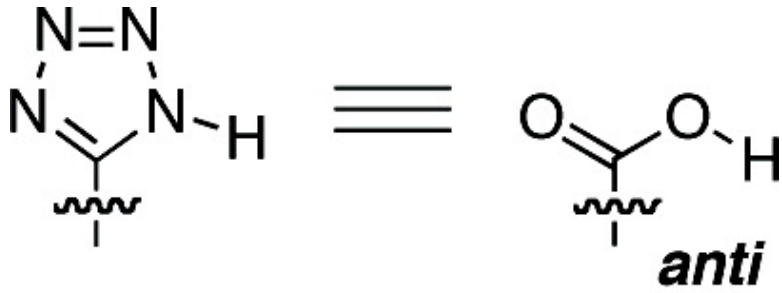
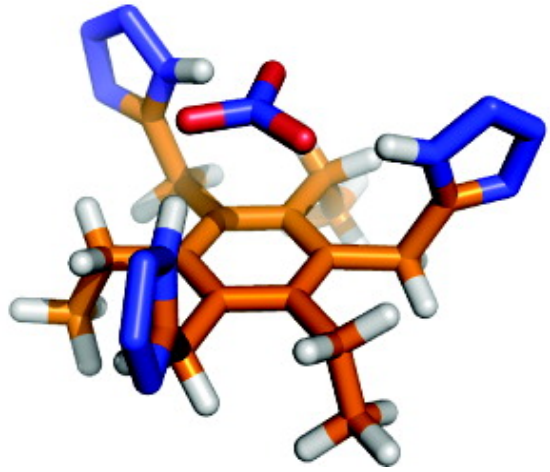
Letter

Tetrazoles are Potent Anion Recognition Elements That Emulate the Disfavored *Anti* Conformations of Carboxylic Acids

Aaron H. McKie, Sayuri Friedland, and Fraser Hof

Org. Lett., **2008**, 10 (20), 4653-4655• DOI: 10.1021/ol801943u • Publication Date (Web): 25 September 2008





More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

ORGANIC LETTERS

2008
Vol. 10, No. 20
4653−4655

Tetrazoles are Potent Anion Recognition Elements That Emulate the Disfavored *Anti* Conformations of Carboxylic Acids

Aaron H. McKie, Sayuri Friedland, and Fraser Hof*

Department of Chemistry, University of Victoria, P.O. Box 3065, Victoria, BC, Canada, V8W 3V6

fhof@uvic.ca

Received August 19, 2008

ABSTRACT

We report here the first study of the protonated, neutral form of tetrazoles as anion binding functional groups. Our studies reveal them to be capable of binding anions with extremely high potency in polar solutions. In studying carboxylic acid-containing congeners, we find a remarkable discrepancy: a strictly analogous acid-containing host binds anions ≥50 000-fold more weakly than the tetrazole under study. We can explain this functional difference by considering tetrazole tautomerization equilibria and carboxylic acid conformational preferences.

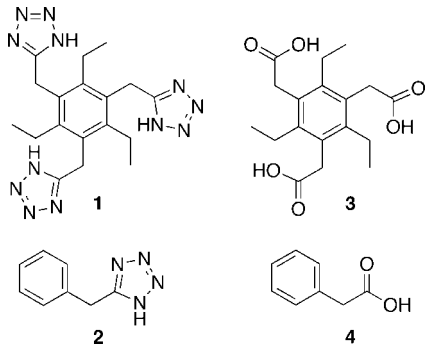
Tetrazoles are valued for the similarity of their pK_a values with those of corresponding carboxylic acids, and are frequently swapped with carboxylic acids during the development of pharmaceuticals.[1] The anionic tetrazolate form dominates at physiological pH, and prior studies of tetrazolates by our group and others have explored their cation-binding properties in a variety of contexts.[2−6] The present study is the first exploration of the recognition properties of neutral, protonated tetrazoles. We find that neutral tetrazoles are superb anion-binding elements with binding properties that can differ radically from those of their carboxylic acid analogues.

