CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900570

Electron Density Shift in Imidazolium Derivatives upon Complexation with Cucurbit[6]uril

Viktor Kolman,[a] Radek Marek,[b] Zora Strelcova,[b] Petr Kulhanek,[b] Marek Necas,[a] Jan Svec,[a] and Vladimir Sindelar*[a]

Abstract: In this study, we have investigated the supramolecular interaction between series of 1-alkyl-3-methylimidazolium guests with variable alkyl substituent lengths and cucurbit[6]uril (CB6) in the solution and the solid state. Correct interpretation of ^{1}H NMR spectra was a key issue for determining the binding modes of the complexes in solution. Unusual chemical shifts of some protons in the ^{1}H NMR spectra were explained by the polarization of the imidazolium aromatic ring upon the complexation with the host. The formation of 1:1 complex between 1-ethyl-3-methylimidazolium and CB6 is in disagreement with previously reported findings describing an inclusion of two guest molecules in the CB6 cavity.

Keywords: cucurbiturils · host–guest systems · ionic liquids · supramolecular chemistry

Introduction

Cucurbit[6]uril (CB6) is the oldest and the most accessible representative of the CB family of macrocycles and its supramolecular interactions with various guests have been extensively investigated.[1] After pioneering work of Behrend, the ability of CB6 to behave as a synthetic receptor was described in detail by Mock and co-workers together with the discovery of the macrocyclic structure of the molecule.[2] They reported the formation of complexes between CB6 and aliphatic amines or diamines. Guest positioning and complex stability strongly depended on the length of alkyl chain of the guest.[3] Since then the complexation between CB6 and many organic guests has been studied including polyamines,[4] viologen derivatives,[5] organic dyes,[6] polypeptides,[7] amino acids, and dipeptides.[8]

Recently, imidazolium derivatives have been investigated as a suitable guests for CBs. CB7 was found to form a strong inclusion complex with the bis(imidazolium) dication.[9] Hydrogen/deuterium (H/D) exchange of the imidazolium acidic proton is significantly inhibited in solution for this complex in D_2O as a result of hydrogen bonding with the carbonyl portal of the macrocycle. Bis(imidazolium) dication was also used as a guest, allowing the formation of ternary complexes.[10] In these complexes, one guest molecule is included in both CB7 and β-cyclodextrin macrocycles leading to a cooperative supramolecular interaction between the macrocycles. Many imidazolium compounds are known to behave as ionic liquids (ILs), a class of organic compounds that have found industrial application as designer solvents[11] and catalysts[12] in organic reactions, and media in separation technologies.[14] It has been published recently that imidazolium ILs are able to form inclusion complexes with CBs.[14] As CB6 is poorly soluble in water and insoluble in organic solvents, its solubility in water increase upon the complexation with IL. Furthermore the presence of CBs decreases the IL solution viscosity.[14b]

The complexation between both pyridinium and ammonium organic guests and CB6 in water is driven by the hydrophobic effect and dipole-cation interactions[3d] between the negatively charged carbonyl portal of CB6 and the nitrogen on the guest, where the positive charge is located. As a result, the hydrophobic part of the molecule is included inside the CB6 cavity while the nitrogen cation sits on the CB6 portal. The mode of binding between these guests and

[a] V. Kolman, Prof. Dr. M. Necas, J. Svec, Dr. V. Sindelar
Department of Chemistry
Masaryk University
Kotlarska 2, 61137 Brno (Czech Republic)
Fax: (+420) 549-49-2443
E-mail: sindelar@chemi.muni.cz

[b] Prof. Dr. R. Marek, Z. Strelcova, Dr. P. Kulhanek
National Centre for Biomolecular Research
Masaryk University
Kamenice 5A4, 62500 Brno (Czech Republic)

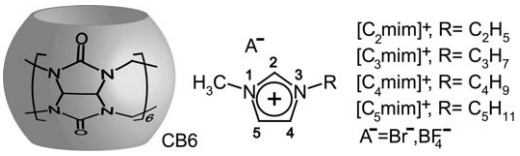
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900570.

