In the high pH limit

$$[E_0] - 2[E_2] = \frac{(1 + [I]K)}{4K_d}\left(\left\{1 + \frac{8[E_0]K_d}{(1 + [I]K)^2}\right\}^{1/2} - 1\right)$$

Since $E_0 - 2E_2$ equals the sum of monomeric species, one may calculate $E_{0,app} = E_0 - 2E_2$ and proceed as in the case at the simple monomer calculation (eq 2). The program for pH's at which E, EH, and E_2 are significant calculates values of both $[H]C_H$ and K_{eff}.

Deoxyribonucleic Acid Replication. A Theoretical Study of Löwdin's Mechanism

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Abstract: Löwdin has proposed a mechanism, based on the stability of the DNA "replication plane," to explain the exclusion of rare tautomeric forms of nucleotide bases from double-stranded DNA. A quantitative theoretical test of this mechanism was carried out using a simple electrostatic model to compute the stability of replication planes. Atomic charges used in the model were obtained by adding π charges calculated by the Pariser–Parr–Pople method to σ charges from Del Re calculations. The model does predict the proper degree of incorporation of adenine and thymine rare forms, but fails for the rare forms of guanine and cytosine. The model further predicts the ratio of bromouracil to thymine incorporation to be 0.2 in agreement with the experimental value of 0.23.

Very early Watson and Crick[1] suggested that DNA replication might take place as a result of the unwinding of the two strands of an original DNA molecule and the synthesis of new strands using the old as templates. In particular, they suggested that the separated original strands would be freely exposed to the environment, and that each of the new strands would grow independently of the other, extending itself by another nucleotide unit only after the correct complementary nucleoside triphosphate happened to drift into place.

However, there is a difficulty with this simple mechanism. In the normal DNA double strand, the nucleotide base guanine (G) is paired with cytosine (C) and thymine (T) with adenine (A). Each of these four is in tautomeric equilibrium with a rare form as shown in Figure 1, and each rare form has the necessary hydrogen bonding and steric requirements to fit into the DNA double helix in the pairs: T–G*, A–C*, G–T*, and C–A* (where the asterisk denotes the rare tautomeric form). Incorporation of rare forms leads to mutations, and if the relative rates of incorporation were simply in proportion to their concentrations in the environment of the separated DNA strand, then the rate of mutation predicted from the tautomerization equilibrium constants[2,3] would be at least 10^3 times as great as observed.[4]

To account for the extra exclusion of the rare forms, Löwdin[5–8] proposed a mechanism in which new strands are built onto the old as they separate (Figure 2). The "replication plane," a cross section through the DNA helix at the point of separation and new growth, is shown schematically in Figure 3. Replication takes place by rotation of the two original strands to expose the hydrogen-bonding areas of the bases (I to II in Figure 3), followed by addition of new bases from the environment (III in Figure 3), and completed by separation of new pairs of strands. Löwdin suggests that rate of incorporation of rare tautomers is governed by the relative stability of the various sets of four bases in the replication plane (III in Figure 3). A drawing (see figures on p 183 of ref 7, but note that the labels of the first and third are interchanged) shows that one hydrogen bond in the set of four normal bases is replaced by a repulsive interaction, either between two protons or between two lone pairs, if a normal base is replaced by a correct rare form. This interaction is between daughter helices, not between base pairs within a daughter helix.

The present paper provides a quantitative test of Löwdin's proposal. A simple quantum mechanical model is set up, and the relative stability of the various four-base replication planes is calculated. As a further check, the rate of incorporation is computed for bromouracil, a molecule which has been found experimentally to take the place of thymine.

Computational Methods

The model adopted assumes that each molecule can be represented as a system of point charges located at the nuclear positions. The interaction energy for a four-base system in a particular configuration is obtained by summing the Coulomb interactions between the sets of point charges, having taken care that no van der Waals contact distances between point charges on different molecules are violated. Hydrogen bonds are allowed to reach a minimum length of 2.90 Å.

(1) J. D. Watson and F. H. C. Crick, *Nature (London)*, **171**, 737, 964 (1953).
(2) A. K. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962); 3046 (1963).
(3) G. W. Kenner, C. B. Reese, and A. R. Todd, *ibid.*, 855 (1955).
(4) E. J. Freese, *J. Theoret. Biol.*, **3**, 82 (1962).
(5) P. O. Löwdin, Technical Note No. QB 7, Uppsala Quantum Chemistry Group, Uppsala University, Sweden, 1963.
(6) P. O. Löwdin, *Biopolymers Symp.*, 1, 161 (1964).
(7) P. O. Löwdin in "Electronic Aspects of Biochemistry," B. Pullman, Ed., Academic Press, New York, N. Y., 1964, p 174.
(8) P. O. Löwdin, Technical Note No. QB 33, Uppsala Quantum Chemistry Group, Uppsala University, Sweden, 1966.

