Supramolecular Assembly of Cucurbit[6]uril and N-butyl-4-pyrrolidinopyridine

Hong-Bo Hou [a,b], Zhong-Zheng Gao[a], Dong Bai [a], Zhu Tao[a] , Timothy J. Prior [c], Carl Redshaw [c], Xin Xiao[a]*

[a] *Key Laboratory of Macrocyclic and Supramolecular Chemistry of Guizhou Province, Guizhou University, Guiyang 550025, People's Republic of China;*
[b] *Department of Resource and Environment, Bao Shan College, Bao Shan, Yunnan, 678000, People's Republic of China.*
[c]*Department of Chemistry, University of Hull, Hull HU6 7RX, U.K.*

Abstract The nature of the supramolecular host-guest complex involving 4-pyrrolidinopyridine (BuPC4) and cucurbit[6]uril (Q[6]) has been investigated by NMR and UV spectroscopy, MALDI-TOF mass spectrometry, X-ray crystallography and isothermal titration calorimetry (ITC). The results revealed that the alkyl chain of the guest BuPC4 is located inside the cavity of the Q[6] host, whereas the other section of the BuPC4 guest remains outside of the portal.

Keywords: Supramolecular; Host-guest interaction; Cucurbit[*n*]uril; Pyrrolidinopyridine; Self-assembly

1 Introduction

The field of supramolecular chemistry, which is based on weak and non-covalent interactions, has been extensively studied over recent decades due to the wide range of applications, for example chemical sensors, enzyme assays, storage and catalysis.[1-4] Among all non-covalent interactions, the study of host–guest interactions is one of the most popular fields, and facilitates the construction of a diverse array of functional materials. [5,6] Host−guest systems formed via molecular recognition by a large molecular receptor with a hydrophobic or hydrophilic cavity can encapsulate small organic molecules, bio-macromolecules, metal ions, or even nanoparticles utilizing electrostatic forces, hydrogen bonding, hydrophobic effects, π–π stacking or charge-transfer interactions have been intensively studied in recent years.[7-12] In addition to the traditional crown ether, cyclophane, cyclodextrin, and calixarene hosts, cucurbit[*n*]urils (n = 5–8, 10, 13-15) are a relatively new class of macrocyclic hosts incorporating a rigid hydrophobic cavity and two identical carbonyl fringed portals[13-18]. Thanks to their excellent host-guest binding ability with a number of guests, different cucurbit[*n*]urils-based supramolecular architectures with fascinating properties and potential applications have been developed[19-30].

In previous work, we found that a cucurbit[6]uril (Q[6]) can complex pyrrole salts, pyridine salts or alkyl chains with high binding constants[31-37]. On the other hand, 4-pyrrolidinopyridine are an important class of N-heteroaromatic compounds, which have been extensively employed as nucleophilic catalysts for acyl transfer and related reactions [38-40]. In the present study, the potential guest molecule possessed a butyl chain at the nitrogen atom of the 4-pyrrolidinopyridine, namely N-butyl-4-pyrrolidinopyridine (BuPC4), which was synthesized as shown in Scheme 1. The BuPC4 guest has multiple active sites which may interact with Q[6] host, *viz* tetrahydropyrrole, pyridyl, and the alkyl moieties. This prompted us to wonder which active site would preferentially reside in the internal cavity of Q[6]. Thus, a host-guest supramolecular structure was constructed between BuPC4 with cucurbit[6]uril, which was investigated by using NMR and UV spectroscopy, MALDI-TOF mass spectrometry, X-ray crystallography and isothermal titration calorimetry (ITC).

2 Results and discussion

2.1 NMR spectroscopy

In order to investigate the complexation of Q[6] with BuPC4 in solution, ^{1}H NMR titration experiments were first performed by adding increasing amounts of Q[6] to the solution of BuPC4 in D_2O. As shown in Fig. 1, the methyl protons and methylene protons H_e, H_f, H_g and H_h attributed to the butane experience significant up-field shifts from 4.01, 1.72, 1.20 and 0.80 ppm to 3.52, 0.93, 0.45 and 0.09 ppm, respectively. Furthermore, the signal at 7.86 ppm due to the pyridine ring proton H_d closest to the pyridine N in free BuPC4 exhibited an obvious downfield shift of 0.66 ppm, suggesting deep inclusion of the alkyl chain moiety of guest BuPC4 in the cavity of Q[6], whilst the pyridine ring is located at its portal. This is further confirmed by the cross-signals between the methyl proton H_f , H_g and H_h of BuPC4 and the methylene proton of Q[6] in the ROESY spectrum of the mixture between BuPC4 and Q[6] in D_2O, Fig. S1.

