Electron Interactions between Nucleoside Pairs in Canonical B-DNA: I. Transfer Integrals

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The valence bond/Hartree−Fock (VB/HF) formalism [F. Castet et al., *J. Phys. I (France)*, **1996**, *6*, 583; *Chem. Phys.* **1998**, *232*, 37] is applied to calculate the transfer integrals between interacting fragments in canonical B-DNA strands. To get a fully consistent picture of these terms, the VB/HF fragments should be defined as the full nucleosides that incorporate the base and the pentose group. The largest transfer integrals are found for intrastrand pairs involving the thymine base. Moreover, the latter integrals are shown to be strongly dependent on the orientation of the methyl group, which is thus an important geometrical parameter to be considered. The VB/HF transfer integrals are compared to the previously published electron coupling elements, calculated at the Hartree−Fock level using a dimer-splitting procedure. The differences and similarities between the two descriptions are analyzed in detail from the master equations of the different models.

1. Introduction

The picture of electronic charge transfer along DNA double helices through $\pi-\pi$ interactions between stacked pairs was first proposed some 40 years ago by Ladik.[1] Early conductivity measurements by Eley and Spivey[2] led to a semiconducting gap of about 2.4 eV for DNA and RNA. In the recent years, the conductivity of DNA was investigated by monitoring the hole transfer occurring in photoinduced donor−acceptor reactions. Intercalated probes or covalently attached probes were used in such studies. The pioneering work of Barton and co-workers[3−7] focusing on a wire-like hole transport in DNA stimulated much experimental and theoretical work on this subject. It soon became apparent that subsequent results did not confirm this appealing picture. Moreover, the single-step mechanism proposed by Barton and colleagues with a transfer occurring over about 25−35 base pairs[3] contradicts the usual mechanisms for the charge transfer: (i) a two-center unistep superexchange mechanism with a transfer rate showing a strong donor−acceptor distance (R) dependence,

$$k = \exp(-\beta R)$$

where β depends on the nature of the donor, the acceptor, and the bridge; and (ii) a multistep hopping transport with a weak R-dependence and β roughly proportionnal to the number of steps.

The observed range of the β values is indeed very large: 0.6 Å^{-1},[8] 0.7 Å^{-1},[8−9] about 1.0 Å^{-1},[10−13] 1.42 Å^{-1}.[14] Very small values of β (0.1 Å^{-1},[5] 0.07 Å^{-1},[15] 0.02 Å^{-1},[16] or 0.017 Å^{-1} [17]) are interpreted in contrasting ways: as a result of a true long-range transport for Barton,[5−7] not to result from a superexchange mechanism for Giese,[15,18] or probing an alternative "phonon-assisted polaron-like" mechanism for Schuster.[16,17]

Finally, while a consensus on DNA conductivity emerged after the last experiments of femtosecond dynamics by Barton and Zewail,[19] who conclude that DNA does not behave as an efficient molecular wire, the true microscopic mechanism that governs the charge migration between π-stacked nucleotides is not yet fully established. It includes both electronic and vibrational effects; the latter (low-frequency medium modes and intramolecular high-frequency modes) being involved in the Franck−Condon factor of the Marcus theory[20] for (unistep) hole transfer rate. The calculation of the electronic couplings is tractable by means of quantum chemistry approaches.

The first attempt for calculating transfer integrals was performed by Ladik[1] within the Hückel framework. Dee and Baur[21] extended in 1974 the model for intermolecular interactions in molecular crystals to the evaluation of charge excitation between the DNA nucleotides. The calculated coupling terms are in the range 0.1−3.5 eV. However, the definition of transfer integrals used by these authors relies on serious approximations regarding the electrostatic contribution to the coupling matrix elements. Priyadarshy et al.[22] calculated the electron transfer rates on different DNA bridges incorporating explicitly donor and acceptor molecules. The CNDO/S molecular orbitals and energies of the entire systems allowed these authors to conclude that DNA is not a molecular wire, but it is not possible to extract the transfer integrals between individual base pairs from these global calculations.

Troisi and Orlandi[23] recently performed direct ab initio Hartree−Fock calculations of the electronic couplings between adjacent bases using the HOMOs (highest occupied molecular orbitals) of the monomers. On the contrary, the recent theoretical work of Jortner and colleagues[24−29] mainly focuses on the determination of the base−base coupling matrix elements using a two-state model. Intrastrand and interstrand coupling terms are evaluated as one-half of the adiabatic state splitting, which is commonly estimated from the molecular energies of the HOMO and HOMO-1 of the XY nucleobase pair (X, Y = A, G, T, C). The dimer orbitals are obtained by Hartree−Fock calculations. The coupling terms calculated by this method range from 30 to 160 meV for intrastrand transfers and they are 1 order of magnitude smaller for interstrand interactions. This "dimer splitting" scheme was used in other domains, in particular in the field of organic conductors, to determine semiempirical (extended Huckel theory) transfer integrals. These

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integrals give reliable results with respect to the bandwidth in these compounds, and they provide tight-binding band structures in a good agreement with density functional theory calculations (for a review, see ref 30).

Whether semiempirical or ab initio, the dimer splitting approximation carries an underlying frontier orbital model that is much more compact since it involves only the valence band, supposedly built out of the HOMOs of the DNA bases instead of the whole set of atomic basis functions. In this way, the frontier orbital model is an effective Hamiltonian. For instance, extended Hückel calculations which are restricted to one-electron interactions implicitly yield a Hückel type model where the various bases are replaced by effective sites carrying a single frontier orbital. The detailed nature of the HOMOs nevertheless ensures that the molecular specificities of the bases are accounted for in the effective picture.