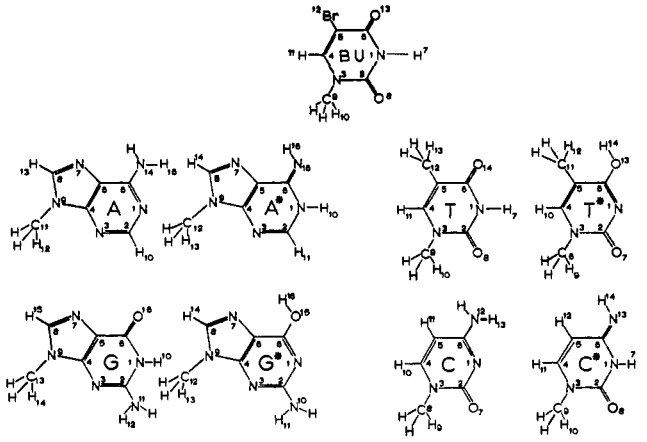


Figure 1. Tautomeric equilibria of nucleotide bases in normal DNA. The asterisk indicates the rare form. Numbering systems used for the bases and for *N*-methylbromouracil are also shown.

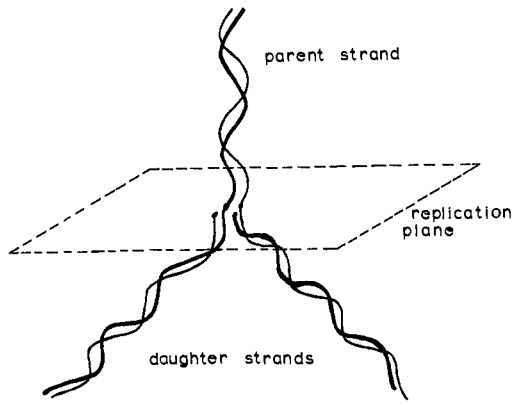


Figure 2. Replicating DNA molecule.

The point charges were obtained by combining separately calculated π and σ charges. The π charges were calculated by the Pariser–Parr–Pople (PPP) method,[9,10] while the Del Re procedure was used for σ charges.[11] The calculations were made on the 9-methyl derivatives of the purine bases and on the 3-methyl derivatives of the pyrimidines, since no specific role was postulated for the ribose and phosphate groups.

One might hesitate to use such a crude model, especially since the hydrogen bond is not purely electrostatic,[12] except that Nash and Bradley[13] have found it to give good results in a study of base pairs. These authors calculated the interaction energies between all possible pairs of A, T, C, and G in all possible coplanar orientations. They found several deep potential minima for each case, and these corresponded to stable orientations of the two molecules as determined by X-ray studies of cocrystallization products and of synthetic and natural polynucleotides. In addition, the relative depths of Nash and Bradley's minima are in line with the general feeling that cocrystallization products are more stable than the polynucleotides.

(9) R. Pariser and R. G. Parr, *J. Chem. Phys.*, 21, 466, 767 (1953).
(10) J. A. Pople, *Trans. Faraday Soc.*, 49, 1375 (1953).
(11) G. Del Re, *J. Chem. Soc.*, 4031 (1958).
(12) C. A. Coulson, *Res. Sci. Its Appl. Ind.*, 10, 149 (1957).
(13) H. A. Nash and D. F. Bradley, *J. Chem. Phys.*, **45**, 1380 (1966).

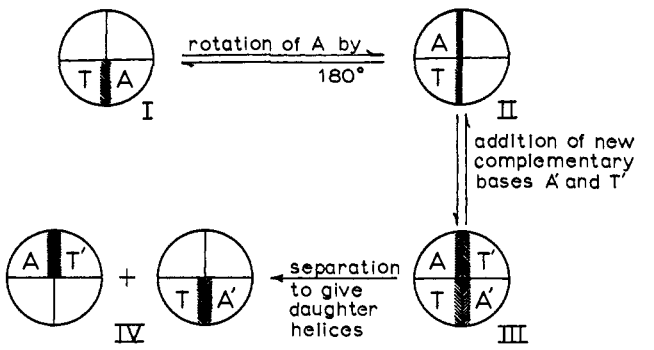


Figure 3. Replication plane of DNA. The hatching denotes the template face of each nucleotide base across which bonding to the complementary strand takes place.

Pullman, Claverie, and Caillet[14] carried out a series of similar calculations and found that the monopole-induced dipole and London dispersion contributions to the stabilization energy are considerably smaller than the Coulomb contribution, and that they vary little from one system to another. In a recent review article, Pullman and Pullman[15] list a multitude of experimental findings in agreement with conclusions drawn from these calculated results. In view of these successes on quite similar systems, we might hope that the simple electrostatic model will provide a useful test of Löwdin's proposal.

π-Electron Calculations. Several groups have calculated π-electron properties of the normal tautomeric forms of the purine and pyrimidine bases using the PPP method, but with rather widely varying schemes for approximating the parameters required. During the course of our work the only π-electron charges available for the rare tautomeric forms were those from the less sophisticated Hückel method. PPP results have since been published by Kunii and Kuroda[16] for the rare forms and we have checked our charges against these.

We have used the variation of the PPP method due to Nagata, Imamura, Tagashira, and Kodama[17] primarily because it can be applied in a consistent manner to the rare forms without requiring the development of special parameter values for the enol and imine groups.

