Ion-Pair Receptors

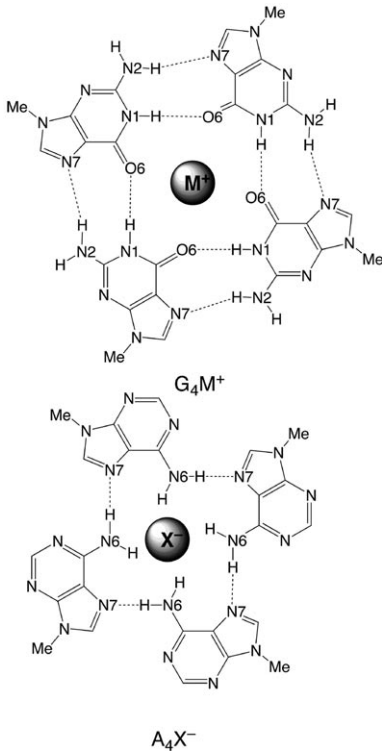
DOI: 10.1002/ange.200900057

A Ditopic Ion-Pair Receptor Based on Stacked Nucleobase Quartets**

Tushar van der Wijst, Célia Fonseca Guerra, Marcel Swart, F. Matthias Bickelhaupt, and Bernhard Lippert**

Ditopic ion-pair receptors can simultaneously coordinate a cation and an anion, and they have the potential to act, among other things, as salt extractors and membrane transport agents.[1–4] Guanine quartets (G_4) are well-known cation receptors (Scheme 1, top).[5,6] Recently, an artificial platinum purine quartet was synthesized which binds anions strongly.[7] Although nucleobase quartets are known for all natural nucleobases and combinations of these,[8] there are, to our knowledge, no reports of anion-binding properties of natural nucleobase quartets. The puzzling binding of a cation to an A_4 quartet (A = adenine) through the four exocyclic amino groups in a tetrastranded RNA molecule[9] prompted us to look into the possibility that what was proposed to be a sodium cation might in fact have been a monoatomic anion (with partial occupancy).

Herein, we present computational evidence for a viable NaCl ion-pair receptor that consists of two stacked DNA-base quartets, namely a G_4 quartet and an A_4 quartet. The idea is based on the fact that the guanine quartet (G_4) has an exceptionally high stability owing to its capacity to form two hydrogen bonds between neighboring guanine units, which is further enhanced through cation binding (Scheme 1, top).[2]



Scheme 1. G_4 cation receptor and A_4 anion receptor.

The stable G_4 quartet, in turn, is a template that assists, through stacking, the formation of other quartets: in our case, the A_4 quartet. The latter can, in principle, bind an anion such as Cl^- through N–H···Cl^- hydrogen bonds (Scheme 1, bottom). This assembly constitutes a stack of two purine quartets G_4A_4, with the potential to act as an NaCl ion-pair receptor, as shown in Equation (1):

$$G_4A_4(aq) + Na^+(aq) + Cl^-(aq) \rightarrow G_4NaClA_4(aq) \quad (1)$$

Our computations demonstrate that the G_4NaClA_4 complex is thermodynamically stable both in the gas phase and, importantly, in aqueous solution. All calculations were performed with the ADF[10] and QUILD[11] programs using dispersion-corrected density functional theory (DFT-D) as developed by Grimme.[12] QUILD is a wrapper around ADF and is used here for its superior geometry optimizer, which is based on adapted delocalized coordinates.[11b] Solvation effects are modeled using the conductor-like screening model (COSMO;[13a–c] for settings, see reference [13d,e]).