However, it is highly desirable to dispose of an effective electronic Hamiltonian that explicitely incorporates electron−electron repulsion but remains as simple as possible (i.e., expressed in the most compact space). This is particularly relevant when more than one hole is involved in the transport properties, a typical case where electron repulsion may profoundly affect the conducting electrons wave function. This effective Hamiltonian may assume various formulations depending on the range of the electrostatic repulsion. In the Hubbard[31] family of model Hamiltonians, electrostatic interactions are short ranged with a phenomenologically imposed self-screening due to the itinerant electrons. On the contrary, the Pariser−Parr−Pople (PPP) model[32] does not assume the screening of electron repulsion in the Hamiltonian. Screening arises only at the outset of the calculation of the eigenstates.

The effect of electron−electron interaction on the charge transport in biomolecules is generally neglected, mainly because the evaluation of the charge-transfer rate rests on the delocalization of a single hole between successive donor−acceptor pairs.[24,25,33] Very few theoretical treatments of the electron correlation in biochemical systems were thus published. In a recent review, Ladik[34] notices that the HF gap of the periodic (homo)polynucleotide base stacks is much too large compared to the experimental estimate of 5.5−6.5 eV from the exciton spectra. It should be reduced by both basis set effect and correlation effect (see also refs 35−37). The observation of high dc conductivity in this material would be possible only under doping. Moreover, the possiblity of strong hole doping by the rhenium/carbon metallic contacts on which double-stranded DNA were deposited was invoked to explain the observed ohmic conductivity and the proximity-induced superconductivity below 1 K in this system.[38] These findings are not consistent with current thinking in bridge mediated electron transfer for which the hopping mechanism involves pushing an extra electron or hole onto the bridge. The ionization potential and electron affinity, which rely to a large extent on electrostatic contributions, are the critical parameters in such processes. This points to the need of a correlated model to describe the electronic properties of DNA.

To build up a consistent effective correlated picture, through a systematic and reliable extraction scheme, one must ensure that the reference one-electron states are defined unambiguously and independently of the type of macrosystem under scrutiny. In other words, the effective site orbitals should not reflect spurious effects such as the spontaneous polarization and delocalization that occurs when the Hartree−Fock description is preimposed on the supramolecular edifice. These reference site orbitals should only characterize the DNA bases independently of the theoretical handling of the strand. Following these guidelines, the main goal of this work deals with the extraction of a PPP type effective Hamiltonian, including one and two electron interactions, using the hybrid valence bond/Hartree−Fock (VB/HF) model[38,39] that was successfully applied to organic superconductors.

We report in the present paper an application of this formalism to the calculation of transfer integrals between interacting fragments in duplex canonical B-DNA, to be checked against the available reference theoretical materials. This paper is organized as follows. In the following section, we summarize the VB/HF extraction procedure. In section 3, we validate a relevant partitioning scheme of the DNA supermolecule. The results on the transfer integrals are collected in section 4 and discussed in section 5. Finally, in section 6, we present the conclusion and the prospects of this work.

2. Theory

2.1. The VB/HF Procedure. The VB/HF method was developed in order to calculate electron interactions between fragments in molecular crystals. It was applied to the consistent extraction of a PPP[32] effective Hamiltonian (transfer integrals and Coulombic parameters) for conducting electrons in organic conductors.[39,40] From the structural similarities between the stacking organic monomers in the organic conductors and the stacking bases in DNA, we applied the same formalism to the determination of the electronic parameters in these latter "supermolecular" systems. We focus in this report on the calculation of transfer integrals. The determination of the electrostatic terms is left for future work.

The VB/HF approach involves calculations on clusters of N interacting molecular fragments. If one is interested in hole transfer, each fragment will bear a net charge 0 or +1. We thus define several molecular charge distributions for a cluster with a fixed global charge. For instance, in a molecular system containing two distinct fragments M and carrying a global net charge equal to +1, one can define two VB configurations M^+-M^0 and M^0-M^+.

The VB wave functions Ψ_M describing the stationnary electronic states of the system are expressed in an active configurational space built from single-determinant, many-electron wave functions Φ_X, which can be associated with the distinct charge transfer states of the system:

$$\Psi_M = \sum_X C_{MX}\Phi_X \tag{1}$$

Within the VB/HF description, the Φ_X functions are written as a single Slater determinant built from the whole set of occupied spin-orbitals of the fragments:

$$\Phi_X = |x_1^1 x_2^1 \ldots x_1^2 x_2^2 \ldots x_1^N x_2^N \ldots| \tag{2}$$

where x_i^k is the ith occupied spin−orbital of the molecule k in the electronic configuration X.

In a full-featured VB/HF calculation, the molecular orbitals (MOs) of each fragment are optimized depending on the net charge of the fragment and on the electrostatic field of the neighboring molecules, following a parallel SCF optimization procedure[39] and using the semiempirical Hamiltonian AM1[41,42] restricted to all valence electrons. So as to keep the global charge of each fragment constant during the SCF cycles and to avoid any charge delocalization issue, each orbital involved in the electronic configurations is required to be strictly localized on

fragments, i.e., to be developed on the atomic orbitals of a specific molecule:

$$x_i^k = \sum_p X_{pi}^k \chi_p^k \tag{3}$$

The local constraint on MOs together with the NDDO approximation[43] involved in the AM1 formalism implies that the distinct VB configurations are orthogonal and normalized:

$$\langle \Phi_X | \Phi_Y \rangle = \delta_{XY} \tag{4}$$

where δ is the Krönecker symbol. Consequently, the VB matrix elements are given by

$$H_{XY} = \langle \Phi_X | \hat{H} | \Phi_Y \rangle \tag{5}$$

and the diagonal terms are the energies associated with the VB configurations.

