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# Van der Waals-London Interaction Energies in Hydrogen Bonding between Purine and Pyrimidine Base Analogues

## I. Interactions Involving 2,6-Diaminopurine*

BERNARD PULLMAN and JACQUELINE CAILLET

Institut de Biologie Physico-chimique, Laboratoire de Biochimie Théorique, associé au CNRS

13, rue Pierre Curie Paris 5è

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The calculation of the Van der Waals-London interaction energies in hydrogen-bonded complexes formed between adenine or its analogue 2,6-diaminopurine and uracil enables to account for the structural differences among these complexes. In particular they indicate, that the most stable A +2U trimer should be of the Watson-Crick—inversed Hoogsteen type, while the most stable 2,6-DAP +2U trimer should be of the reversed Watson-Crick—Hoogsteen type. The observed configurations reflect most probably stable associations formed in solution prior to a possible cocrystallization.

L'évaluation des énergies d'interaction Van der Waals-London se manifestant dans les complexes par liaisons hydrogène formés entre l'adénine ou son analogue 2,6-diaminopurine et l'uracil, permet de rendre compte des différences structurales observées entre ces complexes. Elle indique, en particulier, que la configuration la plus stable du complexe A + 2U devrait être du type Watson-Crick—Hoogsteen inversé, alors que la configuration la plus stable du complexe 2,6-DAP + 2U devrait être du type Watson-Crick inversé—Hoogsteen. Les configurations observées traduisent probablement l'association la plus forte formée en solution avant une cocrystallisation eventuelle.

Die Berechnung der Van-der-Waals-London-Energie in wasserstoffbrückengebundenen Komplexen von Adenin bzw. 2,6-Diaminopurin und Uracil ermöglicht die strukturellen Unterschiede zu erklären. Insbesondere ergibt sich, daß das stabilste A + 2U-Trimere vom „inversen Hoogsteen—Watson-Crick"-Typ, das stabilste 2,6-DAP + 2U-Trimere aber vom „inversen Watson-Crick—Hoogsteen"-Typ sein sollte. Vermutlich geht der Kokristallisation die Bildung stabiler Assoziate in der Lösung voraus.

### Introduction

We have recently studied [*1—6*] the preferential configurations and the interaction energies of hydrogen bonded purine-pyrimidine base pairs, in particular of those formed between the bases of the nucleic acids. We are presently undertaking a systematic investigation of similar interactions involving base analogues. This paper is concerned with the interactions involving 2,6-diaminopurine (2,6-DAP), an analogue of adenine (A) and a potent mutagen.

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Researches carried out on association of 2,6-DAP with uracil (U) in solution (in $CD_3Cl$) [*7, 8, 9*] or on cocrystallization of these molecules [*10*] (the experiments being done in all cases with simple derivatives of these compounds carrying always a substituent at the glycosidic nitrogen), point to a general behaviour very similar to that observed for interactions between similar simple derivatives of adenine and uracil: greater tendancy of the compounds to cross-association than to autoassociation in solution, formation of a 1:1 dimer and possibly of a 2:1 (purine + 2U) trimer, in solution, formation of a trimer upon cocrystallization. However, the configurations of the associations obtained and in particular of those of the trimers seem to be different from those of the two purines. The energies of the associations are also greater in the case of the complexes involving 2,6-DAP than in those involving adenine.

Generally speaking four different types of dimers may be obtained from adenine or 2,6-DAP and uracil, having their glycosidic nitrogen blocked by substitution. They are illustrated in Fig. 1 for the pair adenine-uracil. We also indicate in this figure the denominations by which we are going to designate them. The denomination of "Hoogsteen pair" corresponds to the cupling actually observed, for the first time by HOOGSTEEN, in cocrystallization of 1-methylthymine (or uracil) with 9-methyl- or ethyl-adenine [*11, 12*]; the "reversed Hoogsteen" configuration has been observed between adenine and bromouracil derivatives in mixed crystals [*13, 14*]. Quite similar configurations may be considered for the

