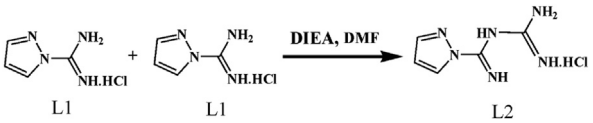
4.5. Molecular modeling

The semiempirical calculations were performed using the Molecular Docking Simulations 2.1 software combined with SYSBL 7.3 to study the host–guest inclusion compounds. The molecular structures were generated by the molecular builder provided in the SYSBL 7.3 and optimized by means of Molecular Docking Simulations. The initial distances between the key atoms of inclusion compounds were summarized in Supplementary data.

4.6. Synthesis of *N*-amidino-amidinopyrazole-1 hydrochloride (L2)

DIEA (0.348 mL, 2.0 mmol) was added to 0.5 mL of DMF solution of amidinopyrazole-1 hydrochloride **L1** (0.293 g, 2.0 mmol). The mixture was stirred for 64 h at room temperature.[36] Then ether (15 mL) was added, and the resulting sticky solid product was collected by filtration, washed with ether, and dried in vacuum to yield 0.34 g (90%) of crude product. Recrystallization of the crude product from ethanol or ether yielded 0.13 g (42%) white crystalline solid.

^{1}H NMR (500 MHz, DMSO-d_6, ppm) 6.57 (1H, s, $C_5H_7N_5NH$), 7.85 (1H, d, $C_5H_7N_5NH$), 8.20 (2H, s, $C_5H_6N_5NH_2$), 8.35–8.37 (3H, m, $C_3H_3N_5H_5$); MS (ESI, H_2O, m/z) $[M+H]^+$ calcd 152, found 153.15. Anal. Calcd for $C_5H_8N_6\cdot HCl\cdot H_2O$: C (28.79), H (5.42), N (40.30). Found C (28.83), H (5.38), N (40.26) (Scheme 2).

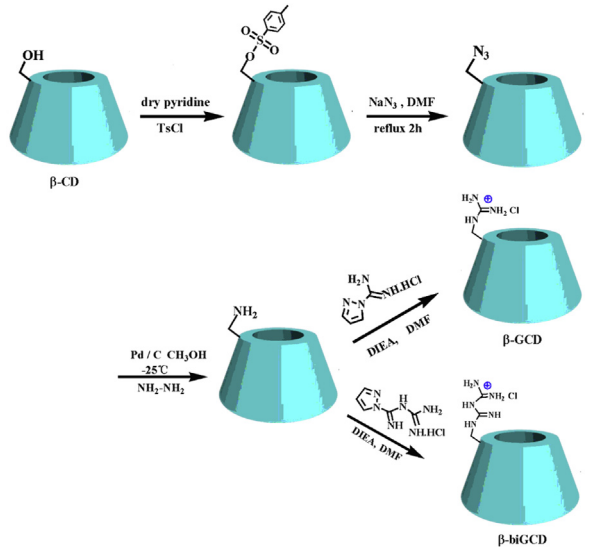


Scheme 2. Synthetic scheme of **L2**.

4.7. Synthesis of mono-6-deoxy-6-biguanidino-β-cyclodextrin (β-biGCD)

β-biGCD was prepared from the intermediate 6-monodeoxy-6-monoamino-β-cyclodextrin (**β-ACD**), which was first prepared from β-cyclodextrin (β-CD) through a series of reactions. To a solution of **β-ACD** (1.134 g, 1.000 mmol) in dry dimethylformamide (DMF) was added diisopropylethylamine (DIEA) (2.5 mL, 0.120 mmol) followed by **L2** (0.230 g, 1.220 mmol). The mixture was stirred for 72 h at room temperature.[36,37] At the end of the reaction, 15 mL of ether was added, and the resulting sticky solid product was collected, washed using ether, and dried in vacuo to yield 0.235 g (19%) of crude product. The crude product was purified by column chromatography on Sephadex G-25 using deionized water as eluent. 0.18 g (16%) pale crystalline solid was precipitated from acetone/ether.

^{1}H NMR (500 MHz, DMSO-d_6, ppm) 7.93 (2H, d, $C_{44}H_{73}N_3O_{34}N_2H_2$), 2.00 (2H, s, $C_{44}H_{73}N_3O_{34}N_2H_2$), 6.57 (2H, s, $C_{44}H_{73}N_4O_{34}NH_2$), 4.30–4.72 (20H, m, $-OH$), 4.88–4.82 (7H, m, $-CH$); ^{13}C NMR δ_H (500 MHz, DMSO-d_6, ppm) 162.7 (1C, s, $C_{43}H_{75}N_2O_{34}CN_3$), 162.1 (1C, s, $C_{43}H_{75}N_2O_{34}CN_3$), 101.9 (7C, s, $-CH$), 59.8–77.9 (m, 34C, $-CH_2$); MS (ESI, H_2O, m/z) $[M+H]^+$ calcd 1218.3, found 1218.5. Anal. Calcd for $(C_{44}H_{75}N_5O_{34})\cdot(H_2O)_8$: C (38.80), H (6.73), N (5.14). Found C (38.83), H (6.67), N (5.18) (Scheme 3).



Scheme 3. Synthetic scheme of **β-biGCD**.

Caution: The perchlorate salts of organic compounds are potentially explosive. These compounds must be prepared and handled with great care!

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.041.

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