2.2. Extraction of the Electronic Parameters. The energy levels associated to the single configuration functions (i.e., the diagonal terms of the VB matrix) are mapped onto the diagonal part of an effective Pariser−Parr−Pople Hamiltonian $\hat{H}_{eff}$, while the coupling terms between different VB configurations compare to the off-diagonal elements (transfer integrals) of $\hat{H}_{eff}$. This effective Hamiltonian is developed on the basis of a single site orbital per molecule, which is assimilated to the HOMO, although this HOMO is never specified explicitly; it appears only through the effective interaction parameters. In the second quantization formalism, a generalized expression for the effective Hamiltonian is written as

$$H_{eff} = -\sum_{i,j}\sum_{\sigma} t_{ij}(c_{i,\sigma}^{+}c_{j,\sigma} + c_{j,\sigma}^{+}c_{i,\sigma}) + \frac{1}{2}\sum_i U_i n_i(n_i - 1) + \frac{1}{2}\sum_{i\neq j} V_{ij}(n_i - Z_i)(n_j - Z_j) + \sum_i \epsilon_i n_i + \sum_{i\neq j} \Delta_{ij}(n_i)Z_j \tag{6}$$

where the t_{ij} are the transfer integrals restricted to first neighbors ($j = i \pm 1$), the U_i are the on-site repulsion energies, and the V_{ij} are the electrostatic interaction terms. The term $c_{i,\sigma}^{+}$ ($c_{i,\sigma}$) is a creation (annihilation) operator for a site orbital located at site i with spin σ, and $n_{i,\sigma} = (c_{i,\sigma}^{+}\, c_{i,\sigma})$ is the operator number of electrons. The Z_i terms are core charges, ϵ_i is the site orbital energy for molecule i, Δ_{ij} is the penetration integral between molecule i and molecule j. The physical meaning of these last terms has been detailed in reference 39.

Whereas the VB/HF method allows to perform an in situ MO optimization, we have shown[39] that the extraction of the electronic parameters is more consistent when using nonpolarized MOs. Thus, the MOs are optimized on the isolated fragments depending on their charge only. With such constraints on the MOs (MOs are local, charge dependent, optimized on the isolated fragments) together with the NDDO approximation of the AM1 Hamiltonian, in which the exchange interactions between disjoint fragments are neglected, all the electronic interactions reduce to a sum of pair interactions. Therefore, calculations are performed on fragment pairs.

2.3. Transfer Integral Calculations. The transfer integrals can be identified to the off diagonal terms of the Hamiltonian matrix, i.e., the coupling term between two distinct VB configurations X and Y. The single determinantal wave functions related to these two configurations are obtained from independent HF processes that consequently produce two sets of nonorthogonal MOs. This requires the evaluation of the overlap matrix $\boldsymbol{S}$ between occupied spin-orbitals involved in the two configurations X and Y, with elements

$$\langle x_i^1 | y_j^2 \rangle = S_{ij}\delta_{12} \tag{7}$$

The transfer integral can be written by separating the one- and two-electron parts. Within the AM1 approximation, only the one electron part gives a non zero contribution and can be written following the Löwdin expression:[44]

$$t = \langle \Phi_X | \hat{h} | \Phi_Y \rangle = \sum_i \sum_j (-1)^{i+j} D_{xy}(x_i^1 y_j^2) \langle x_i^1 | \hat{h} | y_j^2 \rangle \tag{8}$$

where $D_{xy}(x_i^1 y_j^2)$ is the cofactor of the overlap matrix obtained by deleting the row and column that contain the element $\langle x_i^1 | y_j^2 \rangle$. Following eq 3, the molecular orbitals involved in the one-electron integral are developed on the basis of local atomic orbitals:

$$t = \langle \Phi_X | \hat{h} | \Phi_Y \rangle = \sum_i \sum_j \sum_p \sum_q (-1)^{i+j} D_{xy}(x_i^1 y_j^2) X_{pi}^1 Y_{qj}^2 h_{pq} \tag{9}$$

where $h_{pq} = \langle \chi_p^1 | \hat{h} | \chi_q^2 \rangle$. In the AM1 approximation, this integral is written as

$$h_{pq} = \beta_{pq} S_{pq} \tag{10}$$

where S_{pq} is the overlap between the OA χ_p and χ_q, and β_{pq} is an empirical parameter.

In the previous study on organic conductors, we could show that the MOs are barely affected by the molecular charge. The contributions from all core orbitals are thus small with regard to the HOMOs weight. Therefore, the major contribution to the transfer integral arises from the one-electron integral between the HOMOs of the two fragments involved in the electron transfer:

$$t \approx t_{HOMO} = \langle \mathrm{HOMO}(1) | \hat{h} | \mathrm{HOMO}(2) \rangle \tag{11}$$

All the calculations were performed for fixed geometries of bases, nucleosides and interacting nucleosides pairs issued from the MACROMODEL package.[45] A canonical B-form of the duplex DNA was used, with the standard parameters rise = 3.38 Å and twist = 36°.

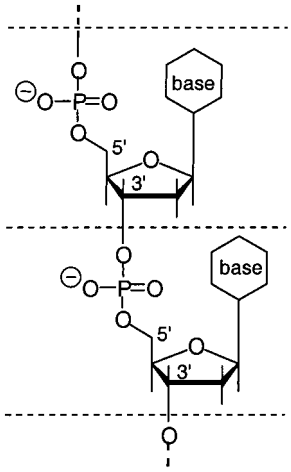
3. Definition of the Fragments

The application of the VB/HF formalism to the calculation of electronic parameters in DNA implies the truncation of the supermolecule in disjoint fragments. Contrary to the study of molecular crystals, the choice of the fragments in DNA, in which the atoms of the backbone are chemically linked as schematized in Chart 1, is less straightforward.