CB6 in the solution is usually determined by ^{1}H NMR spectroscopy. The interior of the CB6 cavity comprises a ^{1}H NMR shielding region while the outside regions near to carbonyl portals on both sides of CB6 are weakly deshielding. Thus, it is generally believed that, upon complexation, the guest protons included inside the host cavity experience an upfield shift and those protons located outside and close to the carbonyl portals are displaced downfield.

Results and Discussion

In this paper, we demonstrate the formation of inclusion complexes between imidazolium guests and CB6. We describe two different binding modes between CB6 and 1-alkyl-3-methylimidazolium ($[C_n\text{mim}]^+$ for which n corresponds to the number of carbons in the alkyl chain) depending on the guest alkyl chain length. Upon the formation of the complexes an unusual chemical shift for some of the guest protons located outside of the CB6 cavity was recorded in the ^{1}H NMR spectra. This unusual observation is also discussed.

We selected for our study series of 1-alkyl-3-methylimidazolium ILs where alkyl ranges from ethyl to pentyl (Scheme 1). These guests where prepared by the alkylation



Scheme 1. Structure of cucurbit[6]uril and imidazolium guests.

of 1-methylimidazole with the corresponding alkylbromide (see the Supporting Information). The prepared imidazoliums were investigated as bromide salts except in the UV/vis experiments where the bromide anion was exchanged by BF_4^-.

The binding interactions were monitored by ^{1}H NMR spectroscopy. We started our investigation with $[C_5\text{mim}]^+$ which was dissolved in D_2O and titrated by addition of solid CB6 (Figure 1). Upon addition of 0.5 equivalents of the macrocycle all the ^{1}H NMR resonances of the guest split into two signals, which indicate that the exchange between free and bound guest is slow on the NMR time scale. A new set of signals for the pentyl chain appeared at higher field, while H2 and H4 experience downfield shifts of 0.32 and 0.37 ppm, respectively. This indicates that the aliphatic protons are included inside the ^{1}H NMR shielding region of the CB6 cavity and protons H2 and H4 are located in the deshielding region outside of the carbonyl portal as illustrated in Scheme 2 A. Surprisingly, upon complexation, proton H5 shifts $\approx$0.13 ppm upfield. As proton H5 is located outside the shielding region of CB6 either a downfield shift or no shift for this proton signal was expected. What is the reason

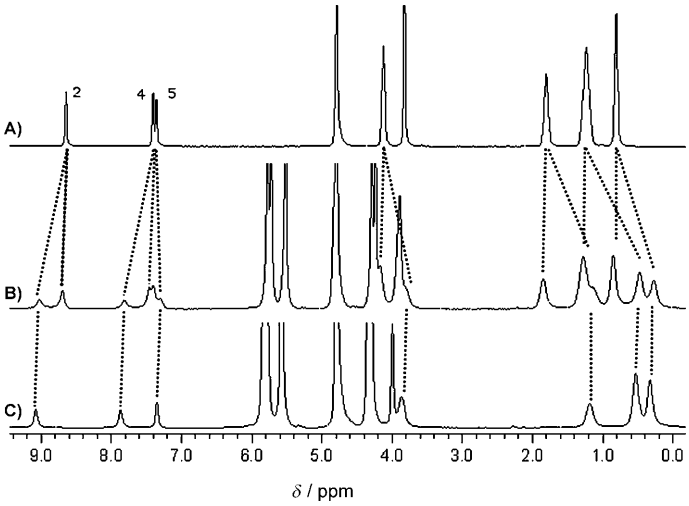
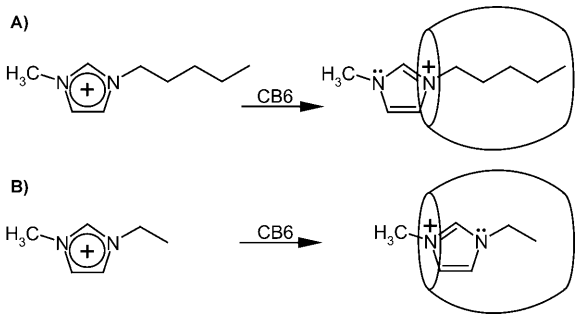


Figure 1. ^{1}H NMR spectra (300 MHz, D_2O) of $[C_5\text{mim}]^+$ in the absence (A) and in the presence of 0.4 equiv (B) and 0.9 equiv of CB6 (C).



