ORGANIC LETTERS

2011
Vol. 13, No. 18
4838–4841

CH···O Hydrogen Bonds in "Clicked" Diketopiperazine-Based Amide Rotaxanes

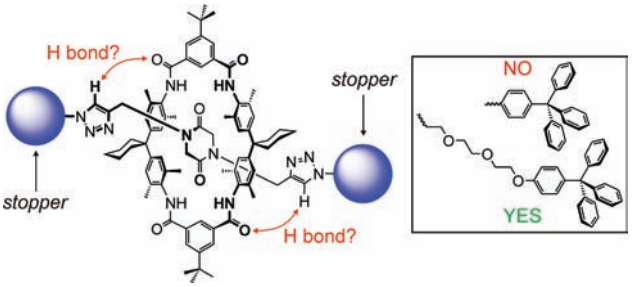
Egor V. Dzyuba,[†] Lena Kaufmann,[†] Nora L. Löw,[†] Annika K. Meyer,[†] Henrik D. F. Winkler,[†] Kari Rissanen,[‡] and Christoph A. Schalley*[,†]

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, D-14195 Berlin, Germany, and Department of Chemistry, Nanoscience Center, University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland

christoph@schalley-lab.de

Received July 15, 2011

ABSTRACT



Two amide [2]rotaxanes were synthesized in high yields using a novel *N,N*′-dipropargyl diketopiperazine axle centerpiece as the template to which the stoppers are attached through "click chemistry". ^{1}H and 2D NMR spectra provide evidence for two different H-bonding motifs, in one of which the triazole CH groups form C−H···O═C bonds with the wheel carbonyl O atoms. This motif can be controlled and switched reversibly by competitive anion binding.

Hunter/Vögtle-type tetralactam macrocycles[1] (TLMs) bind guest molecules, e.g. dicarbonyl compounds,[2] inside their cavities by H-bonding and have thus been used for anion-[3] or amide-templated[4] rotaxane syntheses. Hunter et al. reported diketopiperazine to form very stable host–guest complexes with TLMs ($K_a = 10^6$ M^{-1} in $CDCl_3$ and, depending on substitution, $K_a = 100-760$ M^{-1} in H_2O).[5] Such high binding constants were explained by N−H···π and C−H···π interactions that add to the H-bonds between host and guest. Even though these forces do not contribute as much after substitution of the amide N-atoms with groups suitable for stopper attachment, diketopiperazines should be useful templates for the synthesis of interlocked amide rotaxanes. Here, we report the *N*,*N*′-dipropargyl diketopiperazine-templated synthesis of [2]rotaxanes through "click" reactions, their structural characterization, and their responsiveness to anions as external stimuli.

According to NMR experiments performed at 233 K, the two pseudorotaxanes **PS1** and **PS2** (Figure 1) form with similar free binding enthalpies of $\Delta G \approx 18$ kJ mol^{-1}. Both axles are functionalized at the diketopiperazine N-atoms and bear solubilizing $C_{11}H_{21}$ side chains. The triazole rings in **PS2** do not appear to cause large differences in ΔG.

[†] Freie Universität Berlin.
[‡] University of Jyväskylä.

(1) (a) Hunter, C. A. *J. Am. Chem. Soc.* **1992**, *114*, 5305. (b) Vögtle, F.; Meier, S.; Hoss, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1619. For other TLMs, see:(c) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72. (d) Murgu, I.; Baumes, J. M.; Eberhard, J.; Gassensmith, J. J.; Arunkumar, E.; Smith, B. D. *J. Org. Chem.* **2011**, *76*, 688.

(2) (a) Seel, C.; Parham, A. H.; Safarowsky, O.; Hübner, G. M.; Vögtle, F. *J. Org. Chem.* **1999**, *64*, 7236. (b) Chang, S.-Y.; Kim, H. S.; Chang, K.-J.; Jeong, K.-S. *Org. Lett.* **2003**, *6*, 181. (c) Herrmann, U.; Jonischkeit, T.; Bargon, J.; Hahn, U.; Li, Q.-Y.; Schalley, C. A.; Vogel, E.; Vögtle, F. *Anal. Bioanal. Chem.* **2002**, *372*, 611. (d) Kirchner, B.; Spickermann, C.; Reckien, W.; Schalley, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 484. (e) Spickermann, C.; Felder, T.; Schalley, C. A.; Kirchner, B. *Chem.—Eur. J.* **2008**, *14*, 1216. (f) Sokolowski, M.; Kossev, I.; Reckien, W.; Felder, T.; Kishan, M. R.; Schalley, C. A. *J. Phys. Chem. C* **2009**, *113*, 12870.

