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# Kinetic Acidity of Supramolecular Imidazolium Salts—Effects of Substituent, Preorientation, and Counterions on H/D Exchange Rates

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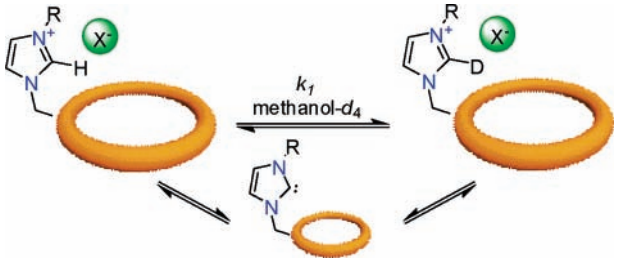
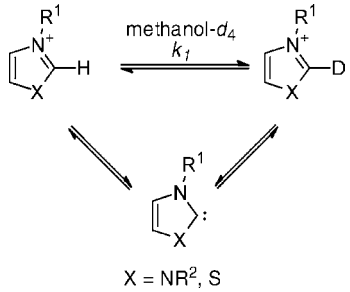



The deprotonation of imidazolium salts to *N*-heterocyclic carbenes is often a decisive step in modern catalytic reactions. Therefore, we studied the H/D exchange of the $C^2$ H of 15 imidazolium-substituted calix[4]arenes and 11 nonmacrocyclic model compounds in methanol/water (97:3). The influence of the counterion, substitution directly on the imidazolium unit or on the preorientating calixarene backbone could be studied. The observed exchange rates might give a rational for the suitability of the imidazolium salts as precursors in the Suzuki coupling.

In 1958, Breslow was the first to postulate uncharged nucleophilic carbenes stemming from the corresponding thiazolium salts as the active catalysts in Stetter-type reactions.[1] Only two years later, Wanzlick introduced cognate *N*-heterocyclic carbenes (NHCs) by trapping the intermediate carbene.[2] The inspiring idea that stable nucleophilic carbenes could be formed easily by the deprotonation of the $C^2$ proton was strongly supported by Olofson[3] and others[4] who could prove the facile H/D exchange of both thiazolium and imidazolium salts. This early work came back into focus since the characterization of a stable crystalline NHC by Arduengo III and co-workers[5] in 1991. Since then, a considerable amount of work has been invested in the preparation and use of novel NHCs mainly as ligands in transition-metal-catalyzed reactions such as the Suzuki−Miyaura reaction[6] or as umpolungs catalysts in organocatalytic processes.[7]

**SCHEME 1**




The formation of the NHC starting from a salt precursor is often a decisive step in catalytic reactions (Scheme 1). Despite the plethora of reports that exploit this basic reaction scheme in catalytic applications, considerably less information is available about the fundamental properties. Both experimental and theoretical investigations[8] characterize nucleophilic carbenes as strong bases ($pK_a \sim 20-30$) with high proton affinities above 250 kcal $mol^{-1}$. Additionally, the rate of the formation of the active catalyst might indicate the suitability of an imidazolium salt in catalysis. Because protonation of the NHC is fast compared to the formation of the NHC, the H/D exchange rates of the $C^2$ H give an indirect estimate for the reaction rate of its formation.

Amyes et al.[9] determined the rate constants of the H/D exchange of some imidazolium salts in $D_2O$ in the presence of $OD^-$ ions, and Diederich and Lutter[10] measured this exchange of thiazolium cyclophanes in different buffers. In contrast to these works, we decided not to study the exchange rates in solutions with constant ion strengths and various pD values but instead to determine rate constants under conditions usually used for the preparative application of NHCs in organo-catalytic or transition-metal-catalyzed reactions. Besides the simple structures **1** and **6**, calix[4]arene-based imidazolium salts **2**−**5** (Chart 1) have been synthesized to investigate the influence of preorientation and cooperativity of the imidazolium units.[11] In

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(1) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
(2) Wanzlick, H.-W.; Schikora, E. *Angew. Chem.* **1960**, *72*, 494.
(3) Olofson, R. A.; Thompson, W. R.; Michelman, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1865.
(4) (a) Vaughan, J. D.; Mughrabi, Z.; Chung Wu, E. *J. Org. Chem.* **1970**, *35*, 1141. (b) Haake, P.; Bausher, L. P.; Miller, W. B. *J. Am. Chem. Soc* **1969**, *91*, 1113.
(5) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
(6) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Bourissou, D.; Guerret, O.; Gabbai, F.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (c) Hillier, A. C.; Nolan, S. P. *Platinum Met. Rev.* **2002**, *46*, 50. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
(7) (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (c) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.
(8) (a) Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267. (b) Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757. (c) Chen, H.; Justes, D. R.; Cooks, R. G. *Org. Lett.* **2005**, *7*, 3949. (d) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717.
(9) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366.
(10) Diederich, F.; Lutter, H.-D. *J. Am. Chem. Soc.* **1989**, *111*, 8438.
(11) Frank, M.; Maas, G.; Schatz, J. *Eur. J. Org. Chem.* **2004**, 607.

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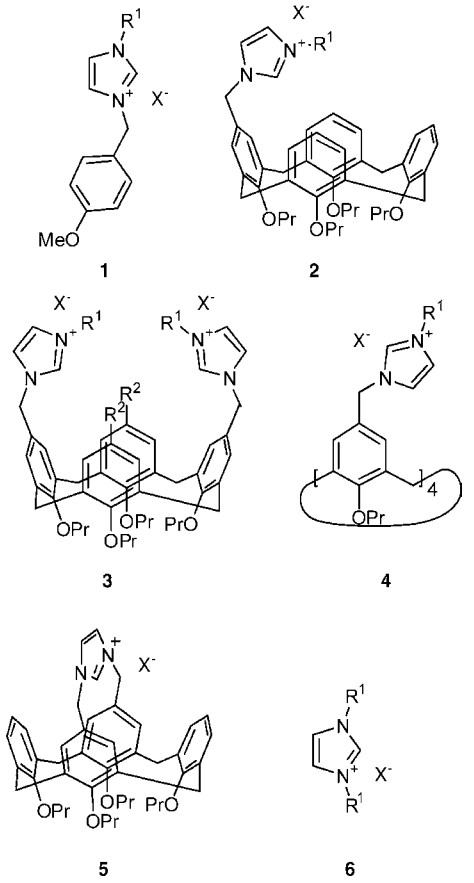
**CHART 1**




all experiments, we chose a 0.155 molar solution of the imidazolium salt, in terms of imidazolium units, in methanol-$d_4$ containing 3% water without any further additives as the reaction medium. The exchange was followed by NMR spectroscopy over a period of 24 h at 300 K by the disappearance of the $C^2$ proton. The rate constants were deduced from standard pseudo-first-order plots. The mean values of the rate constants of all compounds are shown in Table 1, and some remarkable trends are discussed.

With the exception of the methoxymethyl-substituted calix[4]arene **3g**, mesitylimidazolium salts (**1a**, **1f**, **2a**, **3a**, **3i**, **4**, and **6a**) undergo a very fast H/D exchange. This exception might be explained by the fact that, in the molecules **3g** and **3h**, intramolecular hydrogen bonds between $C^2-H\cdots O(CH_2R)Me$ could be formed that stabilize the imidazolium salts and hinder the formation of a carbene. Such a structure is comparable with the adducts of NHCs with phenol, amines,[12a] boranes,[12b] or the biscarbene−proton complex.[12c]

It is obvious that the preorientation of imidazolium units on the calixarene backbone has a large influence on the exchange rate. Whereas the monomesitylimidazolium salt **2a** shows a moderate exchange, the bifunctional calixarene **3a** exhibited a 10-fold higher rate. It is noticeable that calixarene-based imidazolium salts (**2a**, **3a**) exchange with significantly different

(12) (a) Cowan, J. A.; Clyburne, J. A. C.; Davidson, M. G.; Harris, R. L. W.; Howard, J. A. K.; Küpper, P. L. M. A.; Richards, S. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1432. (b) Ramnial, T.; Jong, H.; McKenzie, I. D.; Jennings, M.; Jason, A. C. *Chem. Commun.* **2003**, 1722. (c) Arduengo, A. J., III; Gamper, S. F.; Tamm, M.; Calabrese, J. C.; Davidson, F.; Craig, H. A. *J. Am. Chem. Soc.* **1995**, *117*, 572.

**TABLE 1. Rate Constants of the H/D Exchange in MeOD-$d_4$ Containing 3% Water at 300 K**

| | $R^{1a}$ | $R^2$ | X | $k_1$ ($d^{-1}$) | $k_x/k_{1a}$ |
|---|---|---|---|---|---|
| **1a** | mes | | Cl | 1.060 ± 0.150 | ≡1 |
| **1b** | *i*-pr | | Cl | 0.553 ± 0.061 | 0.52 |
| **1c** | cy | | Cl | ≪0.001 | 0 |
| **1d** | *t*-bu | | Cl | ≪0.001 | 0 |
| **1e** | dip | | Cl | 2.850 ± 0.430 | 2.69 |
| **1f** | mes | | Br | 0.176 ± 0.008 | 0.17 |
| **1g** | *i*-pr | | Br | ≪0.001 | 0 |
| **1h** | cy | | Br | 0.246 ± 0.009 | 0.23 |
| **1i** | *t*-bu | | Br | 0.158 ± 0.014 | 0.15 |
| **2a** | mes | | Cl | 0.603 ± 0.009 | 0.57 |
| **2b** | $CH_3$ | | Cl | ≪0.001 | 0 |
| **3a** | mes | H | Cl | 5.938 ± 0.390 | 5.60 |
| **3b** | $CH_3$ | H | Cl | ≪0.001 | 0 |
| **3c** | *i*-pr | H | Cl | 0.629 ± 0.043 | 0.59 |
| **3d** | cy | H | Cl | 0.241 ± 0.024 | 0.23 |
| **3e** | *t*-bu | H | Cl | ≪0.001 | 0 |
| **3f** | dip | H | Cl | ≪0.001 | 0 |
| **3g** | mes | $CH_2OMe$ | Cl | ≪0.001 | 0 |
| **3h** | *i*-pr | $CH_2OMe$ | Cl | ≪0.001 | 0 |
| **3i** | mes | *t*-bu | Cl | 3.903 ± 0.326 | 3.68 |
| **3j** | $CH_3$ | *t*-bu | Cl | ≪0.001 | 0 |
| **3k** | dip | *t*-bu | Cl | 0.784 ± 0.130 | 0.74 |
| **4** | mes | | Cl | 12.4 ± 0.8/1.03 ± 0.03 | |
| **5** | | | Cl | ≪0.001 | 0 |
| **6a** | mes | | Cl | ≫10 | ≫9.4 |
| **6b** | dip | | Cl | ≪0.001 | 0 |

[a] dip = 2,6-diisopropylphenyl; mes = mesityl; and cy = cyclohexyl.

rates than the open chain analogue **1a**, presumably owing to a micro polarity effect.[10] For the monosubstituted derivative **2a**, the H/D exchange is retarded slightly ($k_{2a}/k_{1a} \sim 0.6$), and for **3a**, the H/D exchange is accelerated ($k_{3a}/k_{1a} \sim 5.6$). For calixarenes **3**, not only the influence of substituents directly bound to the salt unit but also the influence of substitution in positions 5 and 17 ($R^2$) in the calixarene backbone could be studied. As discussed before, the hydrogen-bond acceptor $CH_2$-OMe suppressed the exchange. In the case of **3k**, the *tert*-butyl groups increased the exchange rates (compared to **3f**), and in the case of **3i**, the *tert*-butyl groups decreased the exchange rates (compared to **3a**). The capping of the calixarene backbone (**5**) with an imidazolium group shielded the $C^2$ proton in such a way that no H/D exchange could be observed.

The H/D exchange of the tetraimidazolium calix[4]arene **4** did not obey a simple pseudo-first-order kinetic rate (Supporting Information). However, the observed data could be fit by assuming two independent first-order processes. The first exchange rate is high (12.4 $d^{-1}$), indicating some kind of a cooperative action of two of the four imidazolium moieties. In contrast, the second exchange rate (1.03 $d^{-1}$) is similar to the one observed for the monoimidazolium salts (**1a**, **2a**).

The influence of the counterion on the H/D exchange was investigated for compounds **1**. In no case were similar rate constants for bromide and chloride found in methanol-$d_4$ containing 3% water. The values differ by as much as a factor of 10. For the bromides (**1f**, **1g**), the exchange rate dropped significantly compared to that of the chlorides (**1a**, **1b**). However, in the case of bulky substituents (**1c**, **1h** and **1d**, **1i**), the bromide salts showed a higher exchange rate. A detailed investigation into the recognition properties of the studied imidazolium salts toward anions must clarify this matter because it is known that imidazolium groups can be used as recognition elements in supramolecular anion receptors.[13]

The presented results show that the substitution of the imidazolium salts in distal 5- and 17-positions has a large influence on the H/D exchange rates in wet methanol-$d_4$. These rates play an important role in catalytic reactions, as observed for the Suzuki reaction. For example, the mesitylimidazolium salts show the fastest exchange and also the highest catalytic activity.[11] This is in agreement with the high exchange rate observed for the IMes ligand **6a** ($R^1$ = mesityl) known for its good performance as a ligand precursor in cross coupling reactions.[6c]

In summary, measuring fundamental physicochemical properties illuminated surprising differences in the kinetic acidities of a series of open-chain and macrocyclic imidazolium salts. Mesityl-substituted heterocycles showed the highest H/D exchange rates, whereas alkyl substituents hampered this process. Additionally, the anion had a distinct influence on the exchange process.

## Experimental Section

**General Procedure for the Reaction of Benzyl Halides with 1-Substituted 1-Imidazoles.** To a solution of the benzyl halide in dry $CHCl_3$ was added the corresponding 1-substituted imidazole. After heating the solution for 1−5 d, the solvent was removed under reduced pressure, diethyl ether was added, and the mixture was heated for 2−3 h. After cooling the mixture, the formed colorless hygroscopic precipitate was collected by filtration, washed with several portions of $Et_2O$, and dried in a desiccator.

**5-(1-Mesitylimidazolium)methyl-25,26,27,28-tetrapropoxycalix[4]arene-chloride (2a).** 5-Chloromethyl-25,26,27,28-tetrapropoxycalix[4]arene (2.00 g, 3.12 mmol), 1-mesitylimidazole (652 mg, 3.50 mmol), and $CHCl_3$ (abs; 20 mL) were refluxed for 1 d, $Et_2O$ (70 mL). A colorless product was obtained (yield = 708 mg, 0.86 mmol, 27%). Mp 153−155 °C. IR (KBr, $\nu_{max}$): 3147 (m), 2962 (s), 2932 (s), 2875 (s), 1587 (w), 1546 (m), 1457 (s), 1384 (m), 1302 (m), 1246 (m), 1203 (s), 1160 (m), 1087 (m), 1008 (s), 891 (w), 850 (w), 761 (s). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.96 (t, $J$ = 7.5 Hz, 6H), 1.04 (t, $J$ = 7.5 Hz, 3H), 1.05 (t, $J$ = 7.3 Hz, 3H), 1.87−1.94 (m, 4H), 1.96−2.04 (m, 4H), 2.08 (s, 6H), 2.34 (s, 3H), 3.14 (d, $J$ = 13.4 Hz, 2H), 3.18 (d, $J$ = 13.1 Hz, 2H), 3.75 (t, $J$ = 7.3 Hz, 2H), 3.78 (t, $J$ = 7.2 Hz, 2H), 3.91−4.02 (m, 4H), 4.46 (d, $J$ = 13.3 Hz, 2H), 4.47 (d, $J$ = 13.0 Hz, 2H), 5.45 (s, 2H), 6.39 (s, 2H), 6.43−6.47 (m, 2H), 6.51−6.53 (m, 2H), 6.67 (t, $J$ = 7.5 Hz, 2H), 6.77 (d, $J$ = 7.6 Hz, 1H), 6.78 (d, $J$ = 7.5 Hz, 1H), 6.85 (d, $J$ = 7.5 Hz, 1H), 6.86 (d, $J$ = 7.5 Hz, 1H), 6.93 (t, $J$ = 1.8 Hz, 1H), 7.00 (s, 2H), 10.67 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 9.9, 10.41, 10.42, 17.6, 21.0, 23.0, 23.3, 30.8, 30.9, 53.3, 76.5, 77.1, 77.2, 121.4, 122.0, 122.1, 122.2, 125.8, 127.6, 128.1, 128.3, 128.5, 129.7, 130.7, 134.2, 134.5, 135.3, 135.4, 135.8, 138.7, 141.1, 156.1, 156.7, 156.8. MS $m/z$ (MALDI-TOF): calcd for $C_{53}H_{63}O_4N_2$, 791.5; found, 791.8 [$(M - Cl)^+$]. Anal. Calcd for $C_{53}H_{63}O_4N_2Cl \times 1.1$ $H_2O$: C, 75.13; H, 7.76; N, 3.31. Found: C, 74.92; H, 7.65; N, 3.61.

**5-(3-Methylimidazolium)methyl-25,26,27,28-tetrapropoxycalix[4]arene-chloride (2b).** 5-Chloromethyl-25,26,27,28-tetrapropoxycalix[4]arene (2.00 g, 3.12 mmol), 1-methylimidazole (276 $\mu$L, 3.50 mmol), and $CHCl_3$ (abs, 20 mL) were refluxed for 1 d, $Et_2O$ (70 mL). A colorless product was obtained. (yield = 1.08 g, 1.50 mmol, 48%). Mp 146 °C. IR (KBr, $\nu_{max}$): 3142 (m), 3060 (m), 2962 (s), 2932 (s), 2874 (s), 1725 (w), 1627 (w), 1586 (w), 1458 (s), 1385 (m), 1284 (m), 1247 (m), 1197 (s), 1163 (m), 1008 (s), 890 (w), 838 (w), 759 (m). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.94 (t, $J$ = 7.3, 6H), 1.03 (t, $J$ = 7.5 Hz, 3H), 1.04 (t, $J$ = 7.5 Hz, 3H), 1.85−2.01 (m, 8H), 3.15 (pseudo t, $J$ = 12.6 Hz, 4H), 3.36 (d, $J$ = 7.1 Hz, 2H), 3.75 (d, $J$ = 7.0 Hz, 2H), 3.88−3.99 (m, 4H), 4.05 (s, 3H), 4.44 (d, $J$ = 13.3 Hz, 2H), 4.45 (d, $J$ = 13.3 Hz, 2H), 4.95 (s, 2H), 6.32 (s, 2H), 6.40 (dd, $J$ = 2.3, 6.2 Hz, 1H), 6.43 (t, $J$ = 1.6 Hz, 1H), 6.46−6.48 (m, 2H), 6.73 (t, $J$ = 7.3 Hz, 2H), 6.81 (d, $J$ = 7.5 Hz, 1H), 6.82 (d, $J$ = 7.5 Hz, 1H), 6.87 (d, $J$ = 7.5 Hz, 1H), 6.88 (d, $J$ = 7.5 Hz, 1H), 7.19 (t, $J$ = 1.5 Hz, 1H), 10.28 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 10.0, 10.4, 10.43, 23.0, 23.2, 23.3, 30.8, 30.9, 36.6, 53.1, 76.5, 77.0, 121.1, 121.4, 122.2, 122.8, 125.2, 127.7, 128.2, 128.4, 128.7, 134.4, 135.3, 135.6, 135.9, 137.7, 156.0, 156.8, 156.9. MS $m/z$ (MALDI-TOF): calcd for $C_{45}H_{55}O_4N_2Cl$, 687.4; found, 687.4 [$(M - Cl)^+$]. Anal. Calcd for $C_{45}H_{55}O_4N_2Cl \times 1.7$ $H_2O$: C, 71.68; H, 7.81; N, 3.72. Found: C, 71.61; H, 7.86; N, 3.69.

**5,17-Bis[(3-*tert*-butylimidazolium)methyl]-25,26,27,28-tetrapropoxycalix[4]arene-dichloride (3e).** 5,17-Bis(chloromethyl)-25,26,27,28-tetrapropoxycalix[4]arene (2.00 g, 2.90 mmol), 1-*tert*-butylimidazole (745 mg, 6.00 mmol), and $CHCl_3$ (abs, 20 mL) were refluxed for 1 d, $Et_2O$ (70 mL). A colorless product was obtained (yield = 2.59 g, 2.76 mmol, 95%). Mp 200−202 °C. IR (KBr, $\nu_{max}$): 3061 (m), 2963 (s), 2933 (s), 2875 (s), 1626 (w), 1586 (w), 1554 (m), 1463 (s), 1381 (m), 1283 (m), 1204 (s), 1133 (s), 1153 (m), 1008 (s), 889 (w), 836 (w), 758 (m). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 7.6 Hz, 6H), 1.11 (t, $J$ = 7.3 Hz, 6H), 1.70 (s, 18H), 1.85−2.01 (m, 8H), 3.17 (d, $J$ = 13.6 Hz, 4H), 3.70 (t, $J$ = 6.8 Hz, 4H), 4.02 (t, $J$ = 7.8 Hz, 4H), 4.46 (d, $J$ = 13.4 Hz, 4H), 4.93 (s, 4H), 6.20 (s, 4H), 6.69 (t, $J$ = 1.8 Hz, 2H), 6.95 (t, $J$ = 7.3 Hz, 2H), 7.13 (d, $J$ = 7.6 Hz, 4H), 7.86 (t, $J$ = 2.0 Hz, 2H), 10.51 (t, $J$ = 1.5 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 9.6, 10.6, 22.7, 23.3, 29.9, 30.7, 52.7, 60.0, 76.4, 77.2, 120.2, 120.7, 122.5, 124.8, 128.6, 129.1, 134.8, 134.8, 136.2, 156.5, 157.3. MS $m/z$ (MALDI-TOF): calcd for $C_{56}H_{74}N_4O_4Cl$, 901.5; found, 901.7 [$(M - Cl)^+$]. Anal. Calcd for $C_{56}H_{74}N_4O_4Cl_2 \times 2.6$ $H_2O$: C, 68.29; H, 8.10; N, 5.69. Found: C, 68.23; H, 8.00; N, 5.58.

**5,11,17,23-Tetrakis[(1-mesitylimidazolium)methyl]-25,26,27,28-tetrapropoxycalix[4]arene-tetrachloride (4).** 5,11,17,23-Tetrakis(chloromethyl)-25,26,27,28-tetrapropoxycalix[4]arene (823 mg, 1.05 mmol), 1-mesitylimidazole (1.49 g, 8.00 mmol), and $CHCl_3$ (abs, 10 mL) were reluxed for 2 d, $Et_2O$ (30 mL). A light brown product was obtained (yield = 1.56 g, 1.02 mmol, 97%). Mp >220 °C (dec). IR (KBr, $\nu_{max}$): 2960 (s), 2926 (s), 2873 (s), 1607 (m), 1545 (s), 1464 (s), 1386 (w), 1289 (w), 1205 (s), 1157 (s), 1066 (m), 1007 (m), 854 (m), 754 (m), 669 (w). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.00 (t, $J$ = 14.9 Hz, 12H), 1.88−2.00 (m, 8H), 1.97 (s, 24H), 2.31 (s, 12H), 3.24 (d, $J$ = 13.0 Hz, 4H), 3.82 (t, $J$ = 15.0 Hz, 8H), 4.42 (d, $J$ = 13.0 Hz, 4H), 5.61 (s, 8H), 6.95 (s, 8H), 7.09 (t, $J$ = 1.8 Hz, 4H), 7.26 (s, 8H), 8.41 (t, $J$ = 1.7 Hz, 4H), 10.34 (t, $J$ = 1.5 Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 10.2, 17.5, 21.0, 23.2, 30.4, 52.8, 76.9, 122.8, 124.2, 128.2, 129.3, 129.7, 130.9, 134.2, 135.6, 137.4, 140.9, 156.8. MS $m/z$ (MALDI-TOF): calcd for $C_{92}H_{108}O_4N_8$, 1389.9; found, 1390.5 [$(M - 4\ Cl)^+$]. Anal. Calcd for $C_{92}H_{108}O_4Cl_4N_8 \times 5$ $H_2O$: C, 68.13; H, 7.33; N, 6.91. Found: C, 68.03; H, 7.25; N, 6.67.

**Distal-Bridged Imidazoliumcalix[4]arene-chloride (5).** A solution of 5,17-bis(chloromethyl)-25,26,27,28-tetrapropoxycalix[4]arene (2.00 g, 2.90 mmol) in $CHCl_3$ (10 mL) was added slowly to a solution of imidazole (1.97 g, 29.0 mmol) in $CHCl_3$ (50 mL). After stirring for 4 h at rt, the mixture was heated under reflux for an additional hour. The organic layer was separated and washed (50 mL of 3 N NaOH, 4 × 50 mL $H_2O$). The obtained solid was digerated for 4 h with EtOAc, isolated by filtration, and dried in vacuo (yield = 1.40 g, 1.94 mmol, 67%). Mp >280 °C (dec). IR (KBr, $\nu_{max}$): 3160 (m), 3069 (m), 2960 (s), 2932 (s), 2873 (s), 1614 (m), 1586 (w), 1564 (m), 1464 (s), 1385 (m), 1326 (w), 1281 (m), 1218 (s), 1174 (m), 1133 (s), 1008 (s), 891 (w), 835 (w), 778

(13) (a) Ramos, S.; Alcade, E.; Doddi, G.; Mencarelli, P.; Pérez-García, L. *J. Org. Chem.* **2002**, *67*, 8463. (b) Yun, S.; Ihm, H.; Kim, H. G.; Lee, C.-W.; Indrajit, B.; Oh, K. S.; Gong, Y. J.; Lee, J. W.; Yoon, J.; Lee, H. C.; Kim, K. S. *J. Org. Chem.* **2003**, *68*, 2467. (c) Kim, S. K.; Kang, B.-G.; Koh, H. S.; Yoon, Y. J.; Jung, S. J.; Jeong, B.; Lee, K.-D.; Yoon, J. *Org. Lett.* **2004**, *6*, 4655.

(m). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.93 (t, $J$ = 7.5 Hz, 6H), 1.12 (t, $J$ = 7.3 Hz, 6H), 1.88−1.97 (m, 4H), 2.00−2.10 (m, 4H), 3.22 (d, $J$ = 13.4 Hz, 4H), 3.70 (t, $J$ = 7.0 Hz, 4H), 4.12 (t, $J$ = 8.5 Hz, 4H), 4.51 (d, $J$ = 13.1 Hz, 4H), 4.85 (s, 4H), 5.00 (s, 1H), 6.37 (s, 4H), 6.92 (t, $J$ = 7.5 Hz, 2H), 7.13 (d, $J$ = 7.6 Hz, 4H), 8.12 (d, $J$ = 1.5 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 9.7, 10.6, 22.8, 23.4, 30.8, 53.1, 76.6, 77.7, 123.2, 123.8, 124.2, 129.2, 129.9, 131.1, 135.6, 136.2, 156.4, 156.8. MS *m*/*z* (MALDI-TOF): calcd for $C_{45}H_{53}N_2O_4$, 685.4; found, 685.6 [$(M - Cl)^+$]. Anal. Calcd for $C_{45}H_{53}N_2O_4Cl \times 1.9\ H_2O$: C, 71.53; H, 7.58; N, 3.71. Found: C, 71.51; H, 7.63; N, 3.74.

**Supporting Information Available:** Kinetic details for the measurements of the H/D exchange rates. This material is available free of charge via the Internet at http://pubs.acs.org.

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