


Cite this: *RSC Adv.*, 2021, **11**, 10860

Received 1st February 2021  
Accepted 27th February 2021

DOI: 10.1039/d1ra00859e

rsc.li/rsc-advances

## Development of effective potassium acetate extractant†

Maciej Zakrzewski, Dominika Załubiniak and Piotr Piątek \*

Carboxylates are commonly used in the food and pharmaceutical industry and due to their extensive use, carboxylates present a significant environmental burden. In this context, valine based, heteroditopic receptor **1** was prepared and its ability to bind simultaneously potassium cation and acetate anion in water containing  $\text{CH}_3\text{CN}$  solutions was demonstrated. Under liquid–liquid extraction conditions the receptor **1** was capable of extracting hydrophilic AcOK salt from aqueous solution and was proved to be nearly ten times more effective than the equimolar mixture of monotopic receptors. Furthermore, compound **1** could extract one of the most popular nonsteroidal anti-inflammatory drugs, ibuprofen (IbuOK), from relatively dilute aqueous solutions.

## Introduction

Liquid–liquid extraction (solvent extraction) is one of the most important separation methods in research and industry. For example, in hydrometallurgy this process is frequently used in separation and purification of cations of transition metals (Cu, Co, Ni, Pd) as well as f-block elements (U, Pu) from aqueous solution to organic solvents.<sup>1</sup> On the other hand, anion recognition and transport in liquid–liquid separation systems is an area of growing interest.<sup>2</sup> This interest is mainly stimulated by the need of finding effective methods of the removal of potentially harmful anions, such as nitrate, sulfate, perchlorate or carboxylates from the environment. Molecular receptors which could bind only one kind of ion can be used to facilitate liquid–liquid extraction. However, only ions accompanied by lipophilic counterions are effectively extracted by those monotopic receptors. For example, dicyclohexyl-18-crown-6 extracts 41% of  $\text{KClO}_4$  and 16% of KI but only 0.6% of KBr from water to chloroform phase.<sup>3</sup> To extract hydrophilic salts the use of binary mixture of monotopic receptors or one receptor combining cation and anion binding sites (heteroditopic receptor) is needed.<sup>2,4</sup> The use of heteroditopic receptors in extraction processes has many practical advantages. First, cation–receptor–anion ternary complex is electrically neutral thus it can be directly transported across membranes in a symport process. Then mutual electrostatic interactions between co-bonded ions and allosteric conformational change of the receptor induced by binding events can cause positive

cooperative effects that could substantially increase salt binding affinity.<sup>5</sup> However, the design, synthesis and binding studies of heteroditopic receptors that display substantial positive binding synergy is not a trivial task, yet finding receptors that could facilitate liquid–liquid salt transport is even more challenging. This is because strong salt binding by a heteroditopic receptor is not the only one factor determining transport activity.<sup>2,4,6</sup> The other crucial factor is the lipophilicity of the cation–receptor–anion complex that is transported through liquid–liquid interface.<sup>7</sup> Therefore, the heteroditopic receptors that form less polar complexes in which cation and anion are in close proximity should be more active in salt transport. Therefore, the most effective salt extractants prepared to date have multi-macrocyclic, cryptand-like structure that ensures close spatial proximity of cation and anion binding domains.<sup>8</sup> These extractants bind salts most likely as contact or solvent separated ion-pairs. Some very elegant multimacrocyclic salt extractants are known and proved to be able to extract KF, KCl, CsCl,  $\text{NH}_4\text{NO}_3$  and  $\text{LiNO}_2$ .<sup>5,8</sup> However, due to the “closed” structure of these receptors it is difficult to improve their binding and extracting abilities. Unfortunately, the synthesis of these multimacrocyclic compounds is usually low yielding and requires the application of high-dilution techniques. Therefore, there is a need of simple and relatively cheap receptor which will extract potentially harmful individuals.