Scheme 2. Two different modes of inclusion binding between 1-alkyl-3-methylimidazolium guests and CB6.

for this unexpected observation? Our explanation relies on a shift of electron density within the imidazolium ring of the guest upon complexation with CB6. Close proximity of the carbonyl rim to nitrogen N3 caused partial stabilization of the positive charge on this atom. In response to the cation stabilization, the electron density in the aromatic imidazolium system shifts towards nitrogen atom N1, which bears the methyl substituent. Proton H5 is influenced by the increase in electron density on its vicinity, which results as an upfield shift in the ^{1}H NMR spectra. Also the localization of the charge upon complexation is only partial. For improved clarity, we can represent this mode of binding as a complex, where the resonance structure of imidazolium has positive charge located on N3 and a free electron pair on N1 (Scheme 2 A).

Similar ^{1}H NMR spectra was obtained for the titration of $[C_4\text{mim}]^+$ with CB6 where the resonance of proton H5 shows a chemical shift of 7.36 ppm, compared to its original chemical shift of 7.46 ppm in the absence of the host. It is important to notice that the chemical shifts of protons H4 and H5 on the free guest are very similar and it is therefore difficult to follow their chemical shift changes when the

CB6 is added into the solution. 2D NOESY experiments were used to assign unequivocally the ^{1}H NMR signals for the guest inside the host cavity (see the Supporting Information). Previously, the proposed position of the $[C_4mim]^+$ within CB6 cavity was different, owing to an incorrect assignment of H4 and H5 signals in the ^{1}H NMR spectra of the complex solution.[14a]

Analysis of the ^{1}H NMR spectra indicates that $[C_3mim]^+$ forms an inclusion complex with CB6 in which the alkyl chain is incorporated inside the cavity of the macrocycle, whereas the imidazolium ring remains outside. However, in this case the complexation is fast on the ^{1}H NMR time scale. Fast exchange of the guest molecules inside the CB6 cavity is probably caused by a lower equilibrium association constant, owing to the shorter alkyl substituent $[C_3mim]^+$ compared to $[C_5mim]^+$ and $[C_4mim]^+$. Unfortunately, we were not able to determine the corresponding association constants to support this prediction.

Different binding interactions were observed between $[C_2mim]^+$ and CB6 (Figure 2) compared to those observed

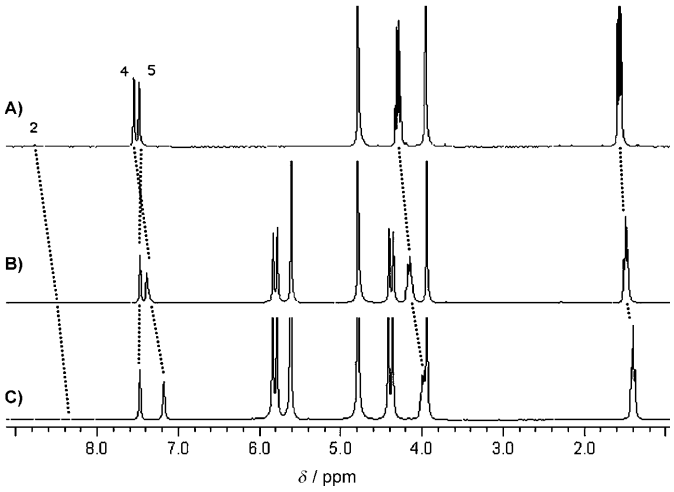


Figure 2. ^{1}H NMR spectra (300 MHz, D_2O) of $[C_2mim]^+$ in the absence (A) and in the presence of 0.25 equiv (B) and 0.5 equiv of CB6 (C).

