Structural and Enthalpic Relationships in Nucleosides

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Summary Differential scanning calorimetric (d.s.c.) data obtained for a number of nucleosides in the crystalline and fused states indicate that purines and pyrimidines each exhibit a characteristic thermal behaviour which reflects the influence of specific features of their individual structures.

RECENT advances in thermal analysis have permitted us to measure the energy associated with nucleosidic structures in the crystalline and fused states. Differential enthalpic data (Figure) obtained from selected nucleosides, over a limited temperature range (300—600 K) indicated an exothermic process which may distinguish purine nucleosides from those of pyrimidines. Furthermore, a second endothermic peak in the thermogram of thymidine differentiated this deoxypyrimidine from the pyrimidines examined (uridine and cytidine). The energy values obtained for these data (Table 1) may be rationalized in terms of the known conformations and stereochemical structures associated with the crystalline state.

The enthalpic values (Table 1) obtained for the purines

TABLE 1

Heats of fusion and endothermic melting decomposition of nucleosides obtained at a heating rate of 20 K/min

Nucleoside	T_{max}/K for endotherm	Heat of fusion (in cal/g)	Enthalpy ΔH/(kcal mol^{-1})
Adenosine ..	515	42·0	11·2
Inosine ..	508	40·8	11·0
Guanosine ..	523	11·8[a]	3·3
Cytidine ..	494	27·2	6·6
Uridine ..	447	30·1	6·9
Thymidine			
(Peak 1 ..	468	29·0	7·0
(Peak 2) ..	596	16·5	4·0

[a] The lower value probably results from overlap of the endotherm with the adjacent exotherm.

and the pyrimidines are within the expected range (*ca.* 10 kcal/mol and 6—7·5 kcal/mol per residue respectively) based on their hyperchromic effect.[1,2]

The heats of fusion of the purines (*ca.* 40 cal/g), except for guanosine, are higher than those of the pyrimidines (*ca.* 28 cal/g). This difference may be attributed to the greater aromaticity of the purines which results in greater π interaction and therefore increases the stacking force. Indeed, methylation of the base fragment usually enhances the association,[3] since the inductive effect of the methyl group increases the availability of the π electrons.

The slightly higher value of adenosine over inosine reflects the additional H bonding resulting from the extra amino-group. It is especially interesting that inosine has the same crystal structure and lattice constants as guanosine[4] despite the fact that it lacks the amino-group, which plays an integral part in H bonding. This suggests that parallel stacking of the bases is of preponderant importance in maintaining the structure. The anomalous enthalpic fusion–decomposition value obtained for guanosine (Table 1) in comparison with adenosine or inosine does not appear to reflect a reduced stacking force for guanosine. This postulate is supported by the fact that the activation energy for the lattice-decomposition of both inosine and guanosine, as calculated from the present thermal data (Table 2), gave

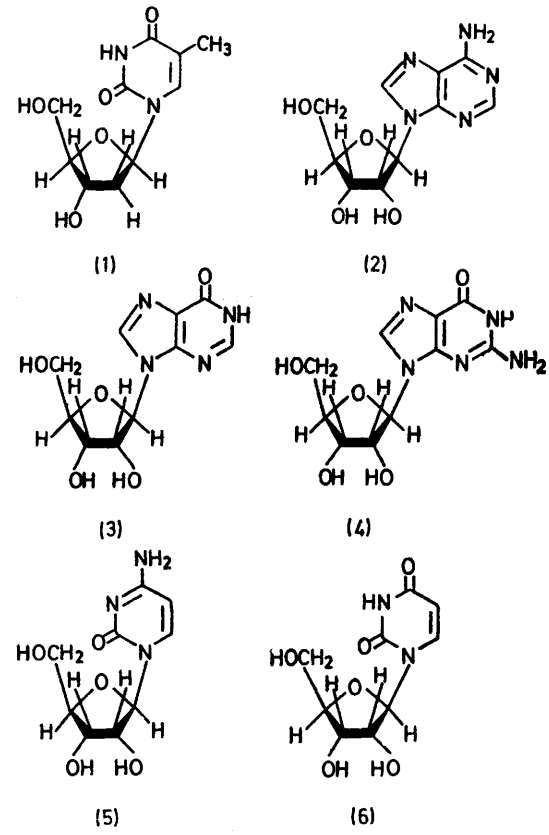

TABLE 2

Exothermic decomposition of nucleosides

Nucleoside	Exothermic reaction (in cal/g)	Activation energy (in kcal/mol)
Inosine	−10·6	63·5
Guanosine	− 4·4	64·5

equal values. The lower endothermic value obtained for guanosine appears to result from the juxtaposition of an endotherm with an exotherm, a condition which reduces the actual value of each (Figure).

Differential thermal analysis (dta) of adenosine, guanosine, thymidine and cytidine exhibited endothermic peaks at 508, 523, 468, and 493 °K[5,6] respectively, in conformity

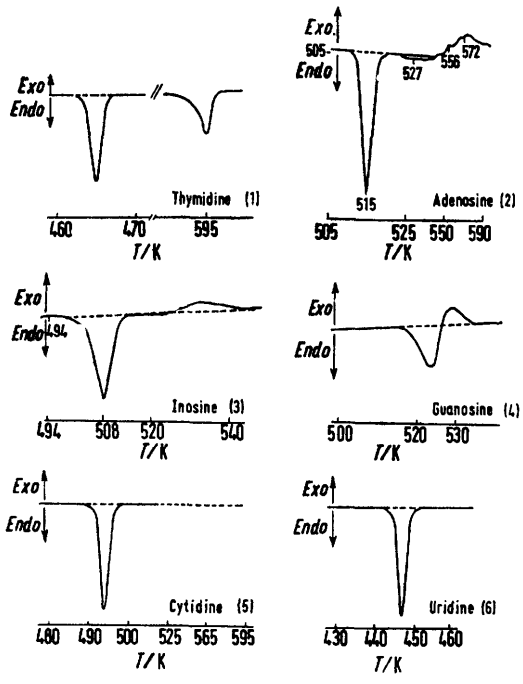

FIGURE. *DSC thermograms of deoxy- and ribo-nucleosides.*

with our data. No mention was made, however, of the exothermic processes which are characteristic of purine nucleosides compared with those of pyrimidines. These exotherms may result from rotation of the base about the glycosidic bond to give the *anti*-configuration followed by a subsequent loss of water to form an anhydro-derivative which is more stable than the purine itself. The structures of these derivatives are presently under investigation.

The deoxypyrimidine, thymidine, differed markedly from the other nucleosides examined in that it exhibited two endotherms—one at 468 K normally associated with melting and one at 596 K, previously unreported. The higher temperature endotherm is associated with a reversible process whereas the one at the lower temperature is not. It is apparent that some physical or chemical change is occurring at the m.p., a change which may account for the anomalous behaviour that has been noted with thymidine.

Thymidine and thymidylic acid are unique in being among the only nucleosides or nucleotides so far examined by *X*-ray analysis in having the C(3′) *exo*-conformation.[7] Thus one possible explanation for the thermal data is that the first endothermic peak is due to a phase change that is related to a change of the C(3′) *exo*-configuration to the C(3′) *endo*-configuration of the deoxynucleosides.

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