Recently, our group has reported non-multimacrocyclic heterotopic receptor **S1** which strongly binds potassium carboxylates due to high cooperativity between co-bonded ions.<sup>9</sup> Moreover, preliminary studies showed that receptor **S1** permits the extraction of hydrophilic  $\text{AcOK}_{\text{aq}}$  into an organic phase. This unprecedented result is very important because carboxylate salts are commonly used in the chemical, pharmaceutical and food industry.<sup>10</sup> Due to their extensive use, carboxylates present a significant environmental burden. New

Department of Chemistry, The University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland. E-mail: ppiatek@chem.uw.edu.pl

† Electronic supplementary information (ESI) available:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, Job's plots, UV-Vis titration spectra and the resulting binding isotherms,  $^1\text{H}$  NMR titration spectra and the resulting binding isotherms, and extraction experiment details. See DOI: 10.1039/d1ra00859e



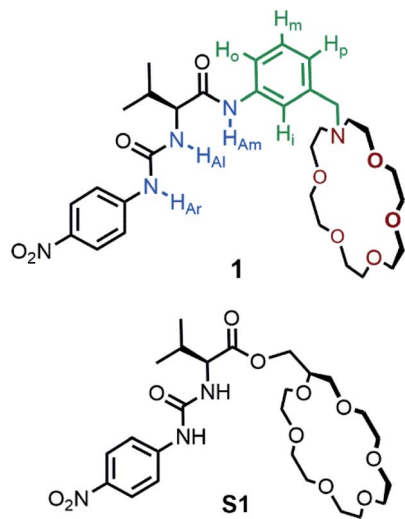


Fig. 1 Structures of receptors **1** and **S1**.

challenges connected with the analysis and removal of the carboxylates used as active pharmaceutical ingredients (such as nonsteroidal anti-inflammatory drugs) have been arising recently.<sup>11</sup> Therefore, the receptors that are capable of recognizing and extracting the carboxylates may help to analyze and remove these salts. Acetate anion is the most hydrophilic unsubstituted carboxylate ( $\Delta G_h^0 = -373 \text{ kJ mol}^{-1}$ ) and hence is a good model anion for testing the transport activity of molecular receptors.

Herein, we describe the design, synthesis, binding and detailed acetate salt extraction studies of the heterotopic receptor **1**. This receptor was developed thanks to the non-macrocyclic and modular structure of parent receptor **S1** that can be easily modified. The main purpose of receptor **S1** structure modifications was to obtain a more practical acetate receptor and extractant in terms of costs and durability. Both receptors are based on L-valine molecular scaffold and share the 4-nitrophenyl urea moiety as anion binding group. However, other groups such as thiourea or squaramide are known to interact stronger with anions. Therefore, thiourea and squaramide derivatives of **1** were prepared and studied (for structures see compounds **S2** and **S3** in ESI†). Unfortunately, these compounds turned out to be impractical. Specifically, the thiourea derivative (**S2**) was unstable in the prolonged presence of  $\text{AcOK}_{\text{aq}}$ , whereas squaramide NHs protons of **S3** were too acidic and underwent deprotonation by weak basic  $\text{AcOK}$  aqueous solution. Nevertheless, 4-nitrophenyl urea group of **1** is stable under these conditions. The strong cation coordination of **S1** is ensured by the substituted 18-crown-6. However, 2-hydroxymethyl-18-crown-6 necessary for assembling of the receptor **S1** is expensive and, what is more, hard to prepare. Therefore, for receptor **1** construction we used *N*-aza-18-crown-6 which is also commercially available but can be easily prepared in large quantities from cheap substrates.<sup>12</sup> However, the most important reason, which forced us to search for more practical cation binding domain, was hydrolysis of **S1** upon prolonged  $\text{AcOK}_{\text{aq}}$  exposure.

**Table 1** UV-Vis spectroscopy  $K_{\text{obs}}$  values (298 K) for interactions of **1** with  $\text{AcO}^-$  in present or absence of potassium cation ( $C_{\text{rec}} = 4.0 \times 10^{-5} \text{ M}$ ;  $C_{\text{titrant}} = 1.3 \times 10^{-3} \text{ M}$ ;  $C_{\text{KPF6}} = 1.5 \times 10^{-3} \text{ M}$ )

	$\text{CH}_3\text{CN}$	1% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$	3% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$
$\text{TBA}^+$	580 000	11 000	970
$\text{K}^+$	1 700 000	52 000	3400
$K_{\text{K}^+}/K_{\text{TBA}^+}$	2.93	4.72	3.51

The last important structural feature of the receptor **1** was the benzyaniline spacer between *N*-aza-18-crown-6 and valine moiety. This group ensures proper spatial arrangement of cation and anion binding domains and enables connection of receptor **1** components *via* chemically robust amide bond. This additional aromatic moiety can also change lipophilicity of receptor and consequently receptor·salt complex.

## Results and discussion

The receptor **1** has been synthesized in three simple synthetic steps. Briefly, the HATU mediated coupling of *N*-Boc-L-valine with *N*-(3-aminobenzyl)-18-crown-6 in the presence of DIPEA gave a valine-crown ether derivative. The subsequent Boc group deprotection and acylation of the resulting TFA ammonium salt with 4-nitrophenyl-isocyanate in the presence of triethylamine led to the receptor **1** in 53% yield. The main problem at this stage was the purification of **1**, which formed strong complexes with  $\text{Et}_3\text{N}$ -TFA salt, drying agents, and ions present in silica gel.