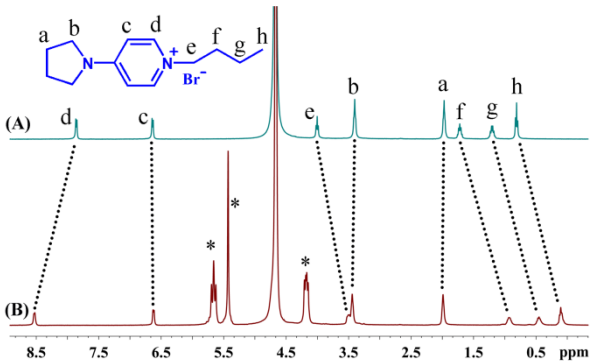

Fig. 1 Interaction of BuPC4 and Q[6] (20 °C): ^{1}H NMR spectra (400MHz, D_2O) of (A) in the absence of Q[6], (B) in the presence of 1.0 equivalent of Q[6].

2.2 MALDI-TOF mass spectrum

The inclusion complex Q[6]-BuPC4 was also established by the MALDI-TOF mass spectrum, as shown in Fig. 2. An intense signal was found at *m*/*z* 1202.30, which corresponds to $\{Q[6]\text{-BuPC4-Br}^-\}^+$ (calculated for $\{Q[6]\text{-BuPC4-Br}^-\}^+$, 1202.15), thereby providing direct support for the formation of the 1:1 host–guest inclusion complex Q[6]-BuPC4.

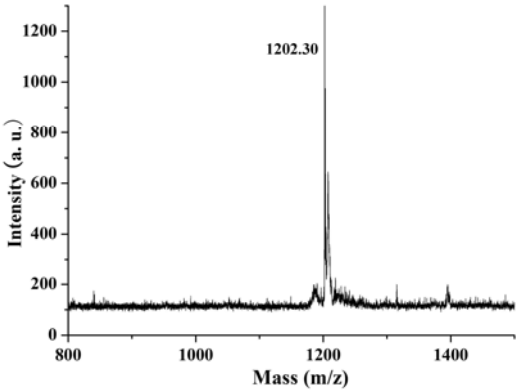

Fig. 2 MALDI-TOF mass spectrum of the complex Q[6]-BuPC4.

2.3 Isothermal titration calorimetry analysis

Isothermal titration calorimetry (ITC) measurements are able to afford quantitative information for the host-guest complexation including both the binding affinity and thermodynamic origin. As a consequence, a solution of BuPC4 was consecutively injected into a solution of Q[6] at 25°C to record the exothermic binding isotherm, Fig. 3, resulting in resolution of the binding molar ratio value of N = 1.012 ± 0.032. This result is very close to the expected value of 1.0, suggesting that the binding stoichiometry of Q[6] to BuPC4 is 1:1. In addition, the association constant K_a = (3.34 ± 0.78) × 10^5 M^{-1} for Q[6] with BuPC4 was also derived from the experimental data. Such a high binding constant suggests a relatively strong host-guest interaction between Q[6] and BuPC4, indicating the formation of a stable inclusion complex in aqueous solution. Meanwhile, the relatively large negative enthalpy value of the Q[6]-BuPC4 system (ΔH = -35.36 ± 1.51 kJ·mol^{-1}) reveals that the assembly process of the inclusion complex of Q[6] with BuPC4 is typically driven by a favorable enthalpy change, Table S1.

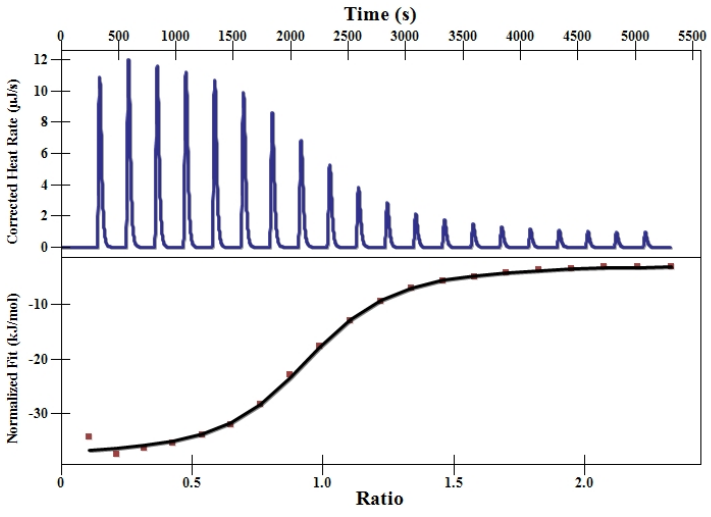

Fig. 3 ITC data for the binding of Q[6] with BuPC4 in aqueous solution at 298.15K.