for $[C_3mim]^+$, $[C_4mim]^+$ or $[C_5mim]^+$. Upon addition of an increasing amount of CB6 into the $[C_2mim]^+$ solution an average spectrum of the free and complexed guest was observed indicating the fast exchange on the NMR time scale. A maximum of 0.5 equiv of CB6 can be added into the solution before precipitation takes place. Upon addition of 0.5 equiv of the host, a substantial upfield shift of 0.55 ppm and 0.31 ppm was observed for the aromatic protons H2 and H4, respectively, and H5 does not experience any chemical shift. The intensity of the H2 proton signal is suppressed as a result of H/D exchange of the proton in D_2O solution. The signals for the ethyl protons shift upfield. The induced upfield shifts correspond to the formation of an inclusion complex in which the imidazolium ring, together with the ethyl substituent, are included inside the cavity of the host. We predict that in this complex the electron density in the imidazolium ring is shifted towards nitrogen N3, while the positive charge is partially localized on N1, owing to the ion-dipole interactions with the portal of CB6. The localization of positive charge on nitrogen N1 is responsible for the lack of chemical shift on proton H5 observed upon complexation despite of the placement of the proton inside the macrocycle. This binding mode is presented in Scheme 2B. For the sake of clarity the charge is fully localized on N1.

As our interpretation of NMR spectra differs from previously published results, we decided to support out findings about the placement of imidazolium derivatives within the CB6 cavity using X-ray crystallography and computational methods. We were able to obtain single crystals of the $[C_4mim]^+$-CB6 complex suitable for X-ray diffraction analysis. The crystal structure shows the superimposition of two $[C_4mim]^+$-CB6 complexes differing in the relative turning of $[C_4mim]^+$ around the CB6 longitudinal axis (Figure 3A,B).[16] In both cases, the butyl chain is located within

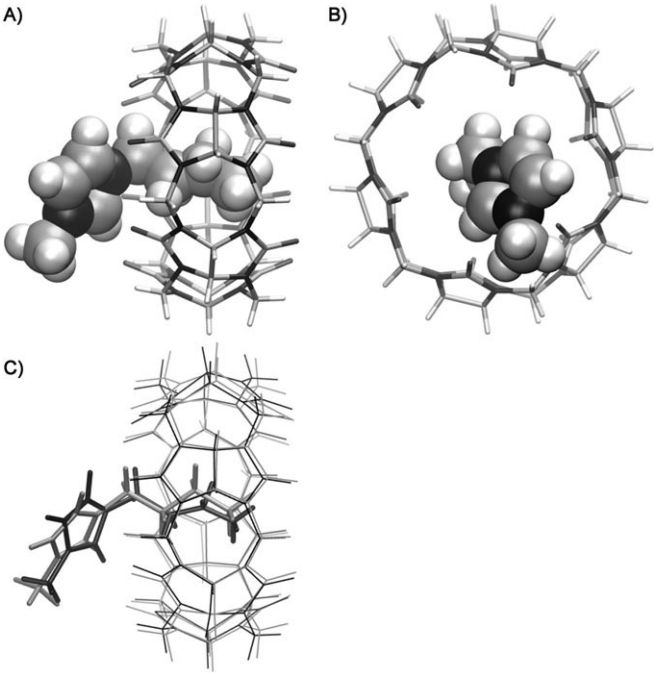


Figure 3. Crystal structure of $[C_4mim]^+$-CB6 complex: A) side and B) front views and C) comparison of crystal structure (black) and structure optimized using HF/6-31G* method (gray).

the cavity, which confirms the complex structure proposed from our NMR spectroscopic data.