Initially, binding capabilities of the receptor **1** binding with acetate salts were tested using UV-Vis spectroscopic titrations in  $\text{CH}_3\text{CN}$ . By fitting the titration curves to a standard 1 : 1 binding profile, association constants ( $K$ ) corresponding to the interactions between the receptor **1** and acetate in the absence (tetra-*n*-butylammonium, TBA salt) and presence of one equivalent of co-bounded potassium cation could be determined (Table 1).

In acetonitrile solution in the absence of the co-coordinated cations (TBA salt) the receptor **1** associates with acetate anions stronger than the receptor **S1** ( $K_{\text{S1AcOTBA}} = 252\,000 \text{ M}^{-1}$ ). However, in the presence of potassium cations the receptor **1** binds acetate anions weaker than **S1** ( $K_{\text{S1AcOK}} > 10\,000\,000 \text{ M}^{-1}$ ). Thus, the binding cooperativity expressed as  $K_{\text{K}^+}/K_{\text{TBA}^+}$  is much lower for the receptor **1** compared to **S1**. This effect was anticipated as *N*-substituted-18-crown-6 associates less strongly with potassium cations than 18-crown-6.<sup>13</sup> However, in water-organic solvent extraction process, ions are hydrated and receptor must compete efficiently with water molecules. Therefore, acetate binding was studied in solutions containing water. The addition of 1% water to acetonitrile, resulted in dramatic decrease of association constants values. Interestingly, under these conditions, in the presence of potassium cations the acetate binding is almost five times stronger than in its absence. This effect is also observed in solution containing 3% of water.<sup>14</sup> Thus, these results suggest that positive cooperation between co-bounded ions can help the receptor **1** to overcome salt and receptor hydration and



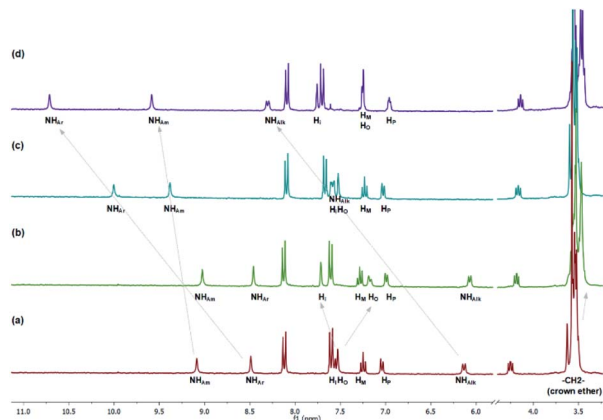


Fig. 2  $^1\text{H}$  NMR spectra: (a) receptor **1**; (b) receptor **1** after addition of 1 eq of  $\text{KPF}_6$ ; (c) receptor **1** after addition of 1 eq of TBA AcO; (d) receptor **1** after addition of 1 eq of  $\text{KPF}_6$  and 1 eq of TBA AcO; (293 K, 3%  $\text{H}_2\text{O}/\text{CD}_3\text{CN}$  solution,  $C_{\text{receptor}} = 3.8 \times 10^{-3} \text{ M}$ ).

therefore this represents an important step towards development of effective salt extractant.

To obtain more direct experimental insights into the binding behavior of **1**,  $^1\text{H}$  NMR spectroscopic titrations were performed in competitive 3%  $\text{H}_2\text{O}/\text{CD}_3\text{CN}$  solvent system. The addition of one equivalent of  $\text{KPF}_6$  results in upfield shifts of  $-\text{N}-\text{CH}_2-$  and  $-\text{O}-\text{CH}_2-$  crown ether methylene protons (Fig. 2). At the same time, a considerable downfield shift of aromatic  $\text{H}_1$  proton and upfield shift of  $\text{H}_6$  proton of the *N*-benzyl aromatic ring is observed. Other signals including urea and amide NH protons remain practically unaffected by the cation addition. This suggests the formation of a receptor **1**· $\text{K}^+$  inclusion complex by the crown ether domain without the involvement of urea and amide groups.