In the quantum chemistry calculations of the energetic and interaction terms in biological systems, the fragment is quite commonly defined by the base and the full backbone is replaced by a methyl group.[24,25,46−49] We report in Table 1 the VB/HF transfer integrals between pairs of identical bases using this truncation. These integrals may be decomposed into a contribution arising from the base itself (noted t_B) and that involving the methyl substituent (noted t_{Me}).

The contribution of the methyl residue is far from being negligible, in particular in the cases involving the pyrimidine bases T and C, where the values of t_{Me} are about 10 meV. The total transfer integral is thus spoiled by a meaningless contribution since this residue does not belong to the real structure.

CHART 1: Linear Sequence of Nucleotides[a]



[a] The oxygen atom linked to the carbon 3′ belongs to the phosphate anion. Thus, the glucide group in the following does not contain this oxygen.

TABLE 1: Transfer Integrals (meV) between Identical Pairs of Fragments in which the Full Backbone Has Been Replaced by a Methyl Group[a]

stacked pairs	t^b	$t_B{}^c$	$t_{Me}{}^d$
AA	7.6	10.4	−2.6
GG	24.7	26.2	−1.5
TT	45.1	53.5	−8.4
CC	7.8	18.8	−11.0

[a] Calculations were performed at the standard geometry (rise = 3.38 Å and twist = 36°). [b] t is the total transfer integral. [c] t_B is the contribution arising from the base only. [d] t_{Me} is the methyl contribution.

TABLE 2: Difference δq between Mulliken Net Charges on the Terminal Part R of the Neutral and Charged Fragments Defined as B + C_5H_8O + R with B = (A, G, T, C)

B	R = $PO_4H^--NH_4^+$	R = H
B	$PO_4H^--NH_4^+$	H
A	0.0020	0.0045
G	0.008	0.0048
T	0.0023	0.0090
C	−0.0012	0.0057

It is thus necessary to establish a better partitioning scheme in DNA. The VB/HF formalism imposes that the fragment should answer two criteria: (i) the main part (including necessarily the base) must show a strict one-electron population decrease between the neutral and charged states, so that the VB/HF procedure can be rigorously applied, and (ii) the weight of the residue in the calculated transfer integral must be vanishingly small.

The first criterion was tested on the nucleotide defined by replacing the remaining chains outside the dashed lines in Chart 1 by hydrogen atoms. Moreover, in agreement with previous work,[50] a cation NH_4^+ was added to mimic the ionic environment in DNA and to neutralize the negative charge on the phosphate group. The position of the cation NH_4^+ was optimized in the structure $(PO_4H_2)^-(NH_4)^+$ at the AM1 computational level. The differences of the Mulliken charges between the neutral and charged nucleotides B + C_5H_8O + $(PO_4H_2)^-$ + $(NH_4)^+$ involving the various bases B were calculated. We report in Table 2 the contributions δq to this difference for the residue $(PO_4H_2)^-$ + $(NH_4)^+$ (column 2) and for the H atom in the simpler fragment B + C_5H_8O + H (column 3).

δq is close to zero so that the criterion (i) is fulfilled for every fragment: the electron transfer takes place on the part B + C_5H_8O only. The ionization of the nucleotide does not change the global electronic distribution on the phosphate and the NH_4^+ counterion. Moreover, these results show that the substitution of the group $(PO_4H)^-$ − $(NH_4)^+$ by an hydrogen atom agrees with the first criterion.

TABLE 3: Transfer Integrals (meV) between Homogeneous Pairs of Fragments Defined as B + C_5H_8O + H, where B = (A, G, T, C)

stacked pairs	t^a	$t_{BS}{}^b$	$t_H{}^c$
AA	9.38	9.38 (10.18)	0.00
GG	25.19	25.19 (25.59)	0.00
TT	43.61	43.56 (47.16)	0.05
CC	13.04	13.00 (15.90)	0.04

[a] t is the total transfer integral. [b] t_{BS} is the contribution arising from the Part B + C_5H_8O. The contribution to t_{BS} arising from the base B only is given in parentheses. [c] t_H is the contribution involving the terminal H atom.

To check the validity of the fragment B + C_5H_8O + H with regard to the second criterion, transfer integral calculations were performed for intrastrand hole transfer in homogeneous fragments. These integrals may be decomposed into a contribution arising from the B + C_5H_8O parts only (noted t_{BS}) and that involving the H atom (noted t_H). The total transfer integrals t and the two contributions t_{BS} and t_H are given in Table 3. The contribution to t_{BS} arising from the base B only is given in parentheses.

The total transfer integrals t range from approximately 10 meV for AA and CC pairs to 50 meV for TT. The hydrogen contributions t_H are close to zero in every case, so that the second criterion is indeed fulfilled. In addition, the base contribution accounts for the largest part of the transfer integrals. This is particularly so for the purines, whereas the pyrimidines show a more significant contribution from the sugar part of the fragment.

To summarize, we have shown in this section that (i) replacing the full backbone by a simple methyl group induces artifacts in the calculation of transfer integrals, (ii) the fragment defined as B + C_5H_8O + H satisfies the requirements imposed by the VB/HF formalism, and (iii) the termination of the structure by an H atom does not introduce artifacts.

4. Electron Couplings between Pairs of Stacked Nucleosides

4.1. VB/HF Transfer Integrals. The transfer integral between pairs of nucleosides for canonical B-DNA are reported in Table 4 for intrastrand and interstrand interactions. The values of the intrastrand integrals range from 0.8 meV for CG to 44.5 meV for GT. The four larger integrals are found for the pairs 5′-XT-3′, which involve the thymine base. In every case, the orientation of the methyl group of the thymine base was optimized on the isolated monomer, which has one of the hydrogen atoms in the molecular plane of the base. The effect of the rotation of the methyl group is detailed in the following section.

The interstrand integrals are very weak, except for nucleoside pairs built from purine bases AA (17 meV) and GG (9 meV), while interactions between nucleosides built from pyrimidine bases CC and TT are negligible. The interstrand integrals between conjugated nucleosides AT and CG are also negligible.

Similar to the organic conductors, the transfer integral values largely depend on the LCAO coefficients of the HOMO and the overlaps between atomic orbitals of the two fragments. The AM1 HOMOs of each fragment are qualitatively depicted in Figure 1 in the base area that gives the major contribution to

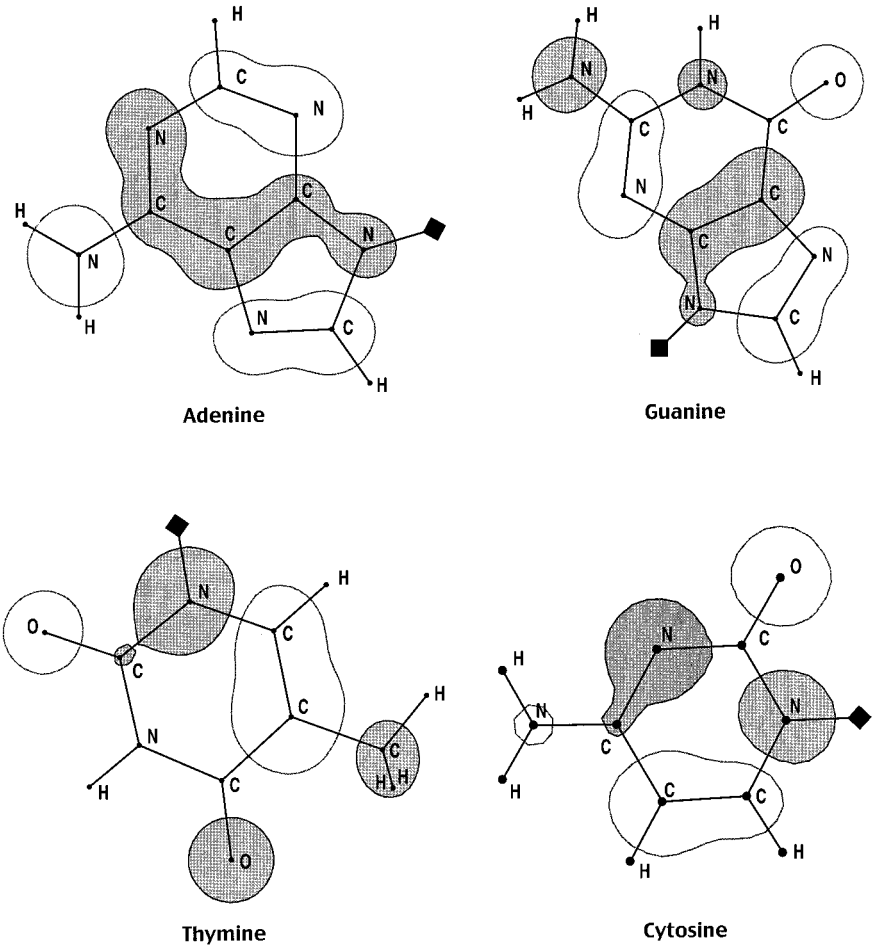


Figure 1. Isodensity surfaces of the HOMOs of DNA nucleosides. Only the base part is represented. The black square figures are C_5H_9O. The plot plane is lifted above the molecular plane by 0.25 Å. The isovalues are equal to ± 0.0175.

TABLE 4: Transfer Integrals (meV) between Pairs XY of Stacked Nucleosides Defined as B + C_5H_8O + H, where B = (A, G, T, C)[a]

	intrastrand	interstrand	
	5′-XY-3′	5′-XY-5′	3′-XY-3′
AA	9.4	3.5	17.3
AC	22.3	0.0	1.0
AG	16.4	0.3	2.6
AT	36.1	0.3	0.7
CA	2.5	0.0	1.0
CC	13.0	0.0	0.0
CG	0.8	0.0	2.2
CT	39.8	0.0	0.0
GA	24.4	0.3	2.6
GC	27.6	0.0	2.2
GG	25.2	0.2	9.1
GT	44.5	0.0	0.7
TA	8.1	0.3	0.7
TC	13.8	0.0	0.0
TG	10.0	0.0	0.7
TT	43.6	0.0	0.0

[a] Calculations were performed at the standard geometry (rise = 3.38 Å and twist = 36°).

the integral. The order of magnitude of the transfer integrals can be related to the intersection areas of the isodensity surfaces for each fragment's HOMO. The intrastrand pair 5′-TT-3′, which corresponds to the largest t value, and the pair 5′-CA-3′, which shows a very small value of t, are sketched in Figure 2, and the nonzero interstrand pairs 3′-AA-3′ and 3′-GG-3′ are shown in Figure 3.

For the 5′-TT-3′ pair (Figure 2a), the overlapping orbitals mostly involve constructive interferences, thus the different contributions sum up with almost no cancellation and t is expected to be quite large. On the contrary, for the 5′-CA-3′ pair (Figure 2b), both constructive and destructive contributions arise from the O and N atoms and cancel out; t is thus quite small. For the interstrand interactions (Figure 3a and 3b), the 3′-GG-3′ transfer integral is half the 3′-AA-3′ integral, because the latter is reduced by the destructive overlaps involving the NH_2 groups.