One-center Coulomb integrals were taken directly from Table I of ref 17. Two-center Coulomb integrals were calculated using an approximation due to Pariser and Parr.[9] Let R_{pq} be the separation in ångströms of the centers p and q. Then

$$(pp|qq) = \tfrac{1}{2}[(pp|pp) + (qq|qq)] + aR_{pq} + bR_{pq}^2 \quad (1)$$

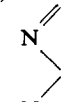
where a and b (Table I) are obtained by equating (1) to a charged sphere model at 2.80 and 3.70 Å.

Core coulomb integrals were obtained using the Goeppert-Mayer–Sklar approximation with neglect of penetration integrals

$$I_{pp} = W_p - \Sigma_q(pp|qq) \quad (2)$$

(14) B. Pullman, P. Claverie, and J. Caillet, *Proc. Nat. Acad. Sci. U. S.*, **55**, 904 (1966).
(15) A. Pullman and B. Pullman, *Advan. Quantum Chem.*, **4**, 267 (1968).
(16) T. L. Kunii and H. Kuroda, Report of the Computer Center, University of Tokyo, Vol. 1, 1968, p 227.
(17) C. Nagata, A. Imamura, Y. Tagashira, and M. Kodama, *Bull. Chem. Soc. Jap.*, **38**, 1638 (1965).

Table I. The Parameters a and b in Equation 1

p	q	a	b
		−3.006	0.2744
		−3.346	0.3233
		−4.656	0.5233
		−4.238	0.4578
		−6.087	0.7422
		−3.676	0.3722
		−4.995	0.5722
		−4.576	0.5067
		−6.422	0.7900
		−6.309	0.7733
		−5.890	0.7078
		−7.733	0.9903
		−5.470	0.6422
		−7.313	0.9248

with W_q from Table I of ref 17 and (pp|qq) from eq 1. Core resonance integrals were approximated by

$$I_{pq} = \eta S_{pq} \tag{3}$$

where S_{pq} is the overlap integral between π atomic orbitals p and q, and the constant η has the empirically chosen value −12.65.

Molecular coordinates for the normal tautomeric forms were derived from the bond lengths and angles given by Spencer.[18] For the rare tautomeric forms, it was assumed that ring atoms and atoms not involved in the tautomerization remained unchanged from those of the normal tautomeric forms. To obtain C–N and C–O bond lengths for the imine and enol groups, Hückel calculations were carried out on the rare forms giving the mobile bond orders and the approximate bond lengths in Table II.

Table II. C–N and C–O Bond Lengths for Imine and Enol Groups Predicted by Hückel Calculations

Base	Bond	Calcd mobile bond order	Predicted length, Å
A*	C–N	0.690	1.323
C*	C–N	0.704	1.321
G*	C–O	0.323	1.336
T*	C–O	0.334	1.333

(18) M. Spencer, *Acta Crystallogr.*, 12, 59 (1959).

A computer program by Janiszewski[19] was used with modifications to follow Nagata's[17] method. Listings of this and all other programs used may be found in the Ph.D. Thesis of G. E. Bass.[20]

σ-Electron Calculations. In the Del Re method one starts, as in the Hückel approach, with the coulomb integral for atom i and resonance integral between atoms i and j given by

$$\alpha_i = \alpha^0 + \delta_i\beta^0$$
$$\beta_{ij} = \epsilon_{ij}\beta^0 \tag{4}$$

where α^0 and β^0 are constants which do not vary from one atom or bond type to another. In fact charge distributions turn out to be independent of α^0 and β^0. The parameters δ_i are obtained from the solution of a set of linear equations

$$\delta_i = \delta_i^0 + \sum_j \gamma_{ij}\delta_j \tag{5}$$

where the sum goes over all atoms j bonded to i. The parameters ϵ_{ij}, δ_i^0, and λ_{ij} are determined empirically and carried from one molecule to another. Then the charge on atom i due to the bond to atom j is

$$q_{ij} = f_{ij}(1 + f_{ij}^2)^{-1/2} \tag{6}$$

$$f_{ij} = (\delta_j - \delta_i)/2\epsilon_{ij} \tag{7}$$

and the total charge on atom i is obtained by summing the q_{ij} over all atoms j bonded to i.

Del Re[11] determined a set of parameters for saturated molecules by equating calculated and experimental dipole moments. Berthod and Pullman[21] obtained parameters for conjugated compounds in a similar way. In addition to these we needed parameters for the imine group in the rare bases and for Br in bromouracil.

Consider the δ_i equations for the imine group >C=NH

$$\delta_C = \delta_C^0 + \gamma_{CN}\delta_N + \dots$$
$$\delta_N = \delta_N^0 + \gamma_{NC}\delta_C + \gamma_{NH}\delta_H \tag{8}$$
$$\delta_H = \delta_H^0 + \gamma_{HN}\delta_N$$

The carbon and nitrogen bonds are considered to be essentially sp^2 hybrids. It was the contention of Berthod and Pullman that δ_i^0 values for a given atom should reflect only changes in hybridization. Thus it was assumed that δ_C^0 and δ_N^0 for the imine group are the same as the values reported by Berthod and Pullman and that δ_H^0 has the value given by Del Re. Further, since Berthod and Pullman found it unnecessary to change γ_{ij} values on going from saturated to unsaturated systems, we used Del Re's values of γ_{NC}, γ_{CN}, γ_{NH}, and γ_{HN}. The only additional parameters required are ϵ_{CN} and ϵ_{NH}. Del Re assumed that ϵ_{ij} depends only upon the bond ij and is independent of the surroundings. Since the C–N bond is an ordinary double bond between sp^2-hybridized atoms, the ϵ_{CN} value reported by Berthod and Pullman for unsaturated systems was used.