(3) (a) Reuter, C.; Vögtle, F. *Org. Lett.* **1999**, *2*, 593. (b) Hübner, G. M.; Gläser, J.; Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 282. (c) Affeld, A.; Hübner, G. M.; Seel, C.; Schalley, C. A. *Eur. J. Org. Chem.* **2001**, 2877. (d) Schalley, C. A.; Silva, G.; Nising, C.-F.; Linnartz, P. *Helv. Chim. Acta* **2002**, *85*, 1578. (e) Li, X.-y.; Illigen, J.; Nieger, M.; Michel, S.; Schalley, C. A. *Chem.—Eur. J.* **2003**, *9*, 1332. (f) Linnartz, P.; Bitter, S.; Schalley, C. A. *Eur. J. Org. Chem.* **2003**, 4819. (g) Felder, T.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2258. (h) Linnartz, P.; Schalley, C. A. *Supramol. Chem.* **2004**, *16*, 263. (i) Ghosh, P.; Federwisch, G.; Kogej, M.; Schalley, C. A.; Haase, D.; Saak, W.; Lützen, A.; Gschwind, R. M. *Org. Biomol. Chem.* **2005**, *3*, 2691.

10.1021/ol201915j
Published on Web 08/16/2011

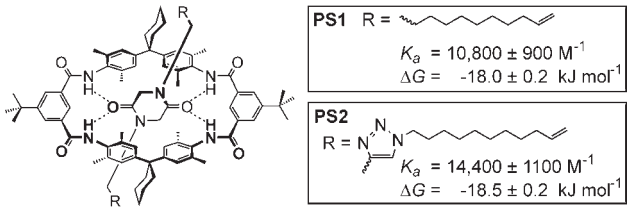


Figure 1. [2]pseudorotaxanes **PS1** and **PS2** and binding data obtained by ^{1}H NMR experiments at 233 K.

The crystal structure[6] of a related pseudorotaxane with a pyridine-bearing TLM and an *N,N′*-dipropargyl diketopiperazine axle confirms the expected formation of four N−H···O=C hydrogen bonds between the four converging TLM amide NH groups and the two axle carbonyl groups (Figure 2). The H-bond N···O distances of 2.94 to 3.10 Å, and N−H···O angles between 146° and 156° are comparable to other amide rotaxanes and catenanes.[3h,i,7] The two acetylene protons interact one with a diethylether and one with a chloroform molecule incorporated in the crystal.

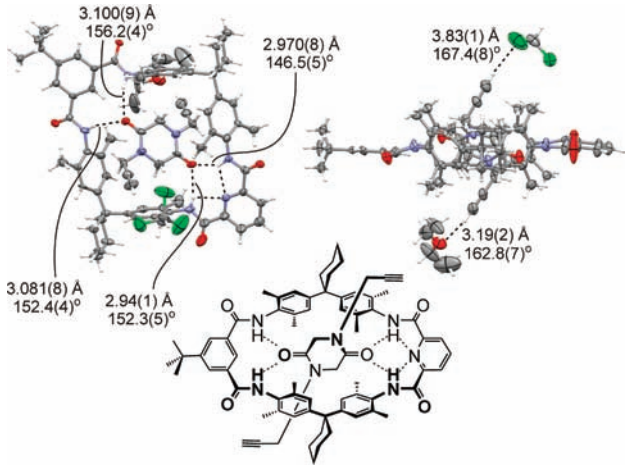


Figure 2. ORTEP plot (50% probability level) of the solid-state structure of the pseudorotaxane shown at the bottom. Left: Top view; right: side view.

These results clearly show the diketopiperazine to be a suitable axle centerpiece for the synthesis of rotaxanes, even though the binding energy is significantly lower than that of unsubstituted diketopiperazine itself due to the absence of N−H···π and C−H···π interactions that are likely diminished by the more upright orientation of the diketopiperazine.

The major difference between the two [2]rotaxanes **R1** and **R2** (Figure 3) is that the tritylphenyl stopper groups are directly attached to the triazole in **R1**, with one of the phenyl groups in conjugation with the triazole, while it is connected to the triazole through a flexible chain in **R2** and thus is not conjugated to it. *N,N′*-Dipropargyl diketopiperazine served as the axle centerpiece and was synthesized by alkylation of diketopiperazine with propargyl bromide after deprotonation with sodium hydride (Supporting Information).[8] The two rotaxanes were prepared by "clicking"[9,10] the corresponding stopper azide to the *N,N′*-dipropargyl diketopiperazine axle centerpiece in the presence of the tetralactam macrocycle.