As it is shown in Fig. 3, significant chemical shift changes were observed when the receptor **1** was treated with acetate anions. Specifically, upon exposure to 1 eq of TBA AcO the urea resonances at 6.1 and 8.5 ppm undergo considerable downfield shifts to 7.6 and 10.0 ppm respectively. These changes in the

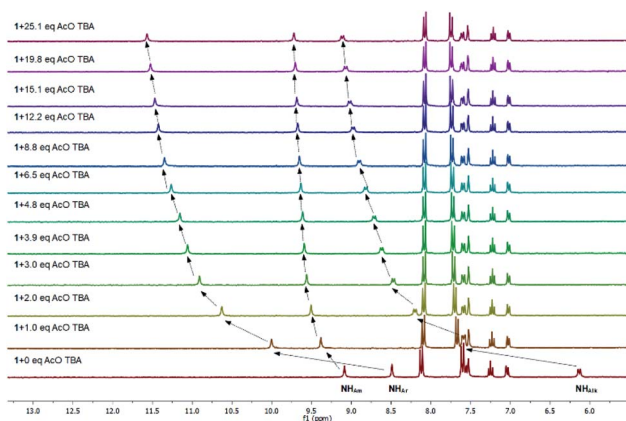


Fig. 3 Partial  $^1\text{H}$  NMR spectra of **1** upon titrant (TBA AcO) addition, (293 K, 3%  $\text{H}_2\text{O}/\text{CD}_3\text{CN}$  solution,  $C_{\text{titrant}} = 1.9 \times 10^{-1} \text{ M}$ ,  $C_{\text{receptor}} = 3.8 \times 10^{-3} \text{ M}$ ).

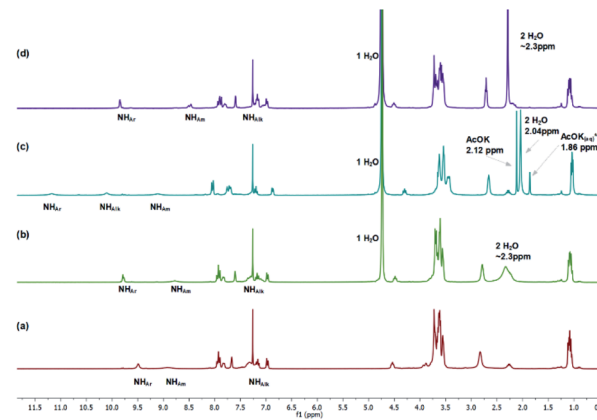


Fig. 4  $^1\text{H}$  NMR spectra stack of extraction experiments: (a) receptor **1** dissolved in 'dry'  $\text{CDCl}_3$  ( $C_{\text{receptor}} = 2.5 \times 10^{-2} \text{ M}$ ); (b) receptor **1** solution after being washed with deionized water; (c) receptor **1** solution after extraction with 50 eq AcOK aqueous; (d) receptor **1** solution after back-extraction to deionized water \*AcOK<sub>(aq)</sub> salt present in droplets of water on the NMR tubes walls (also see ESI†).

chemical shifts are ascribed to hydrogen bonding between the urea NHs and the acetate anion. On the contrary, the amide NH proton shifts downfield only a little, which may suggest that amide NH interacts with acetate anions and forms intramolecular bond with the oxygen atoms of the urea, simultaneously. This interaction may rigidify the conformation of **1**, thus a more defined binding cavity may be created. On the other hand, protons of the *N*-benzyl aromatic ring do not undergo any changes upon acetate addition indicating no association of the TBA cation to the aza-crown ether moiety.

The  $^1\text{H}$  NMR spectra acquired upon the TBA AcO addition to the solution of the receptor **1** pretreated with 1 eq of  $\text{KPF}_6$  shows features characteristic for complexation of both the cation and the anion. Moreover, the chemical shifts induced by the complexation of  $\text{AcO}^-$  in the presence of  $\text{K}^+$  were larger than the corresponding shifts observed upon addition of "single" ions, which clearly showed an increased strength of interactions. The binding constants determined from the  $^1\text{H}$  NMR titrations in the absence and presence of potassium cations was calculated to be 420 and  $2060 \text{ M}^{-1}$  respectively which corresponds to 4.9 binding cooperativity. Other acetate salts such as AcONa and  $\text{AcONH}_4$  were associated with **1** with binding constants of 500 and  $330 \text{ M}^{-1}$  respectively, which gave 1.2 and 0.8 cooperativity. Thus  $^1\text{H}$  NMR experiments validated the high cooperativity

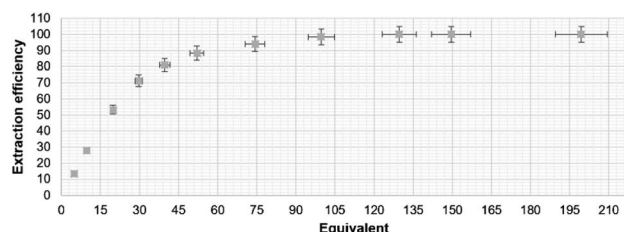


Fig. 5 Efficiency of extraction process in function of salt concentration. Based on  $^1\text{H}$  NMR extraction experiments.