2.4 UV spectroscopy

To better understand the interaction between Q[6] and BuPC4, UV titration experiments were conducted. Usually, the host Q[6] shows no absorbance at $\lambda > 210$ nm, and the guest BuPC4 shows a maximum absorption at 284 nm. Shown in Fig. 4 are UV spectra obtained for aqueous solutions containing a fixed concentration of BuPC4 and variable concentrations of Q[6]. The absorption band of the guest BuPC4 exhibits a progressive increase in absorbance with a red shift from 284 nm to 290 nm as the Q[6]/BuPC4 ratio is increased due to the formation of the supramolecular complex Q[6]-BuPC4. A sharp isosbestic point appears at 290 nm, which verifies the 1:1 stoichiometry between the host and guest and allows the determination of the association constants (*K*a) by applying a non-linear curve-fitting method. The association constant *K*a, $(3.06 \pm 0.16) \times 10^5$ M^{-1}, thus deduced is consistent with that deduced from the ITC analysis as detailed above. Furthermore, the Job's plot (based on the continuous variation method) clearly shows that the UV spectra data fits well to the 1:1 stoichiometry of the host-guest inclusion complex.

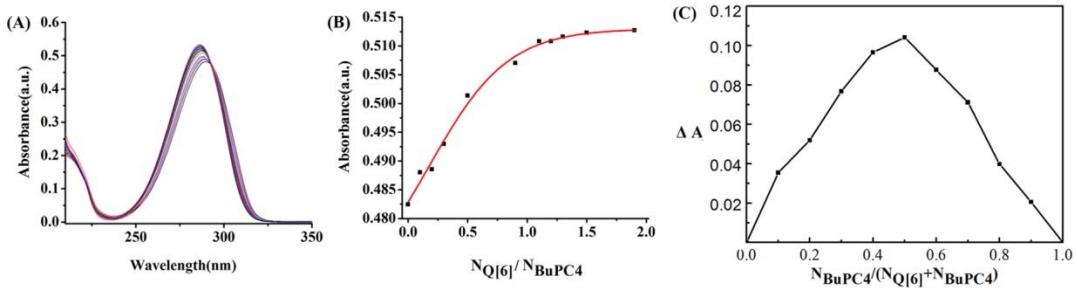

Fig. 4 (A) Electronic absorption of BuPC4 (4×10^{-6} mol L^{-1}) upon addition of increasing amounts (0, 0.2, 0.3, 0.4, 0.6, 0.8, 1.1, 1.3, 1.4, 1.6, 2.0 equiv.) of Q[6]; (B) the concentrations and absorbance *vs.* $N_{Q[6]}/N_{BuPC4}$ plots; (C) the corresponding $\Delta A–N_{BuPC4}/(N_{Q[6]} + N_{BuPC4})$ curves.

2.5 2-D diffusion-ordered NMR spectroscopy (DOSY)

Furthermore, 2-D diffusion-ordered NMR spectroscopy (DOSY) experiments were performed to afford further evidence for the formation of a 1:1 inclusion complex between Q[6] and BuPC4. Fig. S2 depicts the DOSY spectra of the above host-guest system in D_2O at 298 K. It is evident from the spectra that all the peaks correlated to the signals in the chemical shift dimensions are present in a horizontal line. As a consequence, all the proton signals, due to the host and the guest, display the same diffusion co-efficient ($D = 2.69 \times 10^{-10} m^2$ s^{-1}) indicating that they are part

of the same species.