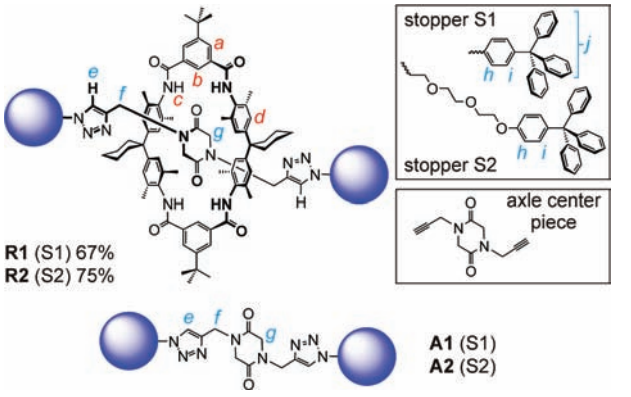


Figure 3. [2]rotaxanes **R1** and **R2** and the corresponding free axles **A1** and **A2** (side products of the rotaxane syntheses).

$(Ph_3P)_3Cu(I)Br$[11] was used as the catalyst for this template-directed click reaction which gave the two desired rotaxanes **R1** and **R2** in good yields of 67% and 75%, respectively. Since the diketopiperazine centerpiece and the stoppers were used in excess,[3d] this reaction also provided the two free axles **A1** and **A2** as side products that can be used for comparison with the rotaxanes.

Evidence for the threaded topology of **R1** comes from the ^{1}H NMR spectra in Figure 4 (see Supporting Information for ^{1}H,^{1}H COSY peak assignments). Low-field shifts of the signals for wheel protons *a*, *b*, and *c* in **R1** relative to those of the free wheel indicate the presence of the axle

(4) (a) Ottens-Hildebrandt, S.; Meier, S.; Schmidt, W.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1767. (b) Vögtle, F.; Dünnwald, T.; Schmidt, T. *Acc. Chem. Res.* **1996**, *29*, 451. (c) Schalley, C. A.; Weilandt, T.; Brüggemann, J.; Vögtle, F. *Top. Curr. Chem.* **2004**, *248*, 141.

(5) (a) Adams, H.; Carver, F. J.; Hunter, C. A.; Osborne, N. J. *Chem. Commun* **1996**, 2529. (b) Allot, C.; Adams, H.; Bernad, P. L., Jr.; Hunter, C. A.; Rotger, C.; Thomas, J. A. *Chem. Commun.* **1998**, 2449.

(6) CCDC-833461. M = 1584.67, colorless prisms, 0.15 × 0.20 × 0.25 mm^3, triclinic, space group $P\bar{1}$, a = 12.3795(8) Å, b = 16.3654(10) Å, c = 21.5944(14) Å, α = 91.210(3)°, β = 94.228(3)°, γ = 112.025(3)°, V = 4039.0(4) $Å^3$, Z = 2, D_c = 1.303 g/cm^3, T = 173(2) K, 923 parameters, R = 0.0947 [$I_o > 2\sigma(I_o)$], wR = 0.3956 (all reflections). See Supporting Information for more details.

(7) (a) Reuter, C.; Seel, C.; Nieger, M.; Vögtle, F. *Helv. Chim. Acta* **2000**, *83*, 630. (b) Mohry, A.; Vögtle, F.; Nieger, M.; Hupfer, H. *Chirality* **2000**, *12*, 76.

(8) Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5709.

(9) (a) Gassensmith, J. J.; Barr, L.; Baumes, J. M.; Paek, A.; Nguyen, A.; Smith, B. D. *Org. Lett.* **2008**, *10*, 3343. (b) Gassensmith, J. J.; Matthys, S.; Lee, J.-J.; Wojcik, A.; Kamat, P. V.; Smith, B. D. *Chem.—Eur. J.* **2010**, *16*, 2916.

(10) For the use of the "click" reaction for rotaxane synthesis, see: (a) Miljanic, O. S.; Dichtel, W. R.; Aprahamian, I.; Rohde, R. D.; Agnew, H. D.; Heath, J. R.; Stoddart, J. F. *QSAR Comb. Sci.* **2007**, *26*, 1165 and literature cited therein.

(11) Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814.

