SELECTIVE CHIRALITY – A CLOSER EXAMINATION

WILLIAM. A. BONNER

Department of Chemistry, Stanford University, CA 94305, U.S.A.

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Abstract. The recent suggestion (Root-Bernstein, 1982) that the homochirality of amino acids and sugars in the current biosphere may have originated as a result of novel organic 'selector molecules' is examined critically. It is concluded that such selector molecules are non-existent as described, and that their postulation is based on chemical and stereochemical misconceptions.

In a recent article provocatively entitled 'Selective Chirility [*sic*] and the Origins of Life' Root-Bernstein (1982) has argued that 'Despite 120 years of research into the origins of chirility [sic], – no solution has been found because the assumptions implicit in the problem statement are invalid'. Thus abiotic mechanisms (for a review cf. Bonner (1988)) involving potential asymmetric forces such as magnetism, electric fields, polarized light, parity non-conseration in weak interactions, catalysis or adsorption on asymmetric inorganic templates (e.g. quartz), chance 'aided by natural selection', or extraterrestrial agents all encounter serious fundamental objections and 'are logically flawed'. After then purporting to demonstrate the 'Flaws in Previous Statements of the Problem', he proposes a 'New Statement of Problem', suggesting that 'something other than asymmetric forces or aggregative chirility [*sic*] must be responsible for differentiating between enantiomers', and that this ''something' must not require asymmetric action for its own synthesis..'. Two 'novel solutions' to the dilemma are then advanced, each involving an *organic* 'selector molecule', a 'chemical combination... synthesized according to the accepted laws of physics and chemistry, but which is found chiefly in the vital realm in preference to the nonvital'. In view of Root-Bernstein's disparaging evaluation of all previous investigations concerned with the origins of chirality, and in view of the fact that several authors have cited his paper more recently (Blumenthal, 1984, 1985), (de Min and coworkers, 1988), (Pleasant and Ponnomperuma, 1984), (Portelli, 1987), we have felt it desirable to examine the potential existence and/or validity of Root-Bernstein's proposed 'selector molecules'.

The first suggested selector molecule is an 'achiral, asymmetric molecule' whose 'mirror image has the identical asymmetry as the original molecule' and is accordingly 'able to select between enantiomers due to its asymmetry; yet, lacking a complementary mirror image, would be specific for only one enantiomer'. Let us first examine these attributes ascribed to this selector molecule. An *achiral* molecule is one which is *not* chiral, that is, one which possesses one or more of the following symmetry elements; a center of symmetry, a plane of symmetry, or an alternating

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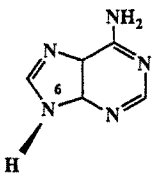
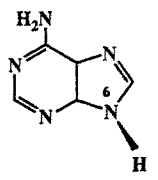
axis of symmetry. An *asymmetric* molecule is one which lacks any elements of symmetry. Thus an archiral molecule cannot possibly be asymmetric. It is equally impossible to have a mirror image of an asymmetric molecule which has 'the identical asymmetry as the original molecule'. Ignoring such logical inconsistencies, Root-Bernstein then suggests that a transparant clock face, visible from both sides (Thomas, 1980), is a model for such a molecule and argues that 'adenine with an asymmetric N' atom at position 6 (I), earlier suggested by Portelli (1981) is, in fact, such a molecule. The asymetric nitrogen, he maintains, would make such bases 'asymmetric yet achiral' and hence potentially 'capable of selecting between D and L isomers of ribose or deoxyribose'. Disregarding the fact that his planar clock model would apply only to a planar adenine molecule, which is clearly incapable of selecting between D and L isomers, Root-Bernstein then uses Portelli's illustration of asymmetric adenine (similar to I), which is quite obviously 3-dimensional. Thus the correct mirror image of the hypothetical asymmetric base I is not I, as Root-Bernstein implies, but rather II. The enantiomeric structures I and II indicate that such asymmetric bases, if they existed, would not constitute achiral structures at all but, like analogous compounds with an asymmetric carbon at position 6, would in fact be chiral.



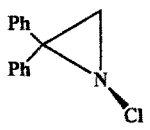
I



II

Leaving the above question of mirror symmetry aside, however, Root-Bernstein's principal error in proposing nucleotide bases such as I as capable of chiral interactions lies in the assumption (along with that of Portelli, 1981) that the nitrogen atom at position 6 can in fact be asymmetric. The barrier to inversion in trivalent amines is 6–7 kcal mol^{-1}, and it is even lower in cyclic π – electron systems, such as adenine, in which the lone electron pair on nitrogen is delocalized (Lehn, 1970). For optically active amines to exist at ambient temperature the barrier to inversion must be $\geq$ 23 kcal mol^{-1} (Kessler, 1970). Only in the highly constrained 3-membered rings of aziridines whose N-atoms contain strongly electronegative substituents, e.g. III, or in diaziridines, e.g. IV, is the inversion barrier large enough to permit the existence of optically active trivalent amines (Davis and Jenkins, Jr., 1984). For larger heterocycle rings, optical activity based on trivalent nitrogen has proved impossible, except in unusual molecules such as Troeger's base (V) (Prelog and Wieland, 1944), where N-inversion is precluded due to geometrical constraints. More pertinent are the facts that microwave spectroscopy (Nygard and coworkers, 1969) has shown that pyrrole is planar at its nitrogen atom, and that recent MNDO

calculations by Sygula and Buda (1985) have indicated that the nitrogen atom at position 6 in adenine is likewise planar. We therefore conclude that Portelli's 'asymmetric adenine' and Root-Bernstein's first novel selector molecule, an optically active nucleotide base, are chemical and stereochemical impossibilities. Even if they did exist, moreover, there would have been equal numbers of the enantiomers of each on the primitive earth, so that in any case no problem would be solved by postulating them.



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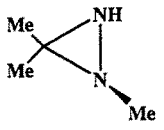

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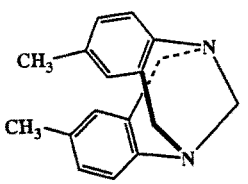
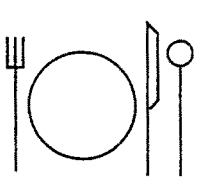
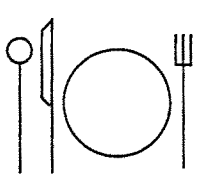


V

Rejecting 'physicochemical consideratioins in favor ... of information theory', Root-Bernstein then proposes a second novel selector molecule, this time one 'comprised of symmetrical elements whose *linear order* creates chiral compounds' and thus 'would determine selective chirility [*sic*]'. His analogy here is a right- (VI) and left-handed (VII) table setting of a fork, bowl, knife and spoon. The analogy is then directly extended to sequences of pyrimidine and purine bases in polynucleotides, which he represents by VIII and IX, where the flat bases 'have an axis of symmetry, just as do utensils'. Now, just as a right-handed person has a preference for place setting VI so, Root-Bernstein argues, the sequence of bases in VIII might provide a codon having a unique preference not only for one specific amino acid, but also for a *specific configuration* of that amino acid. Thus the L-enantiomer of a particular amino acid could be selected over the D-enantiomer (for example) by preferred chiral interactions of the L-amino acid with the specific



VI



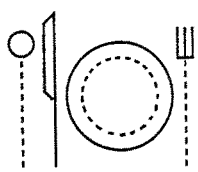
VII

VIII IX

base sequence of VIII. In some such unspecified manner, 'the single selection of L-amino acids by polynucleotides could have led to the subsequent selection of all other biological enantiomers', and the problem of the origin of biomolecular chirality is once and for all solved.

There are numerous flaws and incongruities in the above arguments. First, Root-Bernstein maintains that 'the pyrimidine and purine bases, because they are flat, have an axis of symmetry, just as do the utensils'. But he has just told us that the bases are 3-dimensional because of their asymmetric nitrogen! The statement is further contradicted by the depiction in his Figure 3 of the utensils in VI and VII, which shows realistically that the utensils are definitely *not* flat. Finally, neither the pyrimidine or purine bases nor the utensils in his model have an axis of symmetry. Whether flat or 3-dimensional the fork and spoon have a plane of symmetry perpendicular to the plane of the table (as well as additional symmetry elements if they are flat), while the knife has a plane of symmetry parallel to the table, and the bowl has an infinite number of symmetry planes perpendicular to the plane of the table and intersecting at a central rotation axis perpendicular to the table (as well as a plane of symmetry parallel to the table, if flat). Now, if Root-Bernstein is talking about flat utensils and bowl (in analogy to flat nucleotide bases), VI and VII are clearly not chiral, since they are superposable by merely rotating the entire array VII, for example, through 180° about an appropriate axis in the plane of the table. If, as in real life, the utensils are 3-dimensional then the arrays VI and VII, as shown, do in fact represent chiral entities. However, the same superposition of VII on its mirror image VI may be achieved by simply turning over each component (except the knife) in array VII separately to produce a new 'conformation' X (where dotted lines indicate a view of the 'underside' of each component), then rotating the entire array X again through 180° about an appropriate axis in the plane of the table. If, as in real life, the utensils are 3-dimensional then the arrays VI and VII, as shown, do in fact represent chiral entities. However, the same superposition of VII on its mirror image VI may be achieved by simply turning over each component (except the knife) in array VII separately to produce a new 'conformation' X (where dotted lines indicate a view of the 'underside' of each component), then rotating the entire array X again through 180° around an axis in the plane of the table as before. In this way, and with no change in the actual sequence of the utensils, the left-handed ordering of VII has been converted to the right-handed ordering of VI. Thus the two 3-dimensional arrays, while chiral as shown, are superposable after performing the simple rotations indicated above. The situation is analogous, in chemical terms, to the conversion of one chiral

conformation into its mirror image by rotation around one or more single bonds. An example might be the conversion of one chiral conformation of an optically active biphenyl derivative into its enantiomer by rotation about the bond connecting the two achiral phenyl groups, or the racemization of optically active 1,1′-binaphthyl by rotation about its 1,1′-bond. The only way to prevent the possibility of such a conversion of the chiral 'conformation' VI into the enantiomeric array VII would be to 'freeze' conformation VI by immobilizing its components, for example by embedding the array in a plastic matrix. But then, our right-handed guest could hardly make use of the utensils in his preferred sequence!



X

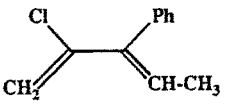
Again, the mirror image IX of Root-Bernsteins's schematic nucleotide sequence VIII is superposable on VIII by a similar series of rotations. If we view the bases of IX edge on, then rotate each through 180° about the bond connecting it to the 3′,5′-backbone, and finally rotate the entire array through 180° in the plane of the backbone, then IX is converted to VIII. In short, as with the previous table setting analogy, if one allows free rotations of the component parts, the mirror image structures VIII and IX may be made superposable. In any case, to be represented more accurately, VIII should be depicted as XI, where -(D)-refers to the D-configuration of the pentoses in the backbone of the polynucleotide having its 5′- and 3′-sequence of linkages. The mirror image of XI is then XII, which

XI XII

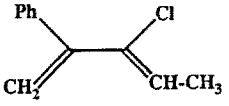
has L-pentoses in the polynucleotide chain. XI and XII are enantiomeric chiral structures which depend for their identity not only on the sequence of attached bases but also on the stereochemical configurations of the pentoses involved. If by some unknown mechanism XI were actually able to select for L-amino acids, its enantiomer XII would, of course, select for D-amino acids. Root-Bernstein's suggestion that polynucleotides (such as XI) utilize D-sugars in preference to L-sugars since the bases select the former 'due to their asymmetric nitrogen' is of course, as seen above, quite untenable.

Finally, Root-Bernstein claims possibly to have solved the problem of 'selective

chirility [*sic*] in the vital realm' by his recognition of a new 'third type of chirility [*sic*]: intra-molecular, linear ordering of diverse, symmetrical subunits'. That such linear ordering of symmetrical subunits on an achiral molecular backbone is quite insufficient *per se* to engender a chiral structure may be illustrated by the following trivial examples. 2-Chloro-3- phenyl-1,3-pentadiene (XIII) and 3-chloro-2-phenyl-1,3-pentadiene (XIV), which have symmetrical chloro and phenyl groups substituted in reverse order on the achiral pentadiene backbone, comprise two molecules whose *identities* are clearly determined by the sequence of the substituents. Nevertheless, neither one is chiral since each has a superposable mirror image, regardless of the linear ordering. Now consider a similar ordering of the same substituents on an achiral pentane backbone. We now have the saturated molecules XV and XVI, whose *identities* are once again established by substituent ordering on the backbone, but whose *chiralities* are determined only by the two asymmetric carbon atoms present. Thus the linear ordering, *per se* has nothing whatsoever to do with the chirality.



XIII



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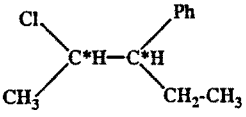
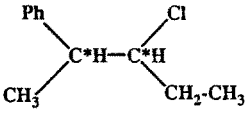


XV



XVI

In summary, we conclude that Root-Bernstein's two 'selector molecule' hypotheses are based upon naive chemical and stereochemical misconceptions, that neither hypothesis provides any solution whatsoever to the question of the origin of biomolecular homochirality in nature, and that all of the ambiguities bedeviling previous attempts to answer this question unfortunately still remain.

Acknowledgment

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