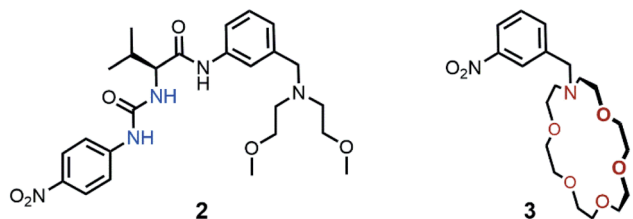


Fig. 6 Structures of monotopic receptors 2 and 3.

between cation and anion binding to the receptor **1** in competitive 3% H<sub>2</sub>O/CD<sub>3</sub>CN solvent system.

To assess whether the receptor **1** might be able to extract hydrophilic acetate salts from water into organic solvent, model liquid–liquid extraction studies were undertaken. Control experiments revealed no acetate transport (<sup>1</sup>H NMR detection) to CDCl<sub>3</sub> phase from AcOK aqueous solution as well as no receptor leaking from organic into aqueous phase. Then extraction studies were carried out using  $2.5 \times 10^{-2}$  M solution of **1** in CDCl<sub>3</sub> layered over 200 molar equivalent solution of AcOK in deionized water in an NMR tube. After shaking thoroughly for 1 minute and after phase separation, the <sup>1</sup>H NMR spectrum of the organic phase was recorded. This spectrum revealed considerable changes in the resonance signals compared to the <sup>1</sup>H NMR spectrum of **1** in wet CDCl<sub>3</sub> (Fig. 4). Urea NHs protons signals centered at 9.5 and 7.3 ppm after extraction underwent considerable downfield shifts to 11.3 and 10.2 ppm respectively. Concurrently, the appreciable upfield shift of crown ether OCH<sub>2</sub>-resonances and shift of H<sub>i</sub> and H<sub>o</sub> protons of the *N*-benzyl aromatic ring were observed (see Fig. 1 for aromatic protons assignment).

This indicates the simultaneous association of the acetate anion and the potassium cation with the receptor **1** under interfacial conditions. In addition, a peak assigned to the methyl group of the acetate anion (at  $\delta = 2.12$  ppm) was

observed. Based on the integration of this signal quantitative transport of AcOK from water to CDCl<sub>3</sub> was calculated. Thus, even that the receptor **1** associates with AcOK weaker than **S1** its extraction transport activity is very similar. This observation can be rationalized in terms of lipophilicity of the ternary potassium–receptor–acetate complex, which is related to the ion and counterion distance in the complex and lipophilicity of the ligand. The calculated clog *P* values for the receptors **S1** and **1** are 1.0 and 2.6 respectively. Therefore, ligand **1** is much more lipophilic than **S1** which may compensate its weaker binding ability.

To further test the extraction effectiveness of **1**, transport of potassium acetate was measured as a function of the concentration of AcOK in the aqueous phase while keeping the extractant concentration constant ( $2.5 \times 10^{-2}$  M) in the organic phase. Under these conditions, the receptor **1** proved to be capable of extracting efficiently potassium acetate from solutions containing up to 50 eq of AcOK (Fig. 5). For example, after extraction of 50 eq of AcOK<sub>aq</sub> with compound **1**, 88% of the receptor loading was observed. Then for unit extraction operation the efficiency of **1** decreased. This result is promising in a context of practical application of **1** for separation and transport of acetate and other more lipophilic carboxylates including active pharmaceutical ingredients.