Since crystal environment might exhibit conditions that are far away from the situation observed in the solution, we decided to probe the structural and dynamical features of the complex by the means of quantum chemical and molecular dynamics methods. One of two observed structures in the crystal was extracted and used as the starting point for further modeling. The structure was subjected to geometry optimization in vacuum employing quantum chemical methods implemented in Gaussian 98[15] and Turbomole 5.6[17]

program suites. Only minor changes in the resulting structure were observed using Hartree–Fock method with 6-31G*[18] basis set, with a root-mean-square deviation (RMSD) of 0.46 Å between the initial and optimized structures (Figure 3C). A similar difference (RMSD = 0.50 Å) was observed using density functional theory (B3LYP[19]) and larger basis set (cc-pVDZ[20]). These results reveal very small impact of the crystal field on the complex but still they do not say anything about the situation in solution. Therefore, the complex was immersed into a box containing about 6000 water molecules. Owing to the extreme complexity of such system, quantum chemical computations had to be replaced by a faster empirical molecular mechanics approach. This change also permits to study the dynamic behavior of the system by means of molecular dynamics. For this purpose, the sander program from the AMBER package[21] was used. The complex was described using the GAFF[22] force field, which is well tuned for the simulation of small organic molecules, whereas water molecules were described using TIP3P[23] potential. At the beginning of the simulation, the system was heated up to 300 K with pressure maintained at 1 bar (for detailed description of used protocols, see the Supporting Information section). After system equilibration, the simulation was run for an additional 10 ns with temperature and pressure maintained at 300 K and 1 bar, respectively. During this period, the complex was stable showing the same structural features as those observed by X-ray diffraction and proposed from the interpretation of NMR spectra. To avoid possible computational artifacts coming from for example, interlocked structure, the simulation was re-run using different initial complex structure. $[C_4mim]^+$ was moved along axial axis of complex in such a way that 3-methyl group was roughly situated in the cavity centre and the butyl chain was outside of CB6. This complex arrangement was stable only for $\approx$600 ps. After this period, $[C_4mim]^+$ was moved back and the resulting complex was stable until the end of the simulation.

We were also able to obtain the single crystals of the $[C_2mim]^+$-CB6 complex. The crystal structure contains two different types of complexes.[16] The first type contains $[C_2mim]^+$ located within the CB6 cavity (Figure 4A,B). The second one is composed of two superimposed structures, both containing $[C_2mim]^+$ within the CB6 cavity, but with opposite head-to-tail orientations. In all cases, the imidazolium moiety is located inside the CB6 cavity, contrary to our findings with the $[C_4mim]^+$-CB6 complex, where imidazolium sits on top of one of the carbonyl portals. One might argue that the small molecule $[C_2mim]^+$ is pushed into the cavity by packing forces dominating in the crystal. However, structure optimization of this complex by quantum chemical methods reveals that the structure is stable even without the crystal field (Figure 4C). Furthermore, the calculated complex formation energy is about 5 kcal mol^{-1} smaller (B3LYP/cc-pVDZ) than that for $[C_4mim]^+$-CB6 complex, which is in agreement with our expectations and with the lower stability of $[C_2mim]^+$-CB6 complex detected by NMR. Lower complex stability is also observed in molecular dynamics simulations. The complex dissociates after 3–5 ns (proved by three simulations starting from different conditions).