4.2. Influence of the Methyl Rotation in the Thymine Base. We focus in this section on the effect of the methyl group orientation on the transfer integral between two neighboring thymine-based nucleosides. The dimer is depicted schematically in Figure 4. The transfer integrals were calculated for a varying dihedral angle ϕ defined by the atoms $C_6-C_5-C-H_3$. The most stable conformation for the first thymine monomer has $\phi = 0°$ (H_3 in the molecular plane). The orientation of the methyl of the second molecule is kept constant.

The values of the total transfer integrals t and the integral t_{HOMO} between the HOMOs of the two nucleosides are reported respectively in the second and third columns of the Table 5 as a function of the dihedral angle ϕ. Moreover, the integral t_{HOMO} may be written as the sum of two distinct contributions

$$t_{HOMO} = \sum_{p=Me}\sum_{q} X_{Mp}\,{}^1Y_{Nq}\,{}^2h_{pq} + \sum_{p\neq Me}\sum_{q} X_{Mp}\,{}^1Y_{Nq}\,{}^2h_{pq} = t_{HOMO}^{Me} + t_{HOMO}^{comp} \quad (12)$$

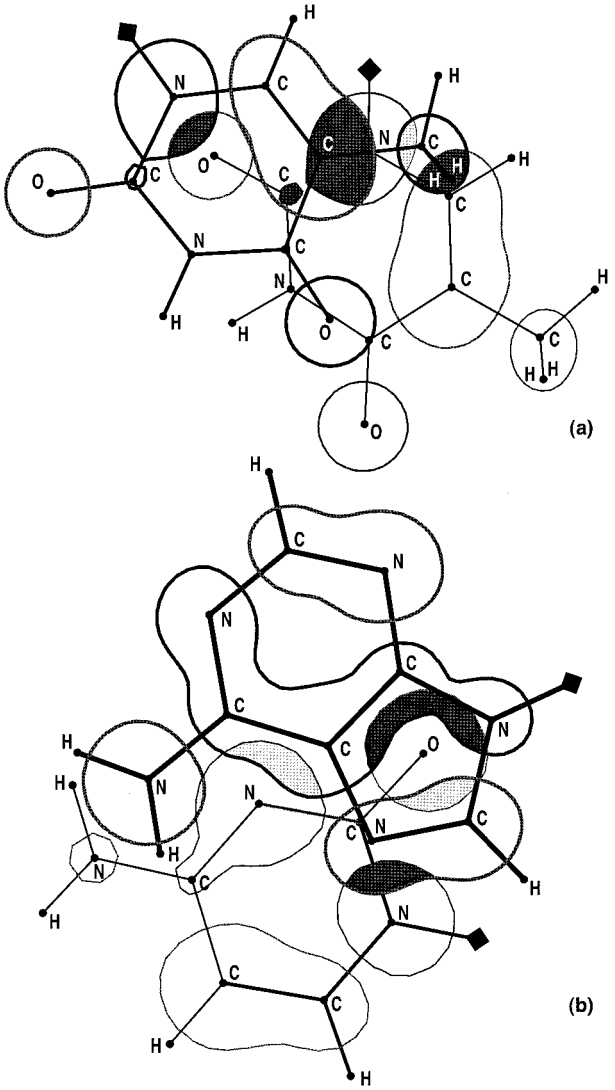


Figure 2. Overlapping orbitals in the intrastrand nucleoside pairs 5′-TT-3′ (a) and 5′-CA-3′ (b). Constructive and destructive interferences are indicated schematically by dark and light areas, respectively. Bold molecules (3′) lie above the plane of the figure.

where M and N are the indices for the HOMOs of the thymine 1 and 2, respectively, t_{HOMO}^{Me} sums up the interactions between atomic orbitals of methyl group in thymine 1 and the atomic orbitals of thymine 2, and the complement t_{HOMO}^{comp} sums the contributions of the atomic orbitals of all the other atoms. These two contributions are listed in the last columns of Table 5.

The transfer integrals strongly depend on the orientation of the methyl group. The largest integral (43.6 meV) is obtained for the $\phi = 0°$ configuration. The smallest value (24.2 meV) occurs for $\phi = 60°$, i.e., when H_2 is in the molecular plane above the carbon atom C_6, with a 45% decrease with regard to the maximum value. These results might be related to the hyperconjugation phenomenon occurring quite generally between methyl groups and conjugated systems. Additionally, these results confirm that t_{HOMO} is quite a good approximation of the total transfer integral, the contribution of the other occupied molecular orbitals being less than 2% of t in all cases.

The contributions t_{HOMO}^{Me} and t_{HOMO}^{comp} show that the variations in the transfer integral result only from the rotation of the methyl group. The methyl contribution to the transfer integral is far from negligible and amounts to more than 50% of the total transfer integral when $\phi = 0°$.

The position of the methyl group thus appears to be a determinant factor to be taken into account in the calculation of transfer terms between interacting fragments involving a thymine base. This supplementary degree of freedom has to be considered together with the standard geometrical parameters related to the stacking of the bases in the strand.