2.6 X-ray structure analysis

X-ray structure analysis provided unequivocal proof of the formation of 1:1 inclusion complex between Q[6] and BuPC4. Crystals of Q[6]-BuPC4 were grown by slow evaporation of a solution containing the host Q[6] and the guest BuPC4 under 3.0 M aqueous hydrochloric acid solution. X-ray structural analysis has established that the Q[6]-BuPC4 crystallize in the monoclinic crystal system with space group *P* 1 21 1. As can be seen in Fig. 5, the alkyl chain of the guest BuPC4 is located inside the cavity of the Q[6] host, whereas the other section of the guest BuPC4 remains outside of the portal, resulting in the formation of a pseudorotaxane, which is in agreement with what we have observed in the aqueous solution by ^{1}H NMR spectroscopy. It is interesting to note that the ionic dipole interaction between the positive nitrogen (N52) of the pyridyl moiety of guest BuPC4 and the portal carbonyl oxygens of Q[6], C-H···O hydrogen bonding interaction between BuPC4 and the carboxyl oxygen atoms of Q[6] portals, as well as the hydrophobic interaction of the cavity of Q[6] with the alkyl chain of BuPC4 could be the driving forces for the formation of such a pseudorotaxane complex. The distances of the charged nitrogen N52 to portal carbonyl oxygens O19, O20, O21 and O24 were between 3.185 and 3.881 Å, the average $N_{pyridyl}…O_{carbonyl}$ short-distance is 3.586 Å and other C-H···O hydrogen bonding distances are C(92)–H···O(20) 2.306 Å, N(93)–H···O(23) 2.204 Å, C(95)–H···O(24) 2.469 Å, respectively.

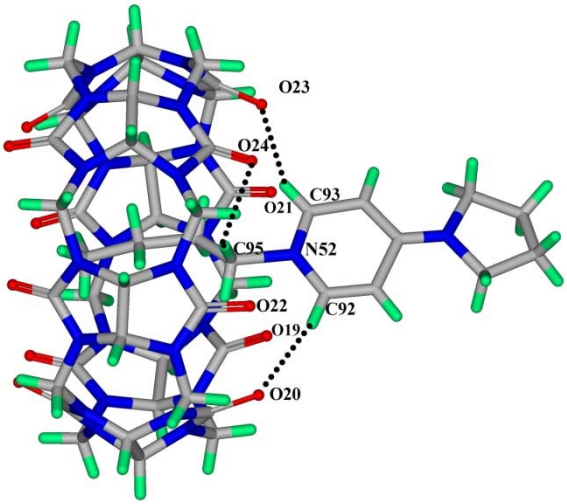

Fig. 5 Crystal structure of the interaction between the Q[6] and BuPC4.

3 Experimental

3.1 General Remarks

4-Pyrrolidinopyridine was purchased from Aldrich, whilst Q[6] and N-butyl-4-pyrrolidinopyridine were prepared and purified according to the previously published methods.[14, 24] All other reagents were of analytical grade and were used as received. Double-distilled water was used for all experiments.

3.2 Measurements

^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer in D_2O. Absorption spectra of the host-guest complexes were recorded using an Aglient 8453 spectrophotometer at room temperature. MALDI-TOF mass spectra were taken on a Bruker BIFLEX III ultra-high resolution Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer with α-cyano-4-hydroxycinnamic acid as matrix. Elemental analysis was performed on an Elementar Vavio El III. Titration experiments were carried out on a NANO ITC SV. from Ta Inc. at 25°C.

3.3 Preparation of the single crystal of Q[6]-BuPC4

To a solution of N-butyl-4-pyrrolidinopyridine (11.52 mg, 0.04 mmol) in 2 ml 3M HCl solution, Q[6] (10.8 mg, 0.009 mmol) was added. The resulting reaction mixture was stirred for 5 min at 60°C and filtered. Slow solvent evaporation of the filtrate in air over a period of about three weeks provided rhombic colorless crystals of Q[6]-BuPC4.

3.4 ITC measurements

Microcalorimetric experiments were performed using an isothermal titration calorimeter Nano ITC (TA, USA). The experiments of guest with Q[6] consisted of 20 consecutive injections (10 μL) of a guest solution into the microcalorimetric reaction cell (1.3 mL) charged with a solution of Q[6] at 25°C. The heat of reaction was corrected for the heat of dilution of the guest solution determined in separate experiments. All solutions were degassed prior to the titration experiments by sonication. Computer simulations (curve fitting) were performed using the Nano ITC analyze software.

3.5 Single-crystal X-ray crystallography

Single crystals of Q[6]-BuPC4 were grown from a 3M HCl solution by slow evaporation. Diffraction data of Q[6]-BuPC4 was collected at 223 K with a Bruker SMART Apex-II CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ=0.71073Å). Empirical absorption corrections were performed by using the multiscan program SADABS. Structural solution and full-matrix least-squares refinement based on F^2 were performed with the SHELXS-97 and SHELXL-97 program packages, respectively[41-43]. All non-hydrogen atoms were treated anisotropically in all cases. All hydrogen atoms were introduced as riding atoms with an isotropic displacement parameter equal to 1.2 times that of the parent atom.

3.6 Crystal data for the complex Q[6]-BuPC4

Q[6]-BuPC4: M_r = 5131.45, monoclinic, space group P 21, a = 19.223(8) Å, b = 20.351(9) Å, c = 19.382(8) Å, β = 117.314(7)°, V = 6737(5) Å^3, Z = 1, Dc = 1.265 g cm^{-3}, F(000) = 2659, GOF = 1.008, R_1 = 0.0944 ($I>2\sigma(I)$), wR_2 = 0.2349 (all data).

4 Conclusion

In summary, a novel supramolecular host-guest complex was successfully constructed between Q[6] and 4-pyrrolidinopyridine derivative BuPC4 depending on the hydrogen bonding interaction together with the ion-dipole interaction and characterized by a wide range of methods including NMR, electronic absorption, MS and ITC. In particular, the nature of this host-guest complex has been unambiguously revealed on the basis of a single crystal X-ray diffraction analysis. The result revealed that the alkyl chain of the guest BuPC4 is located inside the cavity of the Q[6] host, whereas the other groups, including the tetrahydropyrrole and pyridyl moieties of the guest BuPC4 remain outside of the portal.

Acknowledgment

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References

[1] Parvari G., Reany O., Keinan E., *Isr. J. Chem.*, **2011**, *51*, 646–663.

[2] Sambrook M. R., Notmana S., *Chem. Soc. Rev.*, **2013**, *42*, 9251–9267.

[3] Yang H., Yuan B., Zhang X., *Acc. Chem. Res.*, **2014**, *47*, 2106–2115.

[4] Ogoshi T., Yamagishi T., Nakamoto Y., *Chem. Rev.*, **2016**, *116*, 7937–8002.

[5] Meng F. N., Yao X. Y., Ying Y. L., Zhang J. J., Tian H., Long Y. T., *Chem. Commun.*, **2015**, *51*, 1202–1205.

[6] Dong S., Zheng B., Wang F., Huang F., *Acc. Chem. Res.*, **2014,** *47*, 1982-1994.

[7] Cram D. J., Cram J. M., *Science.*, **1974**, *183*, 803-809.

[8] Xiao X., Tian Z. C., He L., Xue S. F., Zhang Y. Q., Zhu Q. J., Tao Z., *J. Mol. Struct.*, **2010**, *965*, 109–115.

[9] Hu J., Liu S., *Acc. Chem. Res.*, **2014**, *47*, 2084-2095.

[10] Mellet C.O., Fernández J. M. G., Benito J. M., *Chem. Soc. Rev.*, **2011**, *40*, 1586–1608.

[11] Wei P. F., Yan X. Z., Huang F. H., *Chem. Soc. Rev.***, 2015**, *44*, 815–832.

[12] Cooke G., Rotello V. M., *Chem. Soc. Rev.*, **2002**, *31*, 275–286.

[13] Kim J., Jung I. S., Kim S. Y., Lee E., Kang J. K., Sakamoto S., Yamaguchi K., Kim K., *J. Am. Chem. Soc.*, **2000**, *122*, 540–541.

[14] Day A. I., Arnold A. P., Blanch R. J., Snushall B., *J. Org. Chem.*, **2001**, *66*, 8094–8100.

[15] Day I. A., Blanch R. J., Arnold A. P., Lorenzo S., Lewis G. R., Dance I., *Angew. Chem. Int. Ed. Engl.*, **2002**, *41*, 275–277.

[16] Cong H., Ni X. L., Xiao X., Huang Y., Zhu Q. J., Xue S. F., Tao Z., Lindoy L. F., Wei G., *Org. Biomol. Chem.*, **2016**, *14*, 4335–4364.

[17] Cheng X. J., Liang L. L., Chen K., Ji N. N., Xiao X., Zhang J. X., Zhang Y. Q., Xue S. F., Zhu Q. J., Ni X. L., Tao Z., *Angew. Chem. Int. Ed.*, **2013**, *52*, 7393-7396.

[18] Li Q., Qiu S. C., Zhang J., Chen K., Huang Y., Xiao X., Zhang Y., Li F., Zhang Y. Q., Xue S. F., Zhu Q. J., Tao Z., Lindoy L. F., Wei G., *Org. Lett.*, **2016**, *18*, 4020–4023.

[19] Lagona J., Mukhopadhyay P., Chakrabarti S., Isaacs L., *Angew. Chem. Int. Ed.*, **2005**, *44*, 4844−4870.

[20] Kaifer A. E., *Acc. Chem. Res.*, **2014**, *47*, 2160−2167.

[21] Assaf K. I., Nau W. M., *Chem. Soc. Rev.*, **2015**, *44*, 394-418.

[22] Ni X. L., Xiao X., Cong H., Zhu Q. J., Xue S. F., Tao Z., *Acc. Chem. Res.*, **2014**, *47*, 1386-1395.

[23] Kim K., Selvapalam N., Ko Y. H., Park K. M., Kim D., Kim J., *Chem. Soc. Rev.*, **2007**, *36*, 267–279.

[24] Yang B., Xiao X., Zhang Y. Q., Zhu Q. J., Xue S. F., Tao Z., Wei G., *RSC Adv.*, **2014**, *4*, 44359-44366.

[25] Gao Z. Z., Zhang J., Sun N. N., Huang Y., Tao Z., Xiao X., Jiang J. Z., *Org. Chem. Front.*, **2016**, *3*, 1144–1148.

[26] Xiao X., Lin R. L., Zheng L. M., Sun W. Q., Tao Z., Xue S. F., Zhu Q. J., Liu J. X., *RSC Adv.*, **2014**, *4*, 53665-53668.

[27] Xu S., Zhang X., Nie C., Pang Z., Xu X., Zhao X., *Chem. Commun.*, **2015**, *51*, 16417-16420.

[28] Isaacs L., *Acc. Chem. Res.*, **2014**, *47*, 2052–2062.

[29] Shetty D., Khedkar J. K., Park K. M., Kim K., *Chem. Soc. Rev.*, **2015**, *44*, 8747–8761.

[30] Jiang R., Wang S., Li J. P., *RSC Adv.*, **2016**, *6*, 4478–4482.

[31] Xiao X., Hu Q. H., Tao Z., Zhang Y. Q., Xue S. F., Zhu Q. J., Wei G., *Chem. Phys. Lett.*, **2011**, *514*, 317–320.

[32] Xiao X., Sun J. S., Jiang J. Z., *Chem. Eur. J.*, **2013**, *19*, 16891–16896.

[33] Lin R. L., Sun W. Q., Yao W. R., Zhu J., Liu J. X., *RSC Adv.*, **2014**, *4*, 18323–18328.

[34] Xiao X., Li W. J., Jiang J. Z., *Inorg. Chem. Commun.*, **2013**, *35*,156–159.

[35] Ko Y. H., Kim K., Kang J. K., Chun H., Lee J. W., Sakamoto S., Yamaguchi K., Fettinger J. C., Kim K., *J. Am. Chem. Soc.*, **2004**, *126*, 1932–1933.

[36] Xiao X., Gao Z. Z., Shan C. L., Tao Z., Zhu Q. J., Xue S. F., Liu J. X., *Phys. Chem. Chem. Phys.*, **2015**, *178*, 618-8621.

[37] Liu P., Shao X. G., Chipotdef C., Cai W. S., *Phys. Chem. Chem. Phys.*, **2014**, *16*, 24169–24172.

[38] Yamanaka M., Yoshida U., Sato M., Shigeta T., Yoshida K., Furuta T., Kawabata T., *J. Org. Chem.*, **2015**, *80*, 3075−3082.

[39] Sammaki T., Hurley T. B., *J. Am. Chem. Soc.*, **1996**, *118*, 8967−8969.

[40] Nguyen H. V., Butler D. C. D., Richards C. J., *Org. Lett.*, **2006**, *8*, 769−772.

[41] Sheldrick G. M., *Crystallogr. Acta, Sect. A: Found. Crystallogr.*, **2008**, *64*, 112.

[42] Sheldrick G. M., SHELXS-97, Program for X-ray Crystal Structure Determination, University of Göttingen, Germany, **1997**.

[43] Sheldrick G. M., SHELXL-97, Program for X-ray Crystal Structure Refinement, University of Göttingen, Germany, **1997**.