The use of dispersion-corrected DFT-D (as opposed to the corresponding uncorrected density functionals) appears to be

[*] T. van der Wijst, Dr. C. Fonseca Guerra, Prof. Dr. F. M. Bickelhaupt
Department of Theoretical Chemistry and Amsterdam Center for Multiscale Modeling
Scheikundig Laboratorium der Vrije Universiteit
De Boelelaan 1083, 1081 HV Amsterdam (The Netherlands)
Fax: (+31) 20-598-7629
E-mail: fm.bickelhaupt@few.vu.nl
Homepage: http://www.few.vu.nl/~bickel
T. van der Wijst, Prof. Dr. B. Lippert
Fakultät Chemie, Lehrstuhl für Bioanorganische Chemie
Technische Universität Dortmund
Otto-Hahn-Strasse 6, 44227 Dortmund (Germany)
Fax: (+49) 231-755-3797
E-mail: bernhard.lippert@tu-dortmund.de
Homepage: http://www.chemie.uni-dortmund.de/groups/lippert
Dr. M. Swart
Institució Catalana de Recerca i Estudis Avançats (ICREA)
08010 Barcelona (Spain)

[**] We thank the International Max Planck Research School in Chemical Biology (IMPRS-CB) in Dortmund for a doctoral fellowship for T.v.d.W, the National Research School Combination—Catalysis (NRSC-C) for a postdoctoral fellowship for C.F.G., the Catalan Institution for Research and Advanced Studies (ICREA) for a research fellowship for M.S., and the Netherlands Organization for Scientific Research (NWO-CW and NWO-NCF) as well as the Deutsche Forschungsgemeinschaft (DFG) for further financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900057.

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

crucial for a correct treatment of the stacking interactions, which are otherwise (erroneously) repulsive. We have explored the performance of three DFT-D variants (BLYP-D, BP86-D, and PBE-D) by comparing them with ab initio results for a set of 24 systems (i.e., the S22 set by Jurecka et al.[14a] and the stacked and hydrogen-bonded GC pair[14b,c]). In all cases, we use a large, doubly polarized basis set of Slater-type orbitals of triple-ζ quality (TZ2P).

The BP86-D and PBE-D results agree very well with the ab initio results for the S22 set (Tables S1–S3 in the Supporting Information), but an even better agreement is obtained with BLYP-D. The hydrogen-bond energy for Watson–Crick AT and GC pairs amounts to −16.7 and −30.1 kcal mol^{-1}, respectively, at BLYP-D/TZ2P, which can be compared with −15.1 and −27.7 kcal mol^{-1} at RI-MP2/aug-cc-pVQZ//RI-MP2/cc-pVTZ.[14b] Also, for the stacked AT and GC pairs, the BLYP-D energies of −11.7 and −16.9 kcal mol^{-1}, respectively, are in excellent agreement with the CCSD(T)/aug-cc-pVQZ//RI-MP2/TZVPP energies of −11.6 and −16.9 kcal mol^{-1}.[14c]

Next, we discuss a number of conceivable steps in the formation of the ditopic receptor in the gas phase and in aqueous solution. All data are based on BLYP-D/TZ2P computations. Our overall point of reference in the energy scheme in Figure 1 is defined as the separate 9-methyl-nucleobases and ions: $4G + 4A + Na^+ + Cl^-$. In general, binding energies in water are smaller than those in the gas phase by a factor of two to three. Trends, however, are similar.

The formation of the guanine quartet G_4 is about twice as exothermic as formation of the adenine quartet A_4. In the gas phase, the associated bond energies amount to −79.2 and −32.5 kcal mol^{-1}, respectively (−33.8 and −16.0 kcal mol^{-1} in water, see Figure 1). The reason is simply that guanine bases in G_4 mutually bind through two hydrogen bonds, whereas adenine bases in A_4 are connected by only one such interaction.

As a next step, we may consider either the inclusion of an ion into one or both quartets or the formation of a stack G_4A_4 between the two "empty" quartets. In the gas phase, the insertion of the ion is energetically much more favorable and leads to an energy gain of −114.5 kcal mol^{-1} for Na^+ in G_4 and of −44.1 kcal mol^{-1} for Cl^- in A_4. The formation of the stack G_4A_4 is exothermic by 54 kcal mol^{-1} in the gas phase.