5. Discussion

The VB/HF transfer integrals must be compared to the previously published electron coupling evaluations with great care. The usual evaluation of these terms relies on the avoided crossing of two eigenstates that are assumed to result from the mixing of the donor (D) and acceptor (A) valence-bond states that are not analytically explicited. The calculated energy difference ΔE can be obtained from a calculation on the whole D−A system, at any theoretical level of approximation (see, for example, ref 51):

$$\Delta E = 2\frac{\sqrt{\left(\frac{E_D - E_A}{2}\right)^2 + H_{DA}^2 - H_{DA}S_{DA}(E_D + E_A) + E_D E_A S_{DA}^2}}{1 - S_{DA}^2} \tag{13}$$

where S_{DA} is the overlap between the donor/acceptor states involved in the transfer.

In the Hartree−Fock approximation, ΔE is generally approximated by the dimer splitting formula

$$\Delta E = \epsilon_{HOMO} - \epsilon_{HOMO-1} \tag{14}$$

where ϵ_{HOMO} and ϵ_{HOMO-1} are the HF energies of the frontier orbitals of the neutral system. Beyond the HF approximation, ΔE must be related to the difference of the total energies for the two eigenstates. The electron coupling $T_{DA}$is defined when E_A and E_D are set to be identical so that ΔE is minimum.

$$\Delta E_{min} = 2T_{DA} = 2\frac{H_{DA} + E_D S_{DA}}{1 - S_{DA}^2} \tag{15}$$

T_{DA} can thus be calculated as an energy difference when A and D are degenerate.

As shown in eq 8, the VB/HF transfer integral is defined as the coupling matrix elements between two VB configurations involved in the electron transfer:

$$t = H_{DA} \tag{16}$$

In the VB/HF scheme, the A and D valence bond configurations are precisely defined and the matrix element H_{DA} is explicitly calculated. The orthogonality of the VB determinants (eq 4) thus leads to

$$\Delta E = 2\sqrt{\left(\frac{E_D - E_A}{2}\right)^2 + H_{DA}^2} \tag{17}$$

The VB/HF energies E_A and E_D can be calculated exactly. The detailed calculation of these necessary diagonal matrix elements will be adressed in a forthcoming paper. When the two states are degenerate, it follows that

$$\Delta E_{min} = 2T_{DA} = 2H_{DA} \tag{18}$$

The VB/HF and dimer splitting values for ΔE have been calculated for various homogeneous nucleosides in the standard

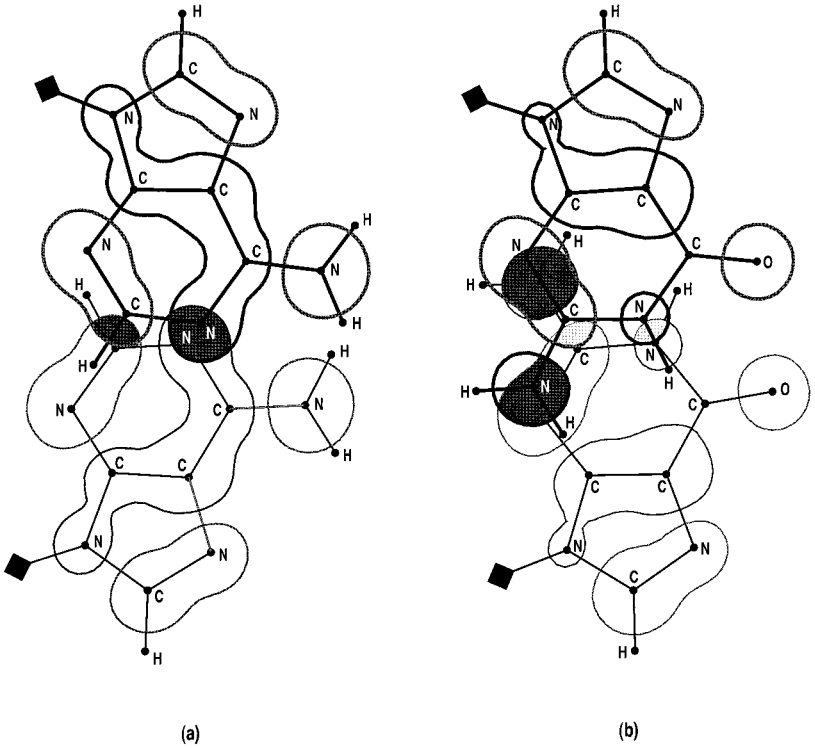


Figure 3. Overlapping orbitals in the interstrand nucleoside pairs 3′-AA-3′ (a) and 3′-GG-3′ (b). Constructive and destructive interferences are indicated schematically by dark and light areas, respectively. Bold molecules (3′) lie above the plane of the figure.

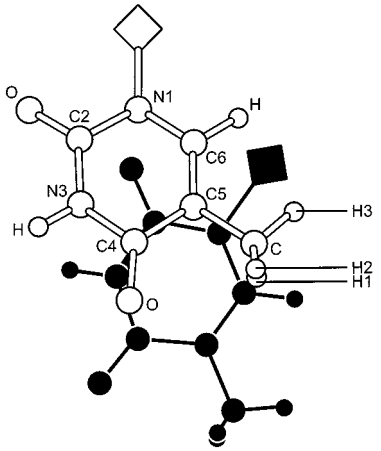


Figure 4. Pair of thymine-based nucleosides 5′-TT-3′. The white molecule lies above the plane of the figure. For clarity, only the atoms of this molecule are labeled.