Under the same conditions as described above, transport of other hydrophilic acetate salts such as AcONa and AcONH<sub>4</sub> was studied. No appreciable changes of the receptor-based proton signals were seen when the receptor **1** was treated with AcOLi<sub>aq</sub>. Upon exposure of **1** to AcONa<sub>aq</sub> only small changes of <sup>1</sup>H NMR spectrum were seen and 4% of acetate was detected in organic phase. On the contrary, AcONH<sub>4</sub> extraction was effective and ~70% of this salt was transported to the organic phase. Therefore, for a constant anion, the cation selectivity order was Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup> ~ NH<sub>4</sub><sup>+</sup>. This trend is in general agreement with the Hofmeister series, in which transport of smaller, more

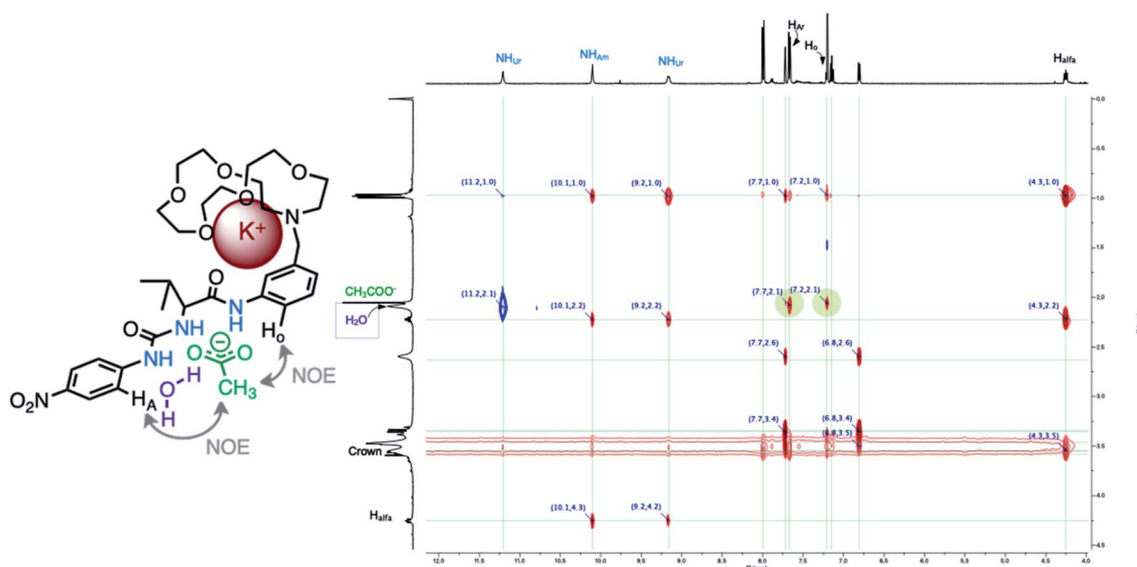


Fig. 7 2D ROESY experiment and concluded structure of **1**·AcOK.





charge-dense ions is harder because they have more unfavorable Gibbs free energy for aqueous to organic phase transfer.<sup>15</sup>

To evaluate the effect of the covalent linkage of the two binding domains in the heteroditopic receptor on salt extraction, the transport of AcOK by **1** and equimolar mixture of monotopic anion **2** and cation **3** receptors was compared (Fig. 6). Control experiments revealed that no <sup>1</sup>H NMR changes were observed when separated monotopic receptors **2** or **3** were treated with aqueous solution containing 100 eq of AcOK (see Fig. S46–S54†). However, when 50 eq of AcOK solution was extracted with equimolar mixture of anion **2** and cation **3** receptors ( $2.5 \times 10^{-2}$  M) small alteration of <sup>1</sup>H NMR spectrum was observed and signal of low intensity of the methyl group of the acetate anion was observed. Based on the integration value of this signal only approximately 12% of extraction efficiency was observed for the mixture of monotopic receptors.<sup>16</sup> The efficiency of dual receptor system can be improved by increasing salt or receptors concentration. For example, when AcOK<sub>aq</sub> concentration is increased to 100 eq, transport of 27% of acetate is observed. However, under these extraction conditions the heteroditopic receptor **1** extracts quantitative amount of AcOK. Therefore, these experiments confirmed that proper covalent connection of binding domains in one heteroditopic receptor results in superior salt extractant compared to the mixture of monotopic receptors.

Then the receptor **1** was applied to the liquid–liquid extraction of potassium salt of one of the most popular nonsteroidal anti-inflammatory drug: ibuprofen (IbuOK). Extraction of aqueous solution containing 50 eq of IbuOK induced considerable changes in the <sup>1</sup>H NMR spectrum of **2**, similar to changes caused by acetate salt. Under this condition quantitative extraction of IbuOK was observed.

As ibuprofenate is more lipophilic anion than acetate, an attempt was made to reduce the salt concentration in the aqueous phase with preservation of extraction efficiency. Series of extraction experiments revealed that IbuOK can be extracted effectively from aqueous solutions containing as low as 0.25 eq of this compound. Thus this result is very promising for practical application of extracting and detecting active pharmaceutical ingredients.