In aqueous solution, the insertion of ions into the separate quartets and the stacking of the two empty quartets lead, coincidentally, to the same energy lowering of 36 kcal mol^{-1}. On the other hand, the insertion of Na^+ into G_4 proceeds with an energy gain of −33.0 kcal mol^{-1}. Note that also the insertion of Cl^- into A_4 leads to a stabilization of −2.9 kcal mol^{-1}, although this is much smaller than the binding energy of the cation in G_4.

Finally, we consider the behavior of the overall ditopic receptor G_4A_4. The inclusion of Na^+ and Cl^- into the G_4A_4 stack [Eq. (1)] and the stacking of G_4Na^+ with A_4Cl^- to form the complete complex (Figure 2) lead in the gas phase to energy gains of 211 and 107 kcal mol^{-1}, respectively. In water, the corresponding stabilization energies both amount to

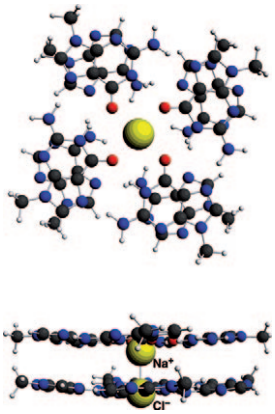


Figure 2. Ditopic receptor G_4NaClA_4 in aqueous solution: top view and side view. Na^+, Cl^- yellow, O red, N blue, C black, H white.

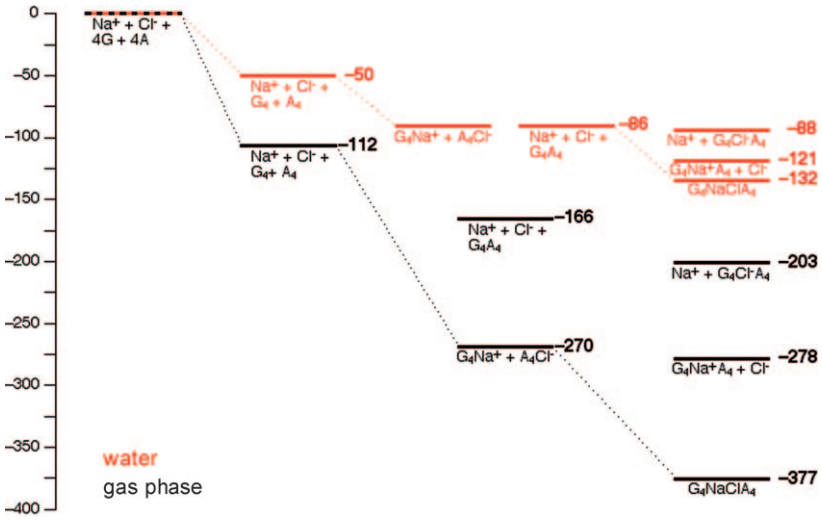


Figure 1. Relative energies (in kcal mol^{-1}) of various stages of complexation in the formation of the ditopic receptor G_4NaClA_4, starting from four 9-methyl-guanines (G), four 9-methyl-adenines (A), and the ions Na^+ and Cl^- in the gas phase (in black) and in aqueous solution (in red), computed at BLYP-D/TZ2P.

46 kcal mol^{-1}. Relative to four separate 9-methylguanine bases, four 9-methyladenine bases, and the ions Na^+ and Cl^-, the G_4NaClA_4 complex is stabilized in aqueous solution by 132 kcal mol^{-1}. Thus, the overall G_4NaClA_4 aggregate is stable with respect to any conceivable dissociation mode. The distance between Na^+ and Cl^- in the ditopic receptor is 2.75 Å. Note that this separation is significantly larger than the Na–Cl distance of 2.40 Å in molecular NaCl in the gas phase, computed consistently at the same level of theory (BLYP-D/TZ2P).