Fixing the parameter ϵ_{NH} was more difficult. No molecules containing imine groups were found for

(19) T. Janiszewski, POPLE-PI, Program 76, Quantum Chemistry Program Exchange, Indiana University.
(20) G. E. Bass, Ph.D. Thesis, Vanderbilt University, Jan 1970.
(21) H. Berthod and A. Pullman, *J. Chim. Phys.*, 62, 942 (1965).

which good dipole moment measurements had been made. As an alternative it was decided to determine ϵ_{NH} to reproduce the charge distribution from the *ab initio* calculation by Schaad and Kinser[22] on *trans*-diimide, N_2H_2. A Mulliken population analysis[23] of the N_2H_2 wave function in Table XII of ref 22 gives a charge of -0.0834 au on each N and $+0.0834$ au on each H. A plot of calculated charge *vs.* ϵ_{NH} then gave $\epsilon_{NH} = 1.75$.

Bromine parameters were determined to give best agreement between calculated and experimental dipole moment for CH_3Br, CH_2Br_2, $CHBr_3$, and C_2H_5Br. This gave $\delta_{Br}^0 = 0.29$, $\gamma_{CBr} = 0.22$, $\gamma_{BrC} = 0.45$, and $\epsilon_{CBr} = 0.50$. To check that these values are also valid for aromatic bromides, the calculated dipole moment of bromobenzene was found to be 1.88 D in reasonable agreement with experimental gas-phase measurements of 1.70–1.79 D.[24] A referee has pointed out a note by Nash, Grossman, and Bradley[25] in which they obtain the values 0.30, 0.20, 0.40, and 0.60 (in the order above) for the bromine Del Re parameters, in good agreement with ours.

Calculated π and σ charges are shown in Tables III–VII.

Table III. Calculated Charges[a] on *N*-Methyladenine

	Normal form			Rare form		
Atom[b]	σ charge	Electrons contributed to π system	π charge	σ charge	Electrons contributed to π system	π charge
1	−0.283	1	−1.372	−0.427	2	−1.715
2	0.202	1	−0.713	+0.186	1	−0.823
3	−0.282	1	−1.380	−0.284	1	−1.317
4	0.240	1	−0.893	+0.240	1	−1.009
5	0.166	1	−1.074	+0.168	1	−1.007
6	0.204	1	−0.782	+0.273	1	−0.810
7	−0.293	1	−1.316	−0.293	1	−1.273
8	0.169	1	−0.868	+0.169	1	−0.893
9	−0.294	2	−1.727	−0.294	2	−1.711
10	0.070	0	0	+0.193	0	0
11	−0.052	0	0	+0.069	0	0
12	0.050	0	0	−0.052	0	0
13	0.067	0	0	+0.050	0	0
14	−0.511	2	−1.875	+0.067	0	0
15	0.224	0	0	−0.242	1	−1.441
16				+0.078	0	0

[a] The charges are listed in atomic units. The net total charge on atom 1 in the normal form equals, for example, $(-0.283 + 1 - 1.372) \times 4.803 \times 10^{-10}$ esu. [b] See Figure 1 for the numbering system.

Search for Best Replication Plane Geometry. We had originally planned to carry out an automatic energy optimization of the replication plane geometry by use of a "pattern search" computer program.[26] This failed because the energy surface contains valleys corresponding to hydrogen bond lengths of 2.90 Å, and the program used was incapable of moving along a valley to its minimum. The alternative of systematically computing the entire energy contour would require a plot in nine dimensions (two coordinates for

Table IV.[a] Calculated Charges on *N*-Methylthymine

	Normal form			Rare form		
Atom	σ charge	Electrons contributed to π system	π charge	σ charge	Electrons contributed to π system	π charge
1	−0.438	2	−1.783	−0.279	1	−1.373
2	0.267	1	−0.717	+0.285	1	−0.679
3	−0.306	2	−1.795	−0.304	2	−1.743
4	0.044	1	−0.959	+0.045	1	−0.905
5	0.009	1	−1.040	+0.017	1	−1.097
6	0.181	1	−0.709	+0.245	1	−0.739
7	0.191	0	0	−0.053	1	−1.547
8	−0.055	1	−1.507	−0.052	0	0
9	−0.052	0	0	+0.050	0	0
10	0.050	0	0	−0.059	0	0
11	0.059	0	0	−0.103	0	0
12	−0.104	0	0	+0.041	0	0
13	0.041	0	0	−0.437	2	−1.919
14	−0.067	1	−1.489	+0.305	0	0

[a] See footnotes to Table III.