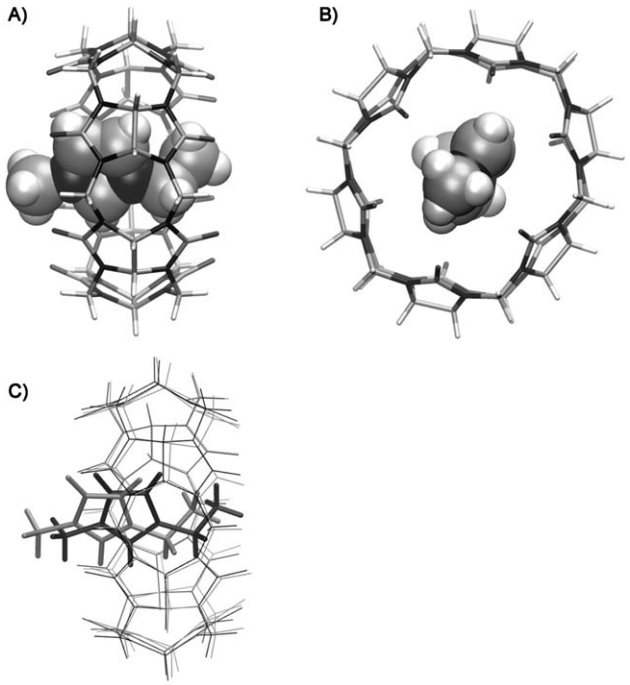


Figure 4. Crystal structure of $[C_2mim]^+$-CB6 complex: A) side and B) front views and C) comparison of crystal structure (black) and structure optimized using HF/6-31G* method (gray).

Our results from crystallographic measurements and computations strongly support a 1:1 binding mode between $[C_2mim]^+$ and CB6. However, our findings contrast with a recent report on the formation of a 2:1 complex between $[C_2mim]^+$ and CB6.[14a] Therefore, to further support our results, we constructed a Job plot using UV-visible spectroscopy. A maximum was found at χ $[C_2mim]^+ = 0.5$, which also indicates a 1:1 stoichiometry between the host and the guest. Furthermore, a major signal at 1107 m/z corresponding to 1:1 $[C_2mim]^+$-CB6 complex was observed in the MALDI TOF MS spectrum, when the complex solution in the presence of more than fourfold excess of the guest was analyzed with no sign of the 2:1 complex. Similar MALDI TOF MS spectra indicating the presence of 1:1 complex were obtained for the remaining guests upon the complexation with CB6 (see the Supporting Information).

The complexation between $[C_5mim]^+$ and CB6 was also investigated using ^{15}N NMR spectroscopy. We anticipated that the shift of electron density in the imidazolium ring presumably induced by complexation with CB6 should affect both ^{15}N resonances on the imidazolium skeleton. A solution containing 1 equiv of $[C_5mim]^+$ and 0.5 equiv of CB6 was used for the ^{15}N NMR measurements.[24] Two sets of signals corresponding to the free and bound forms of the guest were observed because of the slow exchange process. ^{15}N resonances were assigned unequivocally to the N1 and N3 atoms by using ^1H-^{15}N GSQMBC experiments.[25] Interactions of the protons on the methyl group with N1 and pro-

tons on the CH_2 groups of the pentyl chain with N3 undoubtedly confirmed the resonance assignments summarized in Table 1. N1 is shielded by 4.0 ppm upon complexation of

Table 1. ^{15}N NMR chemical shifts (δ in ppm) for free and bound $[C_5mim]^+$ in D_2O at 275.5 K.

	$[C_5mim]^+$ [ppm]		
	Free	Complexed	$\Delta\delta$
N1	169.8	165.8	−4.0
N3	182.7	185.4	+2.7

$[C_5mim]^+$ inside the cavity whereas complexation-induced deshielding of N3 amounts to 2.7 ppm. The observed ^{15}N chemical shifts indicate partial shift of electron density from nitrogen N3 to N1 upon complex formation and is consistent with the hypothesis formulated from the results of our ^1H NMR measurements.

Based on the results obtained from ^1H and ^{15}N NMR measurements we proposed two different modes of binding between 1-alkyl-3-methylimidazolium guests and CB6, which are clearly dependent on the length of alkyl chain (Scheme 2). Similar effect of the alkyl chains on the complex structures was previously described for complexes between CB7 and dialkylviologenes.[26] $[C_3mim]^+$, $[C_4mim]^+$, and $[C_5mim]^+$ bear a long alkyl substituent, which is favored to bind inside the CB6 cavity as a result of hydrophobic effects. As propyl, butyl, and pentyl substituents fit well in the cavity, the imidazolium ring remains outside the host. Positive charge is then partially localized on N3 and stabilizes the inclusion complex by ion-dipole interaction (Scheme 2A). On the other hand $[C_2mim]^+$ contains a short alkyl chain, allowing the inclusion of both the alkyl chain and the imidazolium ring. In this complex, positive charge is partially shifted toward nitrogen N1, thus stabilizing the complex by interaction with the host portal (Scheme 2B). In other words, the binding position of the guest within the cavity is determined by the hydrophobic effect, which also dictates to which of the two nitrogens the positive charge will be predominantly shifted in order to stabilize the complex through interactions with the CB6 portal.