Finally, the solution structure of the complex of **1** and potassium acetate after extraction process was probed by means of 2D ROESY spectra. The through-space interactions show that all three NH-hydrogens point in the same direction. Cross-peaks between crown ether –O–CH<sub>2</sub>– methylene protons and *meta*-substituted aromatic ring protons as well as amino-acid  $\alpha$  proton suggest that crown ether moiety is located above/below this aromatic ring (Fig. 7). To our delight, the intramolecular proton–proton contacts between acetate –CH<sub>3</sub> group and aromatic protons *H<sub>A</sub>* (*para*-nitrophenyl ring) and *H<sub>O</sub>* (*meta*-substituted aromatic ring) are observed. This indicates that acetate anion is positioned between these aromatic rings and the complex is strong enough to be preserved in the ROESY experiment time scale (~200 ms). Interestingly, positive cross-peak is detected between aromatic urea NH and hydration water signal (blue cross-peak on Fig. 7). This cross-peak arises due to slow proton exchange between urea NH and complexed

water molecule.<sup>17</sup> This suggests that at least one “structural water” molecule links the acetate anion and receptor **1**. Based on integration of water signal, total of five water molecules solvates **1**·AcOK complex. This residual hydration may be crucial for stabilizing **1**·AcOK complex and water molecule most probably bridges the co-bounded anion and cation.

The salt binding mode concluded from NMR experiments was supported by DFT-molecular calculations (see ESI†). The AcO<sup>−</sup> anion form H-bond with both urea NH as well as amide hydrogens, the average urea NH...O distance is 3.159 Å and angle 140°, the amide NH...O average distance is 3.48 Å and angle 155°. Potassium cation is positioned inside crown ether cavity (average K<sup>+</sup>...O distance is 2.8 Å) and interact with adjacent aromatic ring through cation  $\pi$  interaction ( $\pi_{Ar} \cdots K^+$  distance is 2.871 Å).

## Conclusions

In summary, non-multimacrocyclic heterotopic receptor **1** carefully designed to maximize carboxylate salt extraction was prepared in three simple synthetic steps. Analysis of UV-Vis and <sup>1</sup>H NMR spectroscopic titrations conducted in water containing acetonitrile solutions revealed cooperative binding of potassium cation and acetate anion to the receptor **1**. This effect is thought to help the receptor to overcome better salt and receptor hydration. The structure of ternary cation–receptor–anion complex was probed by means of 2D ROESY measurements and molecular calculations. When used as a extractant in liquid–liquid extraction process, the receptor **1** was capable of extracting hydrophilic AcOK salt from aqueous solution containing relatively low salt concentrations (~1 M). In contrast, equimolar mixture of monotopic anion **2** and cation **3** receptors proved to be nearly ten times less effective. Finally, the receptor **1** could extract potassium ibuprofenate from relatively diluted aqueous solutions (*C*<sub>IbuOK</sub> = 6.2 mM). These results taken together will allow better understanding of the design criteria for construction of heterotopic salt receptors targeted at extraction of carboxylate salts.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- 1 M. Aquilar and J. L. Cortina, *Solvent Extraction and Liquid Membranes: Fundamentals and Applications in New Materials*, CRC Press, Boca Raton, 2008.
- 2 N. Busschaert, C. Caltagirone, W. Van Rossom and P. A. Gale, *Chem. Rev.*, 2015, **115**, 8038–8155.
- 3 U. Olsher, M. G. Hankins, Y. D. Kim and R. A. Bartsch, *J. Am. Chem. Soc.*, 1993, **115**(8), 3370–3371.
- 4 Q. He, G. I. Vargas-Zúñiga, S. H. Kim, S. K. Kim and J. L. Sessler, *Chem. Rev.*, 2019, **119**, 9753–9835.
- 5 (a) B. Qiao, A. Sengupta, Y. Liu, K. P. McDonald, M. Pink, J. R. Anderson, K. Raghavachari and A. H. Flood, *J. Am. Chem. Soc.*, 2015, **137**, 9746–9757; (b) E. N. W. Howe,



- M. Bhadbhade and P. Thordarson, *J. Am. Chem. Soc.*, 2014, **136**, 7505–7516; (c) L. K. S. von Krbek, C. A. Schalley and P. Thordarson, *Chem. Soc. Rev.*, 2017, **46**, 2622–2637; (d) C. Hunter, H. Anderson, *Angew. Chem., Int. Ed.*, 2009, **48**, 7488–7499.
- 6 (a) J. A. Cooper, S. T. G. Street and A. P. Davis, *Angew. Chem., Int. Ed.*, 2014, **53**, 5609–5613; (b) H. Li, H. Valkenier, L. W. Judd, P. R. Brotherhood, S. Hussain, J. A. Cooper, O. Jurcek, H. A. Sparkes, D. N. Sheppard and A. P. Davis, *Nat. Chem.*, 2016, **8**, 24–32; (c) S. J. Edwards, H. Valkenier, N. Busschaert, P. A. Gale and A. P. Davis, *Angew. Chem., Int. Ed.*, 2015, **54**, 4592–4596.
- 7 For receptors that binds salt very strongly under liquid–liquid extraction conditions binding kinetics may also be important factor determining transport activity. See ref. 6c.
- 8 (a) J. M. Mahoney, G. U. Nawaratna, A. M. Beatty, P. J. Duggan and B. D. Smith, *Inorg. Chem.*, 2004, **43**, 5902–5907; (b) S. K. Kim, J. L. Sessler, D. E. Gross, C.-H. Lee, J. S. Kim, V. M. Lynch, L. H. Delmau and B. P. Hay, *J. Am. Chem. Soc.*, 2010, **132**, 5827–5836; (c) S. K. Kim, G. I. Vargas-Zúñiga, B. P. Hay, N. J. Young, L. H. Delmau, C. Masselin, C.-H. Lee, J. S. Kim, V. M. Lynch, B. A. Moyer and J. L. Sessler, *J. Am. Chem. Soc.*, 2012, **134**, 1782–1792; (d) S. K. Kim, V. M. Lynch, N. J. Young, B. P. Hay, C.-H. Lee, J. S. Kim, B. A. Moyer and J. L. Sessler, *J. Am. Chem. Soc.*, 2012, **134**, 20837–20843; (e) J. Romański and P. Piątek, *J. Org. Chem.*, 2013, **78**, 4341–4347; (f) Q. He, Z. Zhang, J. T. Brewster, V. M. Lynch, S. K. Kim and J. L. Sessler, *J. Am. Chem. Soc.*, 2016, **138**, 9779–9782; (g) Q. He, G. M. Peters, V. M. Lynch and J. L. Sessler, *Angew. Chem., Int. Ed.*, 2017, **56**, 13396–13400.
- 9 M. Zakrzewski, N. Kwietniewska, W. Walczak and P. Piątek, *Chem. Commun.*, 2018, **54**, 7018–7021.
- 10 G. Bellussi, M. Bohnet, J. Bus, K. Drauz, H. Greim, K. P. Jackel, U. Karst, A. Kleemann, G. Kreysa, T. Laird, W. Meier, E. Ottow, M. Roper, J. Scholtz, K. Sundmacher, R. Ulber and U. Wietelmann, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, 7th edn, 2011.
- 11 J. Corcoran, M. J. Winter and C. R. Tyler, *Crit. Rev. Toxicol.*, 2010, **40**, 287–304.
- 12 H. Maeda, S. Furuyoshi, Y. Nakatsuji and M. Okahara, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 212–218.
- 13 M. Zakrzewski, D. Załubiniak and P. Piątek, *Dalton Trans.*, 2018, **47**, 323–330.
- 14 UV-Vis titration technique is not suitable for determining such low  $K_a$ 's, therefore these values should be treated with caution.
- 15 M. Yizhaki, *Ions in Water and Biophysical Implications: From Chaos to Cosmos*, Springer Netherlands, 2012.
- 16 (a) K. Kavallieratos, A. Danby, G. J. Van Berkel, M. A. Kelly, R. A. Sachleben, B. A. Moyer and K. Bowman-James, *Anal. Chem.*, 2000, **72**, 5258–5264; (b) S. J. Moore, M. G. Fisher, M. Yano, C. C. Tong and P. A. Gale, *Chem. Commun.*, 2011, **47**, 689–691; (c) S. J. Moore, M. G. Fisher, M. Yano, C. C. Tong and P. A. Gale, *Dalton Trans.*, 2011, **40**, 12017–12020; (d) I. Ravikumar, S. Saha and P. Ghosh, *Chem. Commun.*, 2011, **47**, 4721–4723.
- 17 (a) N. V. Nucci, M. S. Pometun and A. J. Wand, *J. Am. Chem. Soc.*, 2011, **133**, 12326–12329; (b) I. Deb, Ł. Popenda, J. Sarzyńska, M. Małgowska, A. Lahiri, Z. Gdaniec and R. Kierzek, *Sci. Rep.*, 2019, **9**, 16278.