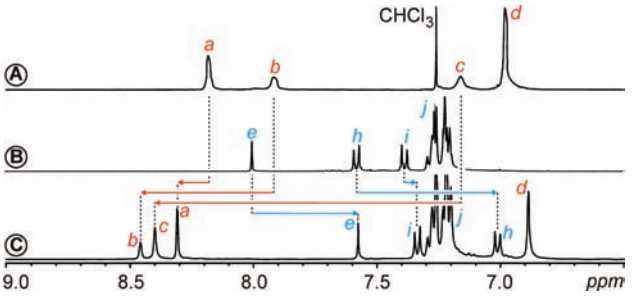


Figure 4. Aromatic region of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) of (A) the wheel, (B) axle **A1**, and (C) [2]rotaxane **R1**.

in the wheel cavity.[12] The largest complexation-induced shift ($\Delta\delta$ = 1.3 ppm) is found for the amide NH proton *c* indicating H-bond formation to the axle. In analogy to earlier findings,[3f,h] signal shifts to higher field are observed for axle protons *e*, *h*, and *i* which experience the anisotropy of the wheel's aromatic rings.

Similar signal shifts are observed for **R2** (Figure 5), with two notable exceptions: (i) The signal for the amide proton *c* splits into two with different low-field shifts of $\Delta\delta$ = 1.0 and 1.4 ppm. (ii) The signal for the triazole protons *e* shifts to lower field. Since the other signal shifts as well as ESI MS strongly support rotaxane formation for both, two different binding motifs are clearly realized in **R1** and **R2**. **R1** is characterized by one set of signals for both axle and wheel indicating high symmetry. Instead, the signal splitting of the amide protons *c* in **R2** agrees with a reduced symmetry with two wheel NH pairs. Since the axle protons appear as a single set of signals, both axle halves reside in equivalent environments. Furthermore, the reversal of the shift of proton *e* points to a significant change in the environment of the triazole proton.

The ^{1}H,^{1}H ROESY NMR spectrum of **R2** (Figure 6) exhibits cross peaks between the amide protons *c* and both wheel protons *b* and *a* in agreement with a wheel conformation in which two amide NH groups point inward and two outward. In addition, cross peaks between triazole proton *e* and wheel proton *b* indicate the triazole protons

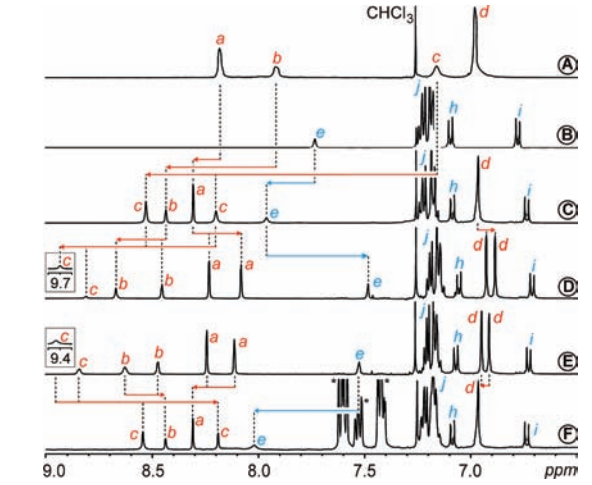


Figure 5. Aromatic region of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) of (A) the wheel, (B) axle **A2**, (C) [2]rotaxane **R2**, (D) **R2** after adding 1 equiv of nBu$_4$OAc, (E) **R2** after adding 1 equiv of nBu$_4$Cl, and (F) the chloride adduct of **R2** after adding $NaBPh_4$ (*: $NaBPh_4$ phenyl groups).

to reside in the proximity of the isophthaloyl diamide moieties. These observations are consistent with triazole–C–H···O=C hydrogen bonding[13] and exclude N–H···N hydrogen bonds between a wheel NH and any of the triazole N-atoms. This interpretation relies on the assumption that the wheel can adopt different conformations, among them an *all-in* as well as a *2-in-2-out* conformation. Indeed, earlier experimental and theoretical studies[14] revealed both conformations to be within ca. 5 kJ mol^{-1} in energy with barriers for the rotation of a whole amide group of ca. 10 kJ mol^{-1}. The TLM can thus easily adapt its conformation to the binding requirements of the axles.