In conclusion, G_4A_4 is a stable complex and a potent ditopic receptor for NaCl in the gas phase as well as in aqueous solution. It remains to be seen whether this feature of G_4A_4 also holds up for negatively charged oligonucleotides. Given the fact that anion binding to the DNA polyanion has indeed been observed,[15] the possibility of Cl^- bind-

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ing to a quartet composed of adenine nucleotides through four hydrogen bonds appears to be anything but unrealistic. Moreover, it has to be taken into consideration that a large proportion of the overall negative charge of DNA or RNA is screened by the effect of cations interacting with the backbone.

Received: January 5, 2009
Published online: March 31, 2009

Keywords: density functional calculations · DNA base quartets · ion-pair receptors · nucleobases · stacking interactions

[1] a) M. D. Lankshear, I. M. Dudley, K.-M. Chan, A. R. Cowley, S. M. Santos, V. Felix, P. D. Beer, *Chem. Eur. J.* **2008**, *14*, 2248; b) M. D. Lankshear, A. R. Cowley, P. D. Beer, *Chem. Commun.* **2006**, 612; c) J. B. Cooper, M. G. B. Drew, P. D. Beer, *J. Chem. Soc. Dalton Trans.* **2001**, 392; d) M. D. Lankshear, I. M. Dudley, K.-M. Chan, P. D. Beer, *New J. Chem.* **2007**, *31*, 684; e) P. R. A. Webber, P. D. Beer, *Dalton Trans.* **2003**, 2249; f) L. H. Uppadine, J. E. Redman, S. W. Dent, M. G. B. Drew, P. D. Beer, *Inorg. Chem.* **2001**, *40*, 2860.

[2] a) X. Shi, K. M. Mullaugh, J. C. Fettinger, Y. Jiang, S. A. Hofstadler, J. T. Davis, *J. Am. Chem. Soc.* **2003**, *125*, 10830; b) X. Shi, J. C. Fettinger, J. T. Davis, *Angew. Chem.* **2001**, *113*, 2909; *Angew. Chem. Int. Ed.* **2001**, *40*, 2827; c) F. W. Kotch, V. Sidorov, Y.-F. Lam, K. J. Kayser, H. Li, M. S. Kaucher, J. T. Davis, *J. Am. Chem. Soc.* **2003**, *125*, 15140.

[3] a) J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F. P. Schmidtchen, G. W. Bates, M. E. Light, P. A. Gale, *J. Am. Chem. Soc.* **2006**, *128*, 12281; b) R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W.-S. Cho, D. Gross, G. W. Bates, S. J. Brooks, M. E. Light, P. A. Gale, *Angew. Chem.* **2005**, *117*, 2593; *Angew. Chem. Int. Ed.* **2005**, *44*, 2537.

[4] a) S. Le Gac, I. Jabin, *Chem. Eur. J.* **2008**, *14*, 548; b) M. K. Chae, J.-I. Lee, N.-K. Kim, K.-S. Jeong, *Tetrahedron Lett.* **2007**, *48*, 6624; c) H. Miyaji, D.-S. Kim, B.-Y. Chang, E. Park, S.-M. Park, K. H. Ahn, *Chem. Commun.* **2008**, 753; d) J. M. Mahoney, K. A. Stucker, H. Jiang, I. Carmichael, N. R. Brinkmann, A. M. Beatty, B. C. Noll, B. D. Smith, *J. Am. Chem. Soc.* **2005**, *127*, 2922; e) C. Suksai, P. Leeladee, D. Jainuknan, T. Tuntulani, N. Muangsin, O. Chailapakul, P. Kongsaeree, C. Pakavatchai, *Tetrahedron Lett.* **2005**, *46*, 2765; f) J. Gong, B. C. Gibb, *Chem. Commun.* **2005**, 1393; g) P. Gunning, A. C. Benniston, R. D. Peacock, *Chem. Commun.* **2004**, 2226; h) X. Liu, C. A. Kilner, M. A. Halcrow, *Chem. Commun.* **2002**, 704; i) D. R. Turner, E. C. Spencer, J. A. K. Howard, D. A. Tocher, J. W. Steed, *Chem. Commun.* **2004**, 1352.