TABLE 5: Transfer Integrals (meV) between a Pair of Thymine-based Nucleosides 5′-TT-3′ as a Function of the Dihedral Angle ϕ Related to the Orientation of the Methyl Group (each nucleoside defined as T + C_5H_8O + H)

ϕ	t^a	$t_{HOMO}{}^b$	$t_{HOMO}^{Me}{}^c$	$t_{HOMO}^{comp}{}^c$
0	43.6	44.8	25.4	19.4
20	41.5	42.8	23.3	19.5
40	31.1	32.3	12.8	19.5
60	24.2	25.4	5.9	19.5
80	25.9	27.1	7.7	19.4
100	35.0	36.2	16.8	19.4

[a] t is the total transfer integral. [b] t_{HOMO} is the contribution arising from the HOMOs of the two nucleosides (see eq 11). [c] The different contributions t_{HOMO}^{Me} and t_{HOMO}^{comp} are defined in eq 12.

geometry (rise = 3.38 Å and twist = 36°) within the AM1 parametrization. They are reported in Table 6. The small discrepancies are related to the actual computation procedures

TABLE 6: VB/HF and Dimer Splitting Values (meV) for ΔE for Various Pairs of Homogeneous Nucleosides (each nucleoside defined as B + C_5H_8O + H)[a]

	ΔE (VB/HF)	ΔE (dimer splitting)
AA	89	100
GG	511	511
TT	194	202
CC	289	268

[a] All calculations were performed at the standard geometry (rise = 3.38 Å and twist = 36°).

that involve (i) a self-consistent optimization of the MOs on the dimer calculation, which produces combinations of the fragments MOs that are not strictly equivalent to the VB/HF local MOs; (ii) distinct local MOs for the two VB configurations used in the VB/HF computation, depending on the net charge of the fragments; and (iii) the SCF left−right overpolarization of the dimer MOs, which may occur due to the lack of flexibility of the minimal basis employed in the semiempirical AM1 model.

The agreement is quite remarkable for the VB/HF procedure and rests upon the assumption of the nature of the VB states (single determinants, strictly local MOs, ZDO approximation), whereas the usual scheme relies on the accurate calculation of the dimer eigenstates, without explicitly defining the VB charge transfer states. The VB/HF methodology may thus be seen as a reverse handling of eq 13; it is the right side that is explicitly calculated so as to provide the energy gaps and in turn the electron coupling term, keeping in mind that the VB formalism also allows for the extraction of an effective Hamiltonian that can eventually be used for the accurate study of more complex supramolecular edifices, beyond the dimer, at a fraction of the computational cost.

The ab initio (HF) electronic couplings T_{DA} for intrastrand and interstrand hole transfer between nucleobase pairs in DNA have been reported by Voityuk et al.[24,25] using the dimer splitting formalism. The couplings related to nonsymmetrical structures correspond to $E_A \neq E_D$ in eq 13. To set E_A identical to E_D, a

homogeneous electric field was applied in the direction from the donor to the acceptor.[25,51−53] However, these coupling terms are not directly comparable with the VB/HF transfer integrals reported in Table 4 since the VB/HF fragment is defined as the complete nucleoside, while the full backbone is replaced by a methyl group in Voityuk's calculations. Nevertheless, a qualitative agreement is found in both calculations for the largest transfer integrals, which involve the intrastrand 5′-XT-3′ pairs and the pair 5′-GC-3′.

The VB/HF transfer integrals are more closely related to the electronic couplings derived from the direct calculation of the Fock matrix elements between the HOMO of the individual bases as proposed by Troisi and Orlandi.[23] The HF ab initio couplings between intrastrand close bases obtained by these authors include a mean-field electrostatic contribution and lie in the range 40−340 meV.

The VB/HF integrals are systematically smaller than the ab initio values. This difference between the two levels of approximation has been previously quoted in the domain of molecular solids involving $\pi-\pi$ interacting fragments, such as the organic conductors.[30] In these molecular crystals, the molecular planes are perpendicular to the stacking axis, and the distance between stacking molecules in the former is approximately 3.5 Å, while the rise is 3.4 Å in DNA. The largest transfer integrals in organic conductors are about 100 meV within the semiempirical VB/HF model, against 300 meV within an ab initio HF procedure involving an a posteriori localization of molecular orbitals.[54] From ab initio band structure calculations on nucleotide base stacks, Bogár and Ladik reported a bandwidth of about 400 meV, using a DZ polarized basis set.[55] This leads to ∼100 meV for the mean transfer integral and is in the same order of magnitude as the semiempirical values. Similar results were observed from DFT level band structure calculations on organic conductors[56] for which the DFT band structure was found to be very similar to extended Hückel calculations that are mostly used in this field. In the ab initio band structure calculations, cancelations of overlap related terms induce significantly reduced values for the transfer integral, compared to the bare dimer value. In this respect, the semiempirical values may be considered as prescreened, the parametrization supposedly counterbalancing the neglect of such long-range effects.

6. Conclusion and Outlook

The VB/HF model was used to calculate the transfer integrals between interacting fragments in canonical B-DNA strands. The calculations are consistent only when defining the fragments as the full nucleosides, i.e., when taking into account the base and the pentose group. The crude replacement of the backbone by a methyl group leads to contributions in the transfer integral with no chemical sense. Moreover, the orientation of the methyl group belonging to the thymine bases was shown to strongly affect the transfer integral, and thus to be an important geometrical parameter to be considered.

The largest transfer integrals obtained within the VB/HF formalism are found for intrastrand pairs involving the thymine base. The nucleosides built from purine bases lead to the largest interstrand transfer integrals, while the interactions between nucleosides built from pyrimidine bases are zero.

The transfer integrals depend essentially on the overlaps between the HOMOs of the interacting fragments. They are geometry sensitive quantities that must be carefully assessed in the prospect of including dynamical effects in the electron transport model for DNA.

Beyond the calculation of the transfer integrals that relate to the one-electron part of the model Hamiltonian, the full description of electron interactions in DNA strands requires the proper determination of intra- and interfragment Coulomb repulsion that will be addressed in a forthcoming publication.

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