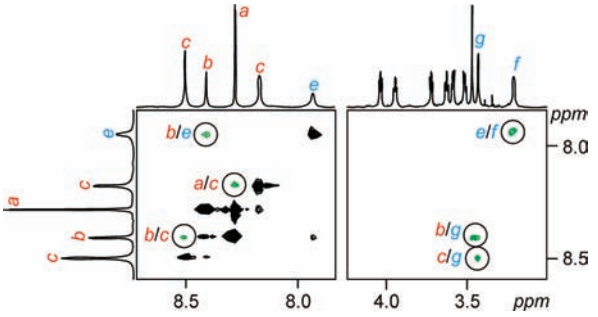


Figure 6. Partial ^{1}H,^{1}H ROESY spectrum (500 MHz, $CDCl_3$, 298 K) of **R2**. Relevant cross peaks are highlighted in green.

(12) Hunter, C. A.; Packer, M. J. *Chem.—Eur. J.* **1999**, *5*, 1891.

(13) For selected references on triazole C–H···X hydrogen bonding, see: (a) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; RSC Publishing: Cambridge, U.K., 2006. (b) Li, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12111. (c) Juwarker, H.; Lenhardt, J. M.; Pham, D. M.; Craig, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 3740. (d) Hecht, S.; Meudtner, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4926. (e) Wang, Y.; Li, F.; Han, Y. M.; Wang, F. Y.; Jiang, H. *Chem.—Eur. J.* **2009**, *15*, 9424. (f) Juwarker, H.; Lenhardt, J. M.; Castillo, J. C.; Zhao, E.; Krishnamurthy, S.; Jamiolkowski, R.; Kim, K.-H.; Craig, S. L. *J. Org. Chem.* **2009**, *74*, 8924. (g) Fisher, M. G.; Gale, P. A.; Hiscock, J. R.; Hursthouse, M. B.; Light, M. E.; Schmidtchen, F. P.; Tong, C. C. *Chem. Commun* **2009**, 3017. (h) Zheng, H.; Zhou, W.; Lv, J.; Yin, X.; Li, Y.; Liu, H.; Li, Y. *Chem.—Eur. J.* **2009**, *15*, 13253. (i) Romero, T.; Caballero, A.; Tárraga, A.; Molina, P. *Org. Lett.* **2009**, *11*, 3466. (j) Müllen, K. M.; Mercurio, J.; Serpell, C. J.; Beer, P. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4781. (k) Gassensmith, J. J.; Matthys, S.; Lee, J.-J.; Wojcik, A.; Kamat, P. V.; Smith, B. D. *Chem.—Eur. J.* **2010**, *16*, 2916. (l) Lee, S.; Hua, Y.; Park, H.; Flood, A. H. *Org. Lett.* **2010**, *12*, 2100. (m) For a recent review, see: Jurícek, M.; Kouwer, P. H. J.; Rowan, A. E. *Chem. Commun.* **2011**, *47*, 8740.

(14) (a) Schalley, C. A.; Reckien, W.; Peyerimhoff, S.; Baytekin, B.; Vögtle, F. *Chem.—Eur. J.* **2004**, *10*, 4777. (b) Kossev, I.; Reckien, W.; Kirchner, B.; Felder, T.; Nieger, M.; Schalley, C. A.; Vögtle, F.; Sokolowski, M. *Adv. Funct. Mater.* **2007**, *17*, 513. (c) Zhu, S. S.; Nieger, M.; Daniels, J.; Felder, T.; Kossev, I.; Schmidt, T.; Sokolowski, M.; Vögtle, F.; Schalley, C. A. *Chem.—Eur. J.* **2009**, *15*, 5040.

In rotaxanes **R1** and **R2**, the axles and wheels are thus connected by different H-bonding patterns: In **R1**, four wheel amide NH groups converge to bind the two diketopiperazine carbonyl oxygens (motif **A**). In **R2**, two wheel amides converge toward the axle's C═O groups, while the carbonyl O-atoms of the other two wheel amides form C−H···O═C bonds with triazole C−H groups (motif **B**). Both binding motifs were calculated with semiempirical AM1 MOZYME calculations (Figure 7),[13a,15] in order to obtain an impression of whether motif **B** is geometrically feasible. These calculations not only result in reasonable structures for both binding motifs but also predict motif **A** to be less favorable by ca. 20 kJ mol^{-1}. One factor in why motif **B** is not realized in **R1** may be the flat, extended, and conjugated triazole-phenyl moiety which can favorably interact with the less electron-rich isophthaloyl units when motif **A** is realized. According to our calculations, this arrangement brings the trityl groups into a favorable position, in which they maximize their van der Waals contacts with the TLM's *t*Bu groups. The long and flexible chains in **R2** instead do not support this interaction and motif **B** is then formed.

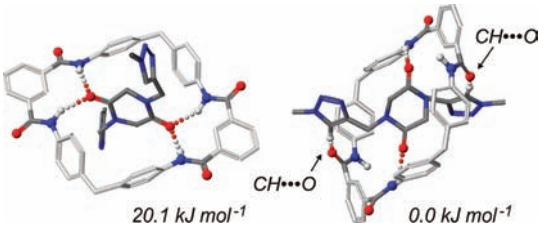


Figure 7. Two AM1MOZYME-optimized structures of **R2**. The structure with four NH···O hydrogen bonds (left) is calculated to be less stable than that with two NH···O and two CH···O hydrogen bonds (right). Glycol chains, cyclohexanes, stoppers, and H-atoms are omitted for clarity.

The addition of 1 equiv of either nBu$_4$NOAc or nBu$_4$NCl (Figure 5D,E) to the NMR solution of **R2** gives rise to two sets of signals for the wheel protons *a*, *b*, and *d* and an additional low-field shift of the NH protons *c*. Most strikingly, the signal of the triazole proton *e* shifts to higher field (ca. 7.5 ppm). This is almost the same position that is observed for the triazole proton *e* in rotaxane **R1**. All these findings are in agreement with the conjecture that the anion binds to one isophthaloyl diamine side of the TLM and changes the axle orientation relative to the wheel. The cleavage of the C−H···O═C hydrogen bonds is then responsible for the signal shift of proton *e*. The second isophthaloyl diamide binds to one of the diketopiperazine carbonyl oxygen atoms as indicated by the very small changes observed for one of the *a* and one of the *b* signals. It is further remarkable that the anion exchange is slow on the NMR time scale at room temperature as indicated by the splitting of the wheel signals into two sets. Chloride binding to **R2** can be reversed by addition of NaBPh$_4$ which precipitates the chloride from the chloroform solution as sodium chloride (Figure 5F). With the exception of the signals for the BPh_4^- anion, the spectra in Figure 5C and 5F are identical confirming the hydrogen bonding pattern in rotaxane **R2** to be reversibly switchable with a chemical signal.

In conclusion, a new disubstituted diketopiperazine axle centerpiece was used for the synthesis of amide rotaxanes. A variant of the click reaction which applies (Ph$_3$P)$_3$Cu(I)Br as the catalyst and operates in nonpolar organic solvents was used for the stoppering reaction. The compatibility of this reaction with noncompetitive solvents is important, because the hydrogen-bond-mediated template effect is quite sensitive to competitive solvents. Depending on the nature of the stoppers, two binding motifs were observed that connect the axle and wheel through hydrogen bonding. One of them involves C−H···O═C hydrogen bonds between the triazole rings and the carbonyl groups of inverted TLM amide groups. Their formation is supported by ROESY NMR contacts between the triazole protons *e* and the inner isophthaloyl protons *b*. The rotaxane formation mechanism is supported by studies of related pseudorotaxanes, which exhibit free binding enthalpies substantially higher than those found for other amide template effects.[2a] For a related pseudorotaxane, a crystal structure confirmed a binding motif in which four converging wheel amide NH groups form hydrogen bonds to the diketopiperazine carbonyl oxygen atoms. Finally, the hydrogen bonding patterns in rotaxane **R2** can be switched by the addition of anions that block one side of the wheel and thus cause large changes in the relative orientations of axle and wheel. The anion binding and binding mode switching are fully reversible. Anion binding desymmetrizes the wheel, and the observation of two distinct sets of signals for the two sides provides evidence that the chloride exchange is slow on the NMR time scale at room temperature.

Acknowledgment. This research has been funded by the Deutsche Forschungsgemeinschaft (SFB 765 "multivalency"), the German Academic Exchange Service (DAAD), and the Academy of Finland (proj. 212588 and 218325). E.V.D. and L.K. thank the Studienstiftung des deutschen Volkes for a PhD scholarship. We thank Dr. Andreas Schäfer (FU Berlin), Sebastian Richter, M. Sc. (FU Berlin) and Dipl.-Ing. Fabian Klautzsch (FU Berlin) for help with NMR and ESI MS experiments.

Supporting Information Available. General experimental methods, synthetic procedures, original spectra of new compounds, and binding constant determination. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) *CAChe 5.0 for Windows*; Fujitsu Ltd., Krakow, Poland, 2001. For a validation of the AM1MOZYME approach with DFT calculations, see ref 13a.