[5] *Quadruplex Nucleic Acids* (Eds.: S. Neidle, S. Balasubramanian), RSC Publishing, Cambridge, **2006**.

[6] a) J. T. Davis, *Angew. Chem.* **2004**, *116*, 684; *Angew. Chem. Int. Ed.* **2004**, *43*, 668, and references therein; b) J. Gros, F. Rosu, S. Amrane, A. De Cian, V. Gabelica, L. Lacroix, J.-L. Mergny, *Nucleic Acids Res.* **2007**, *35*, 3064.

[7] M. Roitzsch, B. Lippert, *Angew. Chem.* **2006**, *118*, 153; *Angew. Chem. Int. Ed.* **2006**, *45*, 147.

[8] a) D. J. Patel, S. Bouaziz, A. Kettani, Y. Wang in *Oxford Handbook of Nucleic Acid Structure* (Ed.: S. Neidle), Oxford University Press, Oxford, **1999**, p. 389; b) P. Amo-Ochoa, P. J. Sanz-Miguel, P. Lax, I Alonso, M. Roitzsch, *Angew. Chem.* **2005**, *117*, 5816; *Angew. Chem. Int. Ed.* **2005**, *44*, 5670, and references therein.

[9] B. Pan, Y. Xiong, K. Shi, J. Deng, M. Sundaralingam, *Structure* **2003**, *11*, 815.

[10] a) G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. Fonseca Guerra, S. J. A. van Gisbergen, J. G. Snijders, T. Ziegler, *J. Comput. Chem.* **2001**, *22*, 931; b) F. M. Bickelhaupt, E. J. Baerends in *Reviews in Computational Chemistry* (Eds.: K. B. Lipkowitz, D. B. Boyd), Wiley, New York, **2000**, *15*, p. 1.

[11] a) M. Swart, F. M. Bickelhaupt, *J. Comput. Chem.* **2008**, *29*, 724; b) M. Swart, F. M. Bickelhaupt, *Int. J. Quantum Chem.* **2006**, *106*, 2536.

[12] a) S. Grimme, *J. Comput. Chem.* **2004**, *25*, 1463; b) S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787.

[13] a) A. Klamt, G. Schüürman, *J. Chem. Soc. Perkin Trans.* **1993**, *2*, 799; b) A. Klamt, *J. Phys. Chem.* **1995**, *99*, 2224; c) C. C. Pye, T. Ziegler, *Theor. Chem. Acc.* **1999**, *101*, 396; d) M. Swart, E. Rösler, F. M. Bickelhaupt, *Eur. J. Inorg. Chem.* **2007**, 3646; e) radii of Na^+ and Cl^- were determined such that they reproduce the experimental solvation energy of the ions; see R. Gomer, G. Tryson, *J. Chem. Phys.* **1977**, *66*, 4413.

[14] a) P. Jurecka, J. Sponer, J. Cerny, P. Hobza, *Phys. Chem. Chem. Phys.* **2006**, *8*, 1985; b) J. Sponer, P. Jurecka, P. Hobza, *J. Am. Chem. Soc.* **2004**, *126*, 10142; c) P. Jurecka, P. Hobza, *J. Am. Chem. Soc.* **2003**, *125*, 15608. CCSD(T) energies herein were calculated as the difference between CCSD(T)/cc-pVDZ(0.25) and MP2/cc-pVDZ(0.25) added to the MP2/aug-cc-pVQZ energy.

[15] a) P. Auffinger, L. Bielecki, E. Westhof, *Structure* **2004**, *12*, 379; b) B. Spingler, *Inorg. Chem.* **2005**, *44*, 831; c) J. Muñoz, J. L. Gelpí, M. Soler-López, J. A. Subirana, M. Orozco, F. J. Luque, *J. Phys. Chem. B* **2002**, *106*, 8849.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim