Charge Transfer

DOI: 10.1002/ange.200602106

Double Proton Coupled Charge Transfer in DNA**

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Charge transfer processes in DNA play an important role in oxidatively generated damage and possibly in repairing mechanisms.[1–3] Furthermore, if conductive, DNA could be used in nanoelectronic devices.[4–6] Unfortunately, the many experiments conducted have provided contradictory results, with conductivities that cover the entire range from metallic to insulator.[7–11] Such experiments are technically difficult as they require handling of single molecules or small bundles of DNA and fine control of their contact to the metallic leads and to the supporting surfaces. Despite experimental difficulties, a general consensus has been reached.[1,12] In particular, experiments on chemically modified or photosensitizer intercalated DNA have demonstrated that wet DNA and DNA bundles can carry charge.[1,13,14] On the other hand, long DNA helices deposited on mica surfaces or in dry conditions were found to be insulators or wide-bandgap semiconductors.[12] These results are not unexpected as the intrinsic randomness of DNA, induced by distortions and defects, can affect its conducting properties. Moreover, oxidation plays an important role as a parasitic event relative to hole (positive radical) migration.[15,16]

As discussed in reference [17], charge transportation in duplex DNA takes place when the Fermi energies of the electrodes fall between the HOMO and the LUMO of the constituents and can occur through two possible mechanisms: a) a coherent single-step transportation from donor to acceptor (superexchange limit)[18] or b) multistep charge hopping.[19,20]

Both mechanisms have been observed in wet DNA. In these experiments, the charge is injected site selectively by either intercalating an oxidizing agent or introducing some modification into the DNA. Similarly a charge sink can be created by the introduction of a modified base or of a GGG sequence; the effect of such modifications is to lower the ionization potential (IP) with respect to that of an isolated G, thus making the site an effective hole trap.[21] By using this approach, Giese et al. determined the effect of the bridge length on the efficiency of hole transfer by varying the number of $(A{:}T)_n$ base pairs between the charge injection site and the GGG.[22] An exponential decay of the charge-transfer efficiency was observed as a function of the interposed $(A{:}T)_n$ sequence for $n<4$,[23] in agreement with a single-step superexchange-mediated transfer mechanism. Similar results have been reported by Nakatanu and Saito in reference [1]. In DNA sequences containing isolated G:C sites between the source and sink, the charge was shown to hop reversibly between all guanines.[24]

Although the role of fluctuations in modulating DNA conductivity and a possible polaron-like hopping mechanism has been investigated in several experiments,[20,25–28] our knowledge of the microscopic changes induced by the charge defect and its transfer is mostly based on indirect evidence. Different localization mechanisms have been proposed: a change in the tilt angle of the bases, a rearrangement of the solvation shell, a fluctuation in the position of counterions, and a change in the protonation state of G. The first was hypothesized on the basis of simplified theoretical models.[29] The importance of the polarization of the solvent shell has been shown to play a role in the charge transfer in poly(A:T).[30] The ion-gated charge-hopping mechanism was proposed from first-principles simulations that showed a correlation between the charge localization and the position

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[**] We acknowledge generous grants from the Earth Simulator Center (ES-JAMSTEC)–Yokohama and from the Swiss National Supercomputing Centre(CSCS) which have made this calculation possible. M.B. is grateful to Takashi Ikeda and Masaru Hirata for their valuable help. F.L.G. is grateful to Y. Mantz for his valuable help.

of the counterion and it was supported by indirect experimental evidence.[31] The proton-coupled charge-transfer mechanism received most attention and different groups found experimental and theoretical supporting evidence.[32–35] In this scenario, the charge hopping is linked to the proton transfer from G to C.

Recently, by performing first-principles dynamical simulations on a crystalline poly-d(GpCp) fiber, we found that the hole can indeed be localized by a proton transfer from G to C.[35] However, we did not observe directly the hole migrating from one site to another as a consequence of a specific change. The same is also true for all the other first-principles calculations performed on realistic models.[31,36,37] Experimentally, only indirect evidence has been reported and the issue remains controversial and much debated.

Herein we report the direct observation of charge transfer from a GGG to a G site upon deprotonation of the latter. This was obtained by a large-scale first-principles quantum-mechanical (QM) simulation coupled to a molecular mechanics (MM) simulation (QM/MM) on a fully hydrated 38-base-pair B-DNA d(5′ACGCACGTCGCATAATATTACGT GGGTATTATATTAGC-3′). The chosen sequence is the same as that used in the experiments of Giese and coworkers[38] The structure was equilibrated at room temperature for 10 ns in a box $38\times41\times154$ Å^3 with 5902 water molecules and Na$^+$ counterions, for a total of 20265 atoms, by using the Amber99 force field.[39] QM/MM calculations were performed within DFT.[40,41] We performed seven different QM/MM molecular-dynamics simulations starting from uncorrelated structures extracted from the MM run. The quantum subsystem was taken to be the central segment d(5′GTGGG-3′), which, to reduce the computational cost, was in some of the calculations replaced by d(5′GTGG-3′). The QM subsystem included the sugar–phosphate backbone for a total of 303 atoms and was terminated with four capping hydrogen atoms. The classical MM part included the remaining 19962 atoms.

The present-day exchange and correlation functionals used in DFT have well-known drawbacks in describing radical states. The most severe is the incomplete cancellation of the electron self-interaction, which artificially favors charge delocalization.[42] Thus, in the case of delocalized states, special care was taken to check the robustness of our results. We repeated our calculations by using the self-energy corrections introduced in reference [43] in which adjustable parameters were fitted to reproduce the distribution of the spin density of a guanine pair stacked at 3.5 and 9 Å obtained with a correlated (MP2) ab initio calculation.[44]

Another important indicator of the quality of the theoretical treatment of open-shell systems is the expectation value of the square total spin operator, $\langle S^2\rangle$. In the present work, it was calculated for all the relevant states following reference [45]. Starting from five different geometries obtained from the classical molecular dynamics run, we removed one electron and performed 2-ps QM/MM equilibrations at 300 K. In Figure 1 A, a typical spin-density, which is the difference between the density of the spin up and spin down electron, is shown. In agreement with previous Hartree–Fock ab initio calculations and with experimental results,[46,21] the hole is localized on the three proximal guanines with a density peak on the central G. The difference between calculations performed on different initial geometries is mainly seen in the amount of spin density localized on the sugar–phosphate backbone of the guanines. We are confident that the localization pattern for the hole is not affected by electron self-interaction problems as very similar results were obtained by Hartree–Fock calculations, which are self-interaction free by construction, on a duplex 4mer 5′-XGGG-3′, where X = T,C.[46,21] This is in good agreement with previous reports of a large polaron state.[20,47,30] During the dynamics, the calculated $\langle S^2\rangle$ turns out to be about 0.8, very

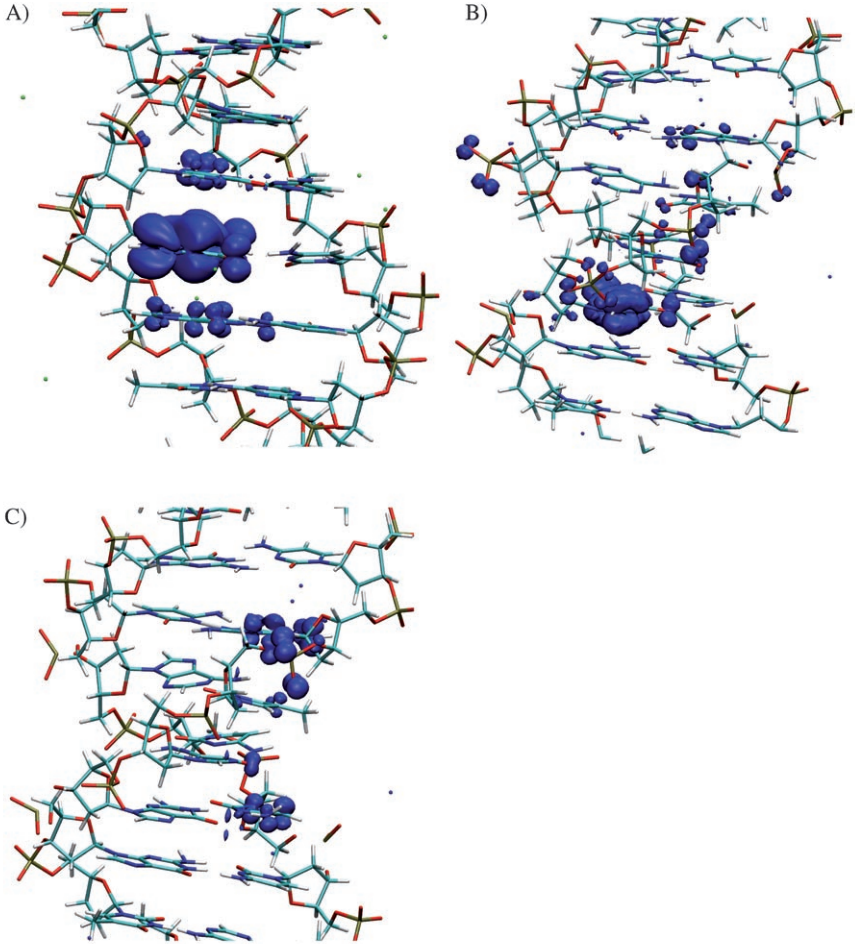

Figure 1. Details of the three-dimensional structure of the B-DNA 38mer and of the spin density isosurface (in blue) associated with the radical cation state. A) In the initial state, the hole is localized on the GGG. B) When the isolated G undergoes double proton transfer, the hole is transferred through the sugar–phosphate backbone. C) The isolated G is deprotonated and the hole is localized on it. The isosurfaces shown have a value of 5×10^{-2} eÅ^3.

close to the correct value for a doublet (0.75), indicating that, in this case, the spin polarization is correctly described by DFT.

We now focus on the hole-hopping mechanism. As we obtained similar localization patterns with the larger and smaller QM subsystems (d(5′GTGGG-3′) and d(5′GTGG-3′)), we used the latter to speed up the calculations. Our goal is to understand how a hole, which is initially localized on the stacked GGG triplet, reversibly hops to a different isolated G, which is separated from the GGG by an AT bridge. It is clear that the hopping will not occur without some change in the structure or solvation of the isolated G as the GGG triplet is a more favorable trap configuration for a hole than a single G.[21] Taking our cue from electron paramagnetic resonance (EPR) experiments[48] and from the results of our former full quantum calculation in which a proton-coupled charge localization was observed,[35] we studied the energetics and the effects on the atomic and electronic structure of the deprotonation of an isolated G by means of our recently developed metadynamics method. This approach is able to escape local minima by overcoming large free-energy barriers and makes it possible to reconstruct the free energy surface in the space of a chosen set of relevant collective variables (CVs).[49] Herein, starting from two independent configurations, we performed two metadynamics simulations by using as CVs the distance of the N^1 hydrogen atom of G from the N^3 of C and the coordination number[16] of the hydrogen atom with respect to the N^3 of C (see Figure 2).

Figure 2 shows the schematic view of the initial and final state of the isolated G. Initially it does not possess any radical character, hence the G N^1 proton is not acidic (Figure 2.1). As the reaction proceeds, the proton is transferred from this G base to the nearby paired C base and, simultaneously, the H^4 proton belonging to C is transferred to G (C*:G*, Figure 2.2). This double proton exchange makes the final state energetically more favorable than a single proton transfer (G_{-H}) : C-H^+. Indeed G, in contrast to G^+, is not acidic and the single proton exchange is highly unfavorable, whereas the double proton exchange, resulting in the formation of two neutral species, is more likely.[50–52] It is important to notice that the metadynamics is acting only on H^1, thus the double proton transfer that we observe is spontaneous and cannot be ascribed to an artificial bias. Soon after the proton transfer, the hole is transferred from the GGG triplet to the isolated G (Figure 2.3). In Figure 1B, a snapshot of the intermediate stage is shown. When the isolated G has radical character, the H^4 proton is transferred back to the C. This has the effect of further localizing the charge, in agreement with reference [35] (Figure 1C and Figure 2.4). To verify this mechanism, we calculated the adiabatic ionization potential of C:G and C*:G* with a B3LYP/6-31++G(d) calculation in the gas phase. The IPs are 6.9 eV and 6.5 eV for C:G and C*:G*, respectively. In agreement with the QM/MM calculations, relaxing the geometry of C*:G* in the radical cation state we obtain (G_{-H}): C-H^+ (Figure 2B).

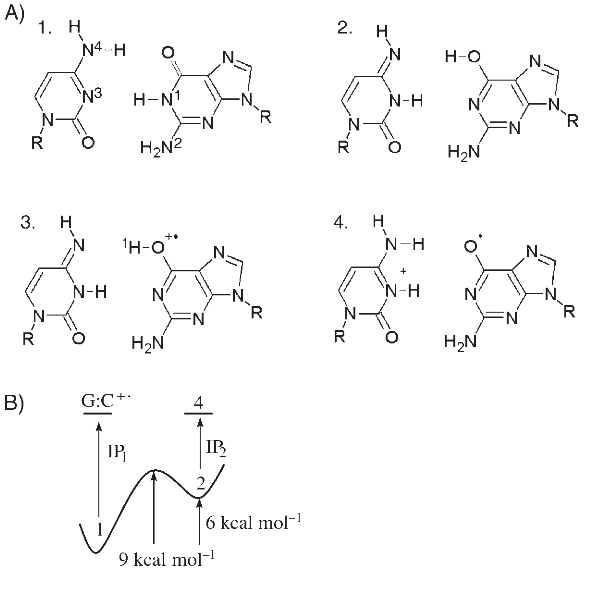

Figure 2. A) Mechanism for the charge transfer from the GGG sink to the isolated G. 1. Initially, the isolated G has a neutral Watson–Crick pair character. 2. The reaction proceeds with a double proton transfer. 3. The hole (radical cation) is transferred from the GGG sink to the isolated G. 4. The final state. B) Qualitative representation of free-energy profiles of the reaction. The free energies reported were obtained on the full QM/MM system with metadynamics. The adiabatic ionization potentials are $IP_1 = 6.9$ eV and $IP_2 = 6.5$ eV. These values were calculated on a gas phase G:C pair by relaxing the geometry with B3LYP functional and a 6-31++G* gaussian basis set.

This mechanism was preserved and the pathway was substantially unchanged during runs starting from different initial coordinates and reversibly repeats itself even when a different collective variable is used. In all these calculations, we checked that the self-interaction corrections have little effect. The intermediate state resulting from our simulations (Figure 1B) is in agreement with the coherent single-step-transfer picture suggested by experiments performed on G:C bases separated by a single A:T bridging pair.[13] Before the hole transfer, the free-energy barrier to double proton transfer is around 9 $kcal\,mol^{-1}$ (Figure 2B), in agreement with the 10 $kcal\,mol^{-1}$ obtained with correlated ab initio calculations for an isolated G:C pair.[50] Once the isolated guanine has radical character, the free-energy profile along the hydrogen atom dissociation coordinate agrees with that of references [35,53]. In this case, the two protonation states have a very similar stability and the interconversion barrier is around 6 $kcal\,mol^{-1}$.

Our calculation provides an important insight into the details of the mechanism that are not directly accessible to experimental probes. We observe directly the proton-coupled charge transfer, a mechanism already proposed on the basis of multiple H/D isotope-effect studies on the charge mobility[34,32] and indirectly shown by us in a previous theoretical paper.[35] Moreover, we find a new and unexpected role for the tautomers of G and C generated by double proton transfer. We observe that the double proton transfer is sufficient to trigger charge hopping from a nearby site even if the nearby site is a GGG triplet, a much better hole trap than an isolated G. We also show that at short donor–acceptor distances, the charge is transferred in a single step.

Received: May 26, 2006

Keywords: density functional calculations · DNA damage · electron transfer · molecular dynamics · nucleobases

[1] "Long-Range Charge Transfer in DNA I–II": *Topics in Current Chemistry, Vol. 236–237* (Ed.: G. B. Schuster), Springer, Heidelberg, **2004**.
[2] T. Douki, J. L. Ravanat, D. Angelov, J. R. Wagner, J. Cadet, *Top. Curr. Chem.* **2004**, *236*, 1 – 25.
[3] E. M. Boon, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12543 – 12547.
[4] C. Dekker, M. A. Ratner, *Phys. World* **2001**, *14*, 29 – 33.
[5] M. D. Ventra, M. Zwolak, *Encyclopedia of Nanoscience and Nanotechnology*, American Scientific Publishers, New York, **2004**.
[6] S. O. Kelley, N. M. Jackson, M. G. Hill, J. K. Barton, *Angew. Chem.* **1999**, *111*, 991 – 996; *Angew. Chem. Int. Ed.* **1999**, *38*, 941 – 945.
[7] R. Holmlin, P. Dandliker, J. Barton, *Angew. Chem.* **1997**, *109*, 2830 – 2848; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2714 – 2730.
[8] H. W. Fink, C. Schonenberger, *Nature* **1999**, *398*, 407 – 410.
[9] A. Y. Kasumov, M. Kociak, S. Gueron, B. Reulet, V. T. Volkov, D. V. Klinov, H. Bouchiat, *Science* **2001**, *291*, 280 – 282.
[10] D. Porath, A. Bezryadin, S. deVries, C. Dekker, *Nature* **2000**, *403*, 635 – 638.
[11] C. Gomez-Navarro, F. Moreno-Herrero, P. J. de Pablo, P. J. Colchero, J. G. Herrero, A. M. Bar, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 8484 – 8487.
[12] R. G. Endres, D. L. Cox, R. R. P. Singh, *Rev. Mod. Phys.* **2004**, *76*, 195 – 214.
[13] B. Giese, *Annu. Rev. Biochem.* **2002**, *71*, 51 – 70.
[14] K.-H. Yoo, D. H. Ha, J. O. Lee, J. W. Park, J. Kim, J. J. Kim, H. Y. Lee, T. Kawai, H. Y. Choi, *Phys. Rev. Lett.* **2001**, *87*, 198102 – 198104.
[15] B. Giese, M. Spichty, *ChemPhysChem* **2000**, *1*, 195 – 198.
[16] F. L. Gervasio, A. Laio, M. Iannuzzi, M. Parrinello, *Chem. Eur. J.* **2004**, *10*, 4846 – 4852.
[17] M. Bixon, J. Jortner, *J. Chem. Phys.* **2005**, *319*, 273 – 282.
[18] A. Nitzan, *Annu. Rev. Phys. Chem.* **2001**, *52*, 681 – 750.
[19] D. Ly, Y. Kan, B. Armitage, G. B. Schuster, *J. Am. Chem. Soc.* **1996**, *118*, 8747 – 8748.
[20] G. B. Schuster, *Acc. Chem. Res.* **2000**, *33*, 253 – 260.
[21] Y. Yoshioka, Y. Kitagawa, Y. Takano, K. Yamaguchi, T. Nakamura, I. Saito, *J. Am. Chem. Soc.* **1999**, *121*, 8712 – 8719.
[22] B. Giese, J. Amaudrut, A. K. Köhler, M. Spormann, S. Wessely, *Nature* **2001**, *412*, 318 – 320.
[23] When the number of A:T bridging bases exceeds four, the distance dependence of charge-transfer efficiency changes from an exponential-decay regime to a very slowly decreasing linear regime. This change was interpreted by the onset of a different mechanism, namely an a-hopping mechanism. In this regime the adenine are oxidized and act as charge carriers (see reference [13]).
[24] B. Giese, S. Wessely, *Angew. Chem.* **2000**, *112*, 3632 – 3634; *Angew. Chem. Int. Ed.* **2000**, *39*, 3490 – 3491.
[25] M. A. O'Neill, H. C. Becker, C. Wan, J. K. Barton, A. H. Zewail, *Angew. Chem.* **2003**, *115*, 6076 – 6080; *Angew. Chem. Int. Ed.* **2003**, *42*, 5896 – 5900.
[26] C. Wan, T. Fiebig, S. O. Kelley, C. R. Tradway, J. K. Barton, A. Zewail, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 6014 – 6019.
[27] D. Ly, L. Sanii, G. B. Schuster, *J. Am. Chem. Soc.* **1999**, *121*, 9400 – 9410.
[28] P. T. Henderson, D. Jones, G. Hampikian, Y. Kan, G. B. Schuster, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 8353 – 8358.
[29] R. Bruinsma, G. Grüner, M. R. D'Orsogna, J. Rudnik, *Phys. Rev. Lett.* **2000**, *85*, 4393 – 4396.
[30] E. M. Conwell, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 8795 – 8799.
[31] R. N. Barnett, C. L. Cleveland, A. Joy, U. Landman, G. Schuster, *Science* **2001**, *294*, 567 – 571.
[32] B. Giese, S. Wessely, *Chem. Commun.* **2001**, 2108 – 2109.
[33] S. Steenken, *Biol. Chem.* **1997**, *378*, 1293 – 1297.
[34] V. Shafirovich, A. Dourandin, N. E. Geacintov, *J. Phys. Chem. B* **2001**, *105*, 8431 – 8435.
[35] F. L. Gervasio, M. Boero, A. Laio, M. Parrinello, *Phys. Rev. Lett.* **2005**, *94*, 158103.
[36] F. L. Gervasio, P. Carloni, M. Parrinello, *Phys. Rev. Lett.* **2002**, *89*, 108102.
[37] A. Hübsch, R. G. Endres, D. L. Cox, R. R. P. Singh, *Phys. Rev. Lett.* **2005**, *94*, 178102.
[38] E. Meggers, M. E. Michel-Beyerle, B. Giese, *J. Am. Chem. Soc.* **1998**, *120*, 12950 – 12955.
[39] W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, Jr., D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell, P. A. Kollmann, *J. Am. Chem. Soc.* **1995**, *117*, 5179 – 5197.
[40] A. Laio, J. VandeVondele, U. Roethlisberger, *J. Chem. Phys.* **2002**, *116*, 6941 – 6947.
[41] All calculations were performed in the local spin density formulation, as implemented in the cpmd code.[54] Hamprecht–Cohen–Tozer–Handy gradient corrections on the exchange-correlation function were included.[55] The interaction between valence electrons and ionic cores was described by martins-troullier pseudopotentials.[56] the kohn-sham valence orbitals were expanded in a plane wave basis set with an energy cutoff of 70 ry.
[42] J. Laegsgaard, K. Stokbro, *Phys. Rev. Lett.* **2001**, *86*, 2834.
[43] J. VandeVondele, M. Sprik, *Phys. Chem. Chem. Phys.* **2005**, *7*, 1363 – 1367.
[44] By using $\alpha = 0.8$ and $\beta = 0.5$, we are able to reproduce both a situation in which the hole is delocalized on two stacked guanines when the distance is 3.5 Å and one where the hole is localized when the distance is 9 Å. Similar results were obtained for a stacked benzene couple.
[45] J. Wang, A. D. Becke, V. H. Smith Jr., *J. Chem. Phys.* **1995**, *102*, 3477 – 3480.
[46] H. Sugiyama, I. Saito, *J. Am. Chem. Soc.* **1996**, *118*, 7063 – 7068.
[47] A. Omerzu, M. Licer, T. Mertelj, V. V. Kabanov, D. Mihailovic, *Phys. Rev. Lett.* **2004**, *93*, 218101.
[48] K. Hildebrand, D. Schulte-Frohlinde, *Free Radical Res. Commun.* **1990**, *11*, 195 – 206.
[49] A. Laio, A. Rodriguez-Fortea, F. L. Gervasio, M. Ceccarelli, M. Parrinello, *J. Phys. Chem. B* **2005**, *109*, 6714 – 6721.
[50] L. Gorb, Y. Podolyan, P. Dziekonski, W. A. Sokalski, J. Leszczynski, *J. Am. Chem. Soc.* **2004**, *126*, 10119 – 10129.
[51] V. Zoete, M. Meuwly, *J. Chem. Phys.* **2004**, *121*, 4377 – 4387.
[52] A. Abo-Riziq, L. Grace, E. Nir, M. Kabelac, P. Hobza, M. S. de Vries, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 20 – 23.
[53] M. Hutter, T. Clark, *J. Am. Chem. Soc.* **1996**, *118*, 7574 – 7577.
[54] CPMD V3.5, Copyright IBM Corp 1990 – 2001, Copyright MPI fuer Festkoerperforschung, Stuttgart, **1997–2001**.
[55] F. A. Hamprecht, A. J. Cohen, D. J. Tozer, N. C. Handy, *J. Chem. Phys.* **1998**, *109*, 6264 – 6271.
[56] N. Troullier, J. L. Martins, *Phys. Rev. B* **1991**, *43*, 1993 – 2006.