Conclusions

In conclusion, we have investigated the formation of inclusion complexes between 1-alkyl-3-methylimidazolium guests and CB6 in the solution and the solid state, using ^1H and ^{15}N NMR spectroscopy, UV/vis spectroscopy, X-ray crystallography, mass spectrometry and computational methods. We have demonstrated that all imidazolium guests form 1:1 complexes with CB6, in which the mode of inclusion binding depends on the length of the alkyl substituent. In the case of the $[C_2mim]^+$ guest, the imidazolium ring together with the alkyl substituents are pushed inside the host cavity, although the guests with longer aliphatic chains form a CB6 complex in which only the alkyl chain is engulfed by the host, leaving the imidazolium ring outside the host cavity. We have also shown that the imidazolium aromatic ring is polarized upon complexation with CB6. For both binding modes, the electron density shifts from the nitrogen located in the proximity of the carbonyl portal of CB6 toward the opposite nitrogen atom.

Experimental Section

Starting materials were purchased from commercial suppliers and were used without further purification. 1D and 2D NMR spectra were recorded using a Bruker Avance 600 spectrometer operating at frequencies of 600.13 MHz (^1H), 150.77 MHz (^{13}C), and 60.76 MHz (^{15}N), a Bruker Avance 500 spectrometer operating at frequencies of 500.13 MHz (^1H), 125.77 MHz (^{13}C), and 50.76 MHz (^{15}N), and a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^1H) and 75.77 MHz (^{13}C). ^{13}C NMR chemical shifts (δ in ppm) were referenced to the signal of tetramethylsilane (TMS), which was used as an external standard to prevent its interference with CB.[6] The ^{15}N NMR chemical shifts were referenced to liquid CH_3NO_2 (381.7 ppm) and are reported relative to liquid NH_3. The MALDI-TOF mass spectra were obtained using Ultraflex III spectrometer. Spectra were measured in reflection positive mode, 200 laser shots were accumulated (Nd:YAG laser - 355 nm). UV/vis absorption spectra were measured on Shimadzu UV 1602 UV-VIS spectrophotometer with 1 cm quartz cell. Diffraction data were collected on a KUMA KM-4 κ-axis CCD diffractometer with MoKα radiation (λ = 0.71073 Å). The temperature during data collection was 120(2) K. The structures were solved by direct methods and refined by full-matrix least-squares methods using ShelXTL software.[19]

Acknowledgements

We are grateful to the Grant Agency of the Czech Republic (203/07/P382 to VS) and Ministry of Education of the Czech Republic (MSM0021622413 and LC06030 to RM, and MSM0021622413 to PK). The access to the METACentrum supercomputing facilities provided under the research intent MSM6383917201 is highly appreciated.

[1] a) J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621–630; b) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem.* **2005**, *117*, 4922–4949; *Angew. Chem. Int. Ed.* **2005**, *44*, 4844–4870.
[2] W. A. Freeman, W. L. Mock, N.-Y. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 7367–7368.
[3] a) W. L. Mock, N.-Y. Shih, *J. Org. Chem.* **1983**, *48*, 3618–3619; b) W. L. Mock, N.-Y. Shih, *J. Org. Chem.* **1986**, *51*, 4440–4446; c) W. L. Mock, N.-Y. Shih, *J. Am. Chem. Soc.* **1988**, *110*, 4706–4710; d) W. L. Mock, N.-Y. Shih, *J. Am. Chem. Soc.* **1989**, *111*, 2697–2699.
[4] a) H. Isobe, N. Tomita, J. W. Lee, H.-J. Kim, K. Kim, E. Nakamura, *Angew. Chem.* **2000**, *112*, 4427–4430; *Angew. Chem. Int. Ed.* **2000**, *39*, 4257–4260; b) H. Isobe, S. Sota, J. W. Lee, H.-J. Kim, K. Kim, E. Nakamura, *Chem. Commun.* **2005**, 1549–1551.
[5] Y. Tan, S. Choi, J. W. Lee, Y. H. Ko, K. Kim, *Macromolecules* **2002**, *35*, 7161–7165.
[6] C. Márquez, R. R. Hudgins, W. M. Nau, *J. Am. Chem. Soc.* **2004**, *126*, 5806–5816.
[7] H.-J. Buschmann, L. Mutihac, R.-C. Mutihac, E. Schollmeyer, *Thermochim. Acta* **2005**, *430*, 79–82.
[8] H.-J. Buschmann, E. Schollmeyer, L. Mutihac, *Thermochim. Acta* **2003**, *399*, 203–208.

[9] R. Wang, L. Juan, D. H. Macartney, *Chem. Commun.* **2006**, 2908–2910.
[10] L. Leclercq, N. Noujeim, S. H. Sanon, A. R. Schmitzer, *J. Phys. Chem. B* **2008**, *112*, 14176–14184.
[11] *Ionic Liquids in Synthesis* (Eds.: T. Welton, P. Wasserscheid), Wiley VCH, Weinheim, **2002**.
[12] P. J. Dyson, T. J. Geldbach in *Metal Catalysed Reactions in Ionic Liquids*, Springer, New York, **2006**.
[13] *Ionic Liquids in Polymer Systems, Vol. 913 of ACS Symposium Series* (Eds.: Brazel, C. S.; Rogers, R. D.), Oxford University Press, New York, **2005**; .
[14] a) L. Liu, N. Zhao, O. A. Scherman, *Chem. Commun.* **2008**, 1070–1072; b) P. Montes-Navajas, A. Corma, H. Garcia, *J. Mol. Catal. A* **2008**, *279*, 165–169.
[15] Gaussian 98 (Revision A.9), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
[16] CCDC 722277 and 722278 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
[17] R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165–169.
[18] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213–222.
[19] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[20] T. H. Dunning, Jr., *J. Chem. Phys.* **1989**, *90*, 1007–1023.
[21] AMBER 9, D. A. Case, T. A. Darden, T. E. Cheatham III, C. L. Simmerling, J. Wang, R. E. Duke, R. Luo, K. M. Merz, D. A. Pearlman, M. Crowley, R. C. Walker, W. Zhang, B. Wang, S. Hayik, A. Roitberg, G. Seabra, K. F. Wong, F. Paesani, X. Wu, S. Brozell, V. Tsui, H. Gohlke, L. Yang, C. Tan, J. Mongan, V. Hornak, G. Cui, P. Beroza, D. H. Matthews, C. Schafmeister, W. S. Ross, P. A. Kollman, University of California, San Francisco, **2006**.
[22] J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman, D. A. Case, *J. Comput. Chem.* **2004**, *25*, 1157–1174.
[23] W. L. Jorgensen, J. Chandrasekhar, J. Madura, M. L. Klein, *J. Chem. Phys.* **1983**, *79*, 926–935.
[24] a) R. Marek, A. Lycka, *Curr. Org. Chem.* **2002**, *6*, 35–66; b) R. Marek, A. Lycka, E. Kolehmainen, E. Sievanen, J. Tousek, *Curr. Org. Chem.* **2007**, *11*, 1154–1205.
[25] R. Marek, L. Kralik, V. Sklenar, *Tetrahedron Lett.* **1997**, *38*, 665–668.
[26] K. Moon, A. E. Kaifer, *Org. Lett.* **2004**, *6*, 185–188.

Received: March 3, 2009
Published online: June 9, 2009