Table V.[a] Calculated Charges on *N*-Methylguanine

	Normal form			Rare form		
Atom	σ charge	Electrons contributed to π system	π charge	σ charge	Electrons contributed to π system	π charge
1	−0.431	2	−1.763	−0.271	1	−1.430
2	0.299	1	−0.807	+0.318	1	−0.721
3	−0.280	1	−1.412	−0.278	1	−1.424
4	0.240	1	−0.976	+0.241	1	−0.870
5	0.163	1	−1.048	+0.170	1	−1.076
6	0.192	1	−0.707	+0.256	1	−0.762
7	−0.294	1	−1.264	−0.292	1	−1.310
8	0.169	1	−0.911	+0.169	1	−0.875
9	−0.294	2	−1.711	−0.294	2	−1.730
10	0.192	0	0	−0.505	2	−1.868
11	−0.506	2	−1.857	+0.226	0	0
12	0.225	0	0	−0.052	0	0
13	−0.052	0	0	+0.050	0	0
14	0.050	0	0	+0.067	0	0
15	0.067	0	0	−0.435	2	−1.934
16	−0.065	1	−1.544	+0.305	0	0

[a] See footnotes to Table III.

Table VI.[a] Calculated Charges on *N*-Methylcytosine

	Normal form			Rare form		
Atom	σ charge	Electrons contributed to π system	π charge	σ charge	Electrons contributed to π system	π charge
1	−0.286	1	−1.383	−0.430	2	−1.762
2	0.284	1	−0.679	+0.268	1	−0.716
3	−0.304	2	−1.750	−0.305	2	−1.798
4	0.048	1	−0.906	+0.048	1	−0.975
5	−0.032	1	−1.105	−0.029	1	−1.034
6	0.196	1	−0.761	+0.265	1	−0.816
7	−0.053	1	−1.559	+0.193	0	0
8	−0.052	0	0	−0.055	1	−1.523
9	0.050	0	0	−0.052	0	0
10	0.059	0	0	+0.050	0	0
11	0.055	0	0	+0.059	0	0
12	−0.512	2	−1.857	+0.055	0	0
13	0.224	0	0	−0.243	1	−1.377
14				+0.078	0	0

[a] See footnotes to Table III.

(22) L. J. Schaad and H. B. Kinser, *J. Phys. Chem.*, 73, 1901 (1969).
(23) R. S. Mulliken, *J. Chem. Phys.*, 23, 1833 (1955).
(24) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963, p 173.
(25) H. A. Nash, S. R. Grossman and D. F. Bradley, *Nature (London)*, 219, 370 (1968).
(26) D. J. Wilde, "Optimum Seeking Methods," Prentice-Hall, Englewood Cliffs, N. J., 1964, p 145.

Table VII.[a] Calculated Charges on *N*-Methylbromouracil

Atom	σ charge	Electrons contributed to π system	π charge
1	−0.434	2	−1.783
2	+0.268	1	−0.717
3	−0.301	2	−1.795
4	+0.070	1	−0.959
5	+0.110	1	−1.040
6	+0.205	1	−0.707
7	+0.192	0	0
8	−0.055	1	−1.507
9	−0.052	0	0
10	+0.050	0	0
11	+0.061	0	0
12	−0.150	0	0
13	−0.062	1	−1.489

[a] See footnotes to Table III.

each of three molecular centers and one angle of rotation for each of the three molecules). To reduce this to manageable proportions, we assumed, as does Löwdin, that in the replication plane each pair of bases which forms a daughter DNA helix is in the same geometry as in the daughter helix. These were computed, following Nash and Bradley,[13] to be those which minimized the Coulomb energy of the pair (Table VIII).

Table VIII. Base Pair Interaction Energies

System	E, kcal/mol
A–T	−8.2
G–C	−23.2
G–T*	−22.4
A*–C	−18.6
G*–T	−11.9
A–C*	−8.6

The best relative orientation of one pair to another was then determined in the same way, thus fixing the geometry of the replication plane.

Results

Consider again the replication process in Figure 1. If I and II are in equilibrium and the rate-determining step is the separation of III to IV, then the rate of replication is given by

$$k[\mathrm{III}] = kK[\mathrm{I}][\mathrm{A}][\mathrm{T}] \tag{9}$$

where k is the rate constant for the step III → IV and K is the equilibrium constant for I + A + T ⇄ III. In the same way the rate of replication with T replaced by C* is

$$k^*[\mathrm{III}^*] = k^*K^*[\mathrm{I}][\mathrm{A}][\mathrm{C}^*] \tag{10}$$

Assuming a steady-state concentration of replication planes gives for the ratio of C* to T incorporation

$$\frac{N_{C^*}}{N_T} = \frac{k^*K^*[C^*]}{kK[T]} \tag{11}$$

If all bases are present in the environment in roughly the same concentration, the ratio [C*]/[T] equals the tautomerization equilibrium K_{taut} which has the value 10^{-4}–10^{-5}. If one may assume further that the two rate constants k and k^* are equal

$$\frac{N_{C^*}}{N_T} = K_{taut}\frac{K^*}{K} = K_{taut}e^{-(\Delta E^* - \Delta E)/RT} \tag{12}$$

where ΔE and ΔE^* are our computed replication plane energies

$$\begin{aligned} 2\mathrm{A} + 2\mathrm{T} &\xrightarrow{\Delta E} \mathrm{III} \\ 2\mathrm{A} + \mathrm{T} + \mathrm{C}^* &\xrightarrow{\Delta E^*} \mathrm{III} \end{aligned} \tag{13}$$

Computed replication plane energies and rare form incorporation ratios N^*/N using $RT = 0.6$ (*i.e.*, $T = 30°C$) and $K_{taut} = 10^{-4}$ are shown in the first columns of Table IX. In order that Löwdin's mechanism explain

Table IX. Results for Minimum Energy Replication Planes

System	$\Delta\epsilon$, kcal/mol	N^*/N
$\binom{\mathrm{TA}}{\mathrm{G^*T}}$	−20.1	2.4×10^{-3}
$\binom{\mathrm{TA}}{\mathrm{AC^*}}$	−17.7	4.3×10^{-5}
$\binom{\mathrm{TA}}{\mathrm{AT}}$	−18.2	
$\binom{\mathrm{CG}}{\mathrm{GT^*}}$	−54.2	5.0×10^{-11}
$\binom{\mathrm{CG}}{\mathrm{A^*C}}$	−54.0	3.6×10^{-11}
$\binom{\mathrm{CG}}{\mathrm{GC}}$	−62.9	

rare form exclusion satisfactorily, N^*/N must be in the range 10^{-8}–10^{-11}. This is found to hold in the case of rare form competition with G and C. But the mechanism does not provide enough extra exclusion for rare forms competing with A and T. In fact, the replication plane with one A replaced by G* is computed to be more stable than the normal plane.

Several variations of this mechanism were tried. One might first ask whether pair stability in the daughter strands, rather than stability of the replication plane, might explain the rare form exclusion. The pair energies in Table VIII show that it does not. Both A–C* and G*–T are computed to be more stable than A–T. G–T* and A*–C are less stable than G–C, but not enough so to account for the observed extent of exclusion. Löwdin's mechanism does work somewhat better than this simpler possibility.

A third possibility is that the size of the replication plane is determined by some external agent—an enzyme perhaps—rather than by the mutual interaction of the bases alone. Figures 4 and 5 show the lowest energy configurations of the two normal replication planes. In both drawings the upper base pair becomes part of one daughter helix and the lower pair of the other. It is seen that the A–T replication plane is larger due to a greater separation between upper and lower pairs. Taking this size for the A–T plane to be common to all does not change the results of Table IX for the competition of G* and C* with A and T. However, the ratio N^*/N for the inclusion of T* and A* increases from about 10^{-11} to about 10^{-8}. Further uniform expansion of the fixed replication plane size would not be expected to change the relative energies of the replication

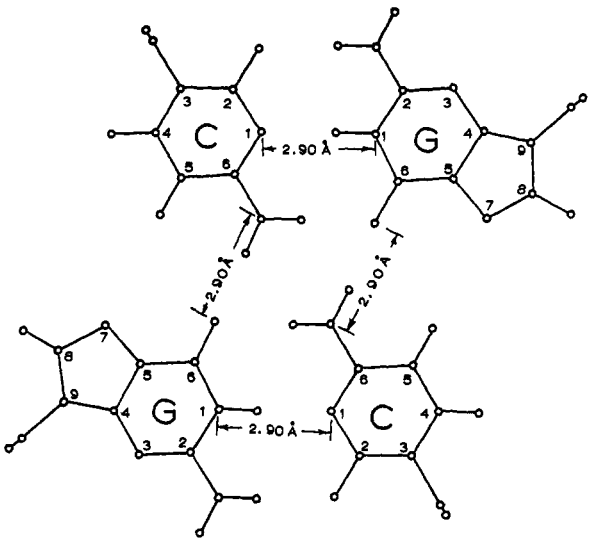


Figure 4. Lowest energy configuration for the G–C replication plane.

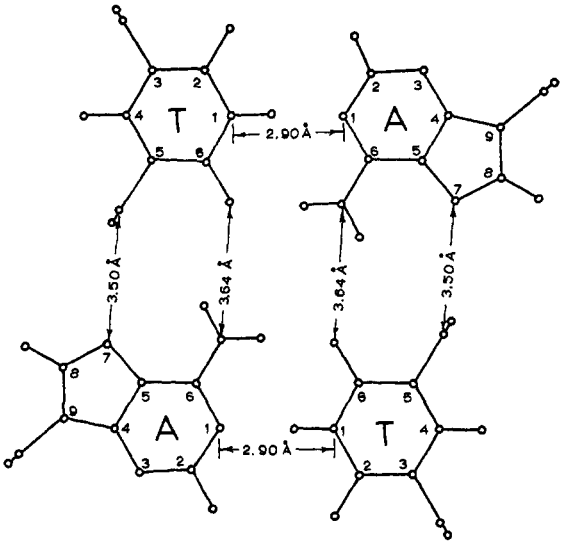


Figure 5. Lowest energy configuration for the A–T replication plane.

planes, but rather to bring all energies closer together, thereby diminishing any stabilization advantage that one four-base system might have over another.

The failure of Löwdin's mechanism centers primarily on the behavior of the A–T systems. One might ask whether there is *any* geometry for these systems which will lead to the required exclusion of rare forms. The answer appears to be that there is not. The relative orientation of one base pair to the other is specified by two coordinates of the center of one pair relative to the other and the angle α (Figure 5) which fixes the rotation around the center. Figure 6 shows the stabilization energy ΔE *vs.* α for the

$$\binom{TA}{AT} \text{ and } \binom{T\ A}{G^*T}$$

systems. For no value of α is the normal system more stable than the one containing G*.

Although our model is crude, there seem to be qualitative differences between A–T and G–C replication planes which account for the failure of Löwdin's mechanism in the A–T cases. Comparing Figures 4 and 5 shows that the separation between upper and lower base pairs is greater for the A–T than for the G–C systems. This is necessary to keep the methyl group on T sufficiently separated from the opposing nitrogen of the five-membered ring of A. This forces the N–H···O hydrogen bonds between the upper and lower pairs to be lengthened from the assumed normal 2.90 to about 3.64 Å. In the G–C systems no such expansion is necessary. Thus the interaction between upper and lower pairs is weakened and discrimination between the various four-base systems lowered in the A–T cases.

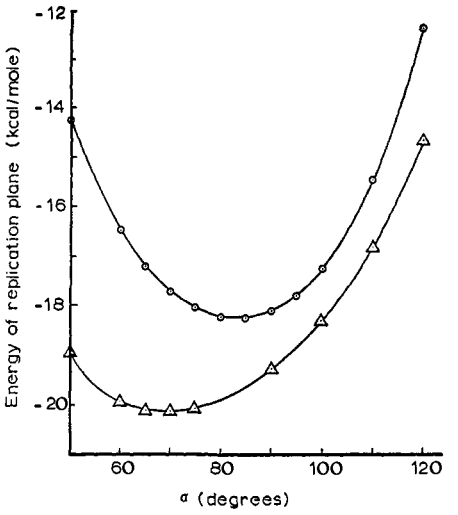


Figure 6. Replication plane energy as a function of base pair orientation. Circles are for the normal A–T replication plane. Triangles are for this plane with one A replaced by G*. Referring to Figures 1 and 5, α is the angle formed by a line from atom 11 in the upper left T to atom 7 in the upper right A to atom 11 in the lower right T.

A second qualitative difference between G–C and A–T systems concerns the drawing (p 183, ref 7) on which Löwdin bases his mechanism. Although the upper and lower base pairs in the G–C replication plane (Figure 4) are aligned so that the hydrogen bonds form a parallelogram, in the A–T plane (Figure 5) they are not. The lower A–T pair would have to be shifted to the right to obtain Löwdin's drawing. The result of this shift is that the interactions between upper and lower base pairs are weaker than described by Löwdin and rare form exclusion is lower for the A–T planes. Furthermore, the G*–T base pair in particular involves the formation of three hydrogen bonds whereas the A–T pair it replaces involves only two. This, in large part, explains the finding that the normal A–T replication plane is less stable than the one containing G*. It seems unlikely that the difficulties would be removed by a more sophisticated calculation.

On the other hand, we do find that Löwdin's mechanism does account for the observed rate of bromouracil (BU) incorporation. Hackett and Hanawalt[27] have found that BU will replace T in the first round of replication. With [BU] = [T] = 0.5×10^{-6} *M* at 37°, $N_{BU}/N_T = 0.23$. This level of incorporation would require that the normal A–T replication plane be about 1

(27) P. Hackett, Jr., and P. Hanawalt, *Biochim. Biophys. Acta*, 123, 356 (1966).

kcal/mol more stable than the plane with T replaced by BU. Using the methods above we find the best

$$\begin{pmatrix} A & T \\ BU & A \end{pmatrix}$$

plane to have a stabilization energy of -17.3 kcal/mol compared with the best

$$\begin{pmatrix} AT \\ TA \end{pmatrix}$$

energy of -18.2 kcal/mol. The difference gives $N_{BU}/N_T = \exp[-0.9 \times 10^3/1.987 \times 310] = 0.2$, in excellent agreement with experiment.

Finally, two related calculations should be mentioned. Although no details are given, Rein, McMullen, and Pollak[28] have calculated the energy of normal replication planes. In both cases they find considerable stabilization energy. Replication planes incorporating rare tautomeric forms were not considered. MacIntyre and Löwdin[29] have studied replication planes containing pairs of rare forms A*–T* and C*–G*. These might arise in the normal DNA strand by simultaneous proton tunneling in the base pair,[30] as well as by incorporation of two rare bases from the environment. Such replication planes were found to be less stable than the normal forms.

Acknowledgment. The authors are grateful to the du Pont and Monsanto Companies for Fellowships to G. E. B. and to Vanderbilt University for computing support.

(28) R. Rein, A. I. McMullen, and M. Pollack, Abstract No. 138, Second International Biophysics Congress, Vienna, 1966.

(29) W. M. MacIntyre and P.-O. Löwdin, *Int. J. Quantum Chem.*, 2S, 207 (1968).

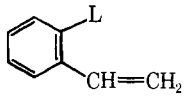
(30) P.-O. Löwdin, *Advan. Quantum Chem.*, 2, 286 (1965).

Communications to the Editor

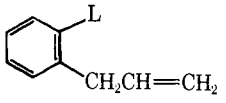
Formation of Gold(III)–Carbon σ Bonds in the Bromination of Linear Gold(I) Complexes of Olefinic Tertiary Phosphines

Sir:

The ligands *o*-styryldimethylarsine, *o*-CH_2=$CHC_6H_4As(CH_3)_2$ (SA; **1a**), and (*o*-allylphenyl)dimethylarsine, *o*-CH_2=$CHCH_2C_6H_4As(CH_3)_2$ (AA; **2a**) form both olefin-coordinated chelate complexes such as $PtBr_2$ligand and monodentate As-coordinated complexes of formula $PtBr_2(ligand)_2$.[1,2] These molecules have two potential sites for reaction with an electrophile such as bromine, the metal[3] and the double bonds.



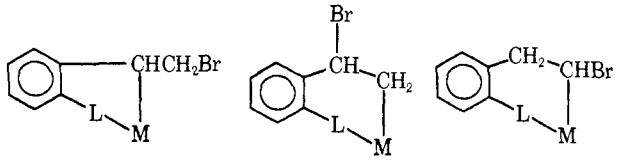
1a, L = $As(CH_3)_2$ (SA)
b, L = $P(C_6H_5)_2$ (SP)



2a, L = $As(CH_3)_2$ (AA)
b, L = $P(C_6H_5)_2$ (AP)

Addition of 1 equiv of bromine to $PtBr_2(SA)_2$ and $PtBr_2(AA)_2$, respectively, gives complexes of general formula $PtBr_4(ligand)_2$ which have been formulated on the basis of chemical and spectroscopic evidence[1] as octahedral tribromoplatinum(IV) complexes containing a Pt–C σ bond to one of the ortho substituents, *i.e.*, one bromine atom has added to the metal and the other has added to one of the double bonds. The precise structure of these complexes is unknown; *e.g.*, for $PtBr_4(SA)_2$ (**3**), there are three structural possibilities (I–III) for the chelate ring containing the Pt–C σ bond.

Prompted by the similarity between the chemistries of gold and platinum (especially the stability of their



I II III

alkyls), we have studied the halogenation of the linear gold(I) complexes of *o*-styryldiphenylphosphine, *o*-CH_2=$CHC_6H_4P(C_6H_5)_2$ (SP; **1b**) and (*o*-allylphenyl)-diphenylphosphine, *o*-CH_2=$CHCH_2C_6H_4P(C_6H_5)_2$ (AP; **2b**).

The linear P-coordinated complexes AuBr(SP) (**4**) and AuBr(AP) (**5**) react with bromine in benzene at room temperature to give yellow crystals of empirical formula $AuBr_3$(SP) (**6**) and $AuBr_3$(AP) (**7**), respectively, which are monomeric in $CHCl_3$. The characteristic signals due to the uncoordinated olefinic protons of **4** and **5** are absent from the proton nmr spectra of **6** and **7**, and the characteristic olefinic deformation frequencies which appear in the ir spectra of **4** and **5** are absent from the spectra of **6** and **7**. Thus, **6** and **7** cannot be formulated as planar tribromogold(III) complexes[4] containing monodentate P-bonded SP or AP. The only reasonable alternative is that they are planar dibromogold(III) complexes with an Au–C σ bond to the ortho substituent, and this is confirmed by a single-crystal X-ray study of both compounds.

Crystal Data for 6. Crystals from CH_2Cl_2 belonged to space group $P2_1n$, with $Z = 4$; $a = 8.59$, $b = 13.70$, $c = 17.91$ Å; $\beta = 97.3°$. Structure analysis was based on 1705 independent reflections (Pailred diffractometer, Mo Kα) for which $F_o^2/\sigma(F_o^2) \geq 3.0$; least-squares refinement was carried out to a discrepancy index of 0.06; esd's average 0.004 Å (Au–Br), 0.008 Å (Au–P), 0.03 Å (Au–C), and 0.04 Å (C–C).

(1) M. A. Bennett, J. Chatt, G. J. Erskine, J. Lewis, R. F. Long, and R. S. Nyholm, *J. Chem. Soc. A*, 501 (1967).

(2) M. A. Bennett, G. J. Erskine, and R. S. Nyholm, *ibid.*, 1260 (1967).

(3) The metal atom in planar platinum(II) complexes such as $PtCl_2[P(C_2H_5)_3]_2$ and $PtBr_2[AsCH_3(C_6H_5)_2]_2$ is halogenated to give octahedral tetrahalo complexes of the type $PtX_4(ligand)_2$ (X = Cl or Br): R. S. Nyholm, *ibid.*, 843 (1950); J. Chatt, *ibid.*, 2301 (1950).

(4) F. G. Mann and D. Purdie, *ibid.*, 1235 (1940).