We studied the anion binding capabilities of tetrazoles **1** and **2** as well as those of their acid congeners **3** and **4** (Scheme 1) in two competitive solvent systems: pure CD_3CN and a 95:5 (v/v) $CDCl_3/CD_3OD$ mixture. NMR dilution studies show that **1**−**4** are monomeric in solution at less than 5 mM. NMR binding titrations (Figure 1a) and Job plots[7] (Figure S1, Supporting Information) reveal that host **1** forms 1:1 complexes with a variety of weakly basic oxyanions and halides under the conditions studied.[8]

(1) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
(2) Mahnke, D. J.; McDonald, R.; Hof, F. *Chem. Commun.* **2007**, 3738–3740.
(3) Tominey, A.; Andrew, D.; Oliphant, L.; Rosair, G. M.; Dupre, J.; Kraft, A. *Chem. Commun.* **2006**, 2492–2494.
(4) Tominey, A. F.; Docherty, P. H.; Rosair, G. M.; Quenardelle, R.; Kraft, A. *Org. Lett.* **2006**, *8*, 1279–1282.
(5) Peters, L.; Froehlich, R.; Boyd, A. S. F.; Kraft, A. *J. Org. Chem.* **2001**, *66*, 3291–3298.
(6) Kraft, A.; Osterod, F.; Froehlich, R. *J. Org. Chem.* **1999**, *64*, 6425–6433.
(7) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626–4636.
(8) More basic oxyanions, such as benzoate, pyrophosphate, and dihydrogen phosphate, give complex titration data that indicate the simultaneous occurrence of proton transfer processes and binding (Figure S2, Supporting Information). Proton transfer is not a significant factor for the anions reported in Table 1. See the Supporting Information for a detailed discussion. For related examples see also: (a) Winstanley, K. J.; Sayer, A. M.; Smith, D. K. *Org. Biomol. Chem.* **2006**, *4* (9), 1760–1767. (b) Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem. Eur. J.* **2005**, *11*, 120–127.

10.1021/ol801943u CCC: $40.75
Published on Web 09/25/2008

Scheme 1. Tetrazoles and Carboxylic Acids Employed in This Study



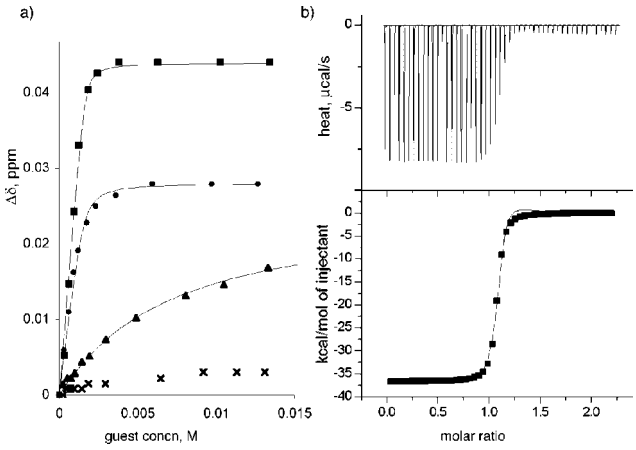


Figure 1. (a) ^{1}H NMR titration data for hosts **1** and **3**. Titrations carried out at 295 K in CD_3CN. Titrant containing Bu_4N^+ salt at 30−50 mM and host at 1−2 mM was added to a solution containing a matched concentration of host. Lines resulting from nonlinear fits to 1:1 binding isotherms are superimposed on experimental data for binding of **1** to Br^- (■), NO_3^- (●), and I^- (▲). Data for titration of **3** with NO_3^- (×) are also shown. (b) Representative ITC data (raw and integrated) for binding of Cl^- by host **1** in CH_3CN at 303 K. The line resulting from fitting to a "one site" binding model is superimposed on the integrated data. See text for thermodynamic parameters and Supporting Information for experimental details.

The association constants for the binding of a variety of anions by **1** are listed in Table 1. In acetonitrile, both Cl^- and Br^- are bound too strongly by **1** to measure accurately with NMR ($K_{assoc.} > 5 \times 10^5$ M^{-1}). The average of three determinations by isothermal titration calorimetry (ITC) in anhydrous acetonitrile gives $K_{assoc.}$ values of ca. 10^7 M^{-1} for the binding of each of these halides (Figure 1b and Figure S3 in the Supporting Information). The binding of both is enthalpically driven, indicating the formation of strong hydrogen bonds to both Cl^- and Br^-. (Parameters for **1**•Cl^-: $\Delta H = -37.1$ kcal mol^{-1}, $-T\Delta S = 27.3$ kcal mol^{-1}, $N = 0.97$; parameters for **1**•Br^-: $\Delta H = -38.1$ kcal mol^{-1}, $-T\Delta S = 28.5$ kcal mol^{-1}, $N = 1.01$. See the Supporting Information for details.) The affinity of host **1** for I^- ($K_{assoc.} = 490$ M^{-1}) is reduced by a factor of 20 000 (or $\Delta\Delta G$ of 6 kcal/mol) relative to the smaller halides. This selectivity can have two sources: (1) the inherent differences of hydrogen bonding and solvation energies[9] for various halides and (2) the size selectivity of the cavity of **1**. We quantified the inherent differences among halides by determining the strength of binding to control tetrazole **2** (Table 2). Host **2** binds Cl^- 59-fold more strongly than I^- ($\Delta\Delta G = 2.4$ kcal/mol, or 7.2 kcal/mol if additive across the three tetrazoles of **1**).

Table 1. Anion Affinities of Tris(tetrazole) **1** and Tricarboxylic Acid **2**[a]

guest	tris(tetrazole) (**1**) $K_{assoc.}$ in $CDCl_3$:MeOD[b] (M^{-1})	tris(tetrazole) (**1**) $K_{assoc.}$ in CD_3CN (M^{-1})	triacid (**3**) $K_{assoc.}$ in CD_3CN (M^{-1})
Bu_4N^+ Cl^-	1.9×10^3	1.1×10^7[d]	2.2×10^2
Bu_4N^+ Br^-	3.8×10^2	1.1×10^7[d]	<10[c]
Bu_4N^+ I^-	1.1×10^2	4.9×10^2	<10[c]
Bu_4N^+ NO_3^-	5.6×10^2	1.3×10^4	<10[c]
Bu_4N^+ TsO^-	8.0×10^2	1.9×10^5	40
Bu_4N^+ ClO_4^-	1.9×10^2	<10[c]	<10[c]
Bu_4N^+ HSO_4^-	4.8×10^2	1.3×10^4	n.d.

[a] Determined by duplicate or triplicate ^{1}H NMR titrations at 295 K unless otherwise noted. Estimated errors ±20%. [b] 95:5 (v/v) $CDCl_3$:MeOD. [c] Insignificant chemical shifts observed during NMR titrations. [d] Average of three determinations by isothermal titration calorimetry in CH_3CN at 303 K.

Table 2. Halide Binding in CD_3CN by Monofunctional Tetrazole **3** and Monocarboxylic Acid **4**[a]

guest	tetrazole (**2**) $K_{assoc.}$ (M^{-1})	acid (**4**) $K_{assoc.}$ (M^{-1})
Bu_4N^+ Cl^-	590	220
Bu_4N^+ Br^-	90	<10[b]
Bu_4N^+ I^-	10	<10[b]

[a] Determined by duplicate or triplicate ^{1}H NMR titrations at 295 K. Estimated errors ±20%. [b] Insignificant chemical shifts observed during NMR titrations.

This is sufficient to account for the selectivity displayed by **1** without having to invoke a size-selectivity argument. To further analyze the contributions of size matching to the observed selectivity, we determined the gas-phase structures of a variety of complexes of **1** at the HF/6-31+G* level of theory (Figure S3, Supporting Information). These calculations suggest that **1** is larger than optimal for Cl^- binding,[10] offering one explanation for the observation that the affinity of **1** for Cl^- is *not* higher than that for Br^-.

Given the similar chemical properties (and perceived interchangeability) of tetrazoles and carboxylic acids, com-

(9) Marcus, Y. *Chem. Rev.* **2007**, *107*, 3880–3897.

(10) Only two crystal structures in the CSD (SUKPET and VURTOR) contain tetrazoles donating hydrogen bonds to halide partners. Both involve tetrazole-containing drugs H-bonding to Cl^- counterions, and display N−Cl distances of 3.07 and 3.06 Å, respectively, while the N−Cl distance calculated for monotetrazole **2**•Cl^- is slightly longer at 3.19 Å. The N−Cl distance of 3.27 Å calculated for **1**•Cl^- is longer than these values.

paring the binding properties of these two classes of compounds is of special interest. Monofunctional tetrazole **2** displays slightly higher binding constants than its congener phenylacetic acid **4** across the panel of halides tested (Table 2). A comparison of the tricarboxylic acid host **3** to tris(tetrazole) host **1** shows more dramatic differences—host **1** complexes Cl^- 50 000-fold more strongly than does triacid **3** (Table 1), and the triacid's lack of observable binding for Br^- suggests an even larger discrepancy. Examination of a modeled structure of **3**•Cl^- shows that all three carboxylic acids must be in the *anti* conformation to engage the guest (Figure 2). But the *anti* conformations of carboxylic acids

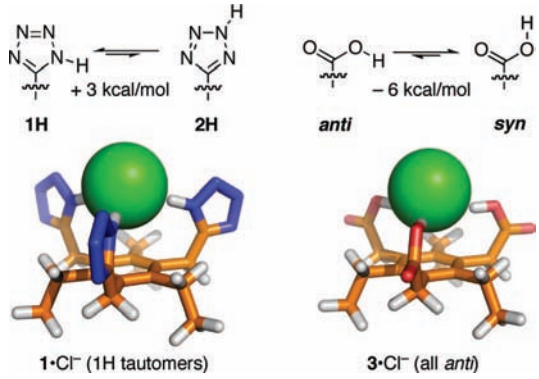


Figure 2. The energetically favored 1H-tautomer of tetrazole mimics the disfavored *anti* conformation of a corresponding carboxylic acid, while the disfavored 2H-tautomer replicates the hydrogen bonding geometry of a *syn* carboxylic acid. Models of **1**•Cl^- and **3**•Cl^- (HF/6-31+G*)[20] suggest the origins of different chloride affinities for the two hosts.

are disfavored by ca. 6 kcal/mol relative to the *syn* conformations,[11] meaning that **3** must pay a large reorganization penalty upon binding. The identical chloride binding constants for **3** and **4** suggest that, instead, tricarboxylic acid host **3** can use only a single acid to engage the halide (Figure S5, Supporting Information). This reorganization penalty is not incurred by the tetrazoles of host **1**, which are each predicted to favor the 1H tautomer over the 2H tautomer by ca. 3 kcal/mol in a calculation using the dielectric constant of acetonitrile solution.[12] These data suggest that the favored 1H tautomer of a tetrazole bears a functional resemblance to the energetically disfavored *anti* conformation of a carboxylic acid (Figure 2), while in a complementary manner the disfavored 2H tautomer of tetrazole mimics the favored *syn* conformation of a carboxylic acid. It is intriguing to consider that 1H-tetrazoles may be employed as functional mimics of otherwise unattainable carboxylic acid *anti* conformers in other settings.

Tetrazoles are easily synthesized and chemically stable under a wide variety of conditions.[1,13,14] Unlike other, less acidic anion binding elements,[15] the usefulness of tetrazoles for anion recognition is limited to acidic conditions. Despite this limitation, tetrazoles are made attractive as anion binders because of their remarkable potency: tetrazole **2** binds Cl^- via a single N−H−Cl hydrogen bond worth −3.8 kcal mol^{-1} in solution; the $K_{assoc.}$ for **1**•Cl^- surpasses by 2 or 3 orders of magnitude the chloride affinity of other anion receptors that decorate the same 1,3,5-trisubstituted benzene scaffold with three cationic[16−18] binding elements; and the unadorned tetrazole host **1** offers halide affinity and selectivity comparable to strapped calix[4]pyrroles—the gold standards of anion recognition by neutral heterocycles.[19] We are currently setting tetrazoles into more complex structural contexts to test their mimicry of *anti* carboxylic acids and the limits of their anion-binding potential.

Acknowledgment. A.M. is a UVic Pacific Century Scholar, and F.H. is a Career Scholar of the Michael Smith Foundation for Health Research. This research was supported by NSERC and the University of Victoria

Supporting Information Available: Experimental procedures and data for NMR and ITC experiments, molecular modeling of complexes, and a detailed discussion of binding vs proton transfer. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801943U

(11) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943.
(12) Wong, M. W.; Leungtoung, R.; Wentrup, C. *J. Am. Chem. Soc.* **1993**, *115*, 2465–2472.
(13) Aureggi, V.; Sedelmeier, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8440–8444.
(14) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950.
(15) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev.* **2003**, *240*, 3.
(16) Sato, K.; Arai, S.; Yamagishi, T. *Tetrahedron Lett.* **1999**, *40*, 5219.
(17) 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*, 2467–2470.
(18) Wallace, K. J.; Belcher, W. J.; Turner, D. R.; Syed, K. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 9699–9715.
(19) Lee, C.-H.; Miyaji, H.; Yoon, D.-W.; Sessler, J. L. *Chem. Commun.* **2008**, 24–34.
(20) *Spartan '04*; Wavefunction, Inc.: Irvine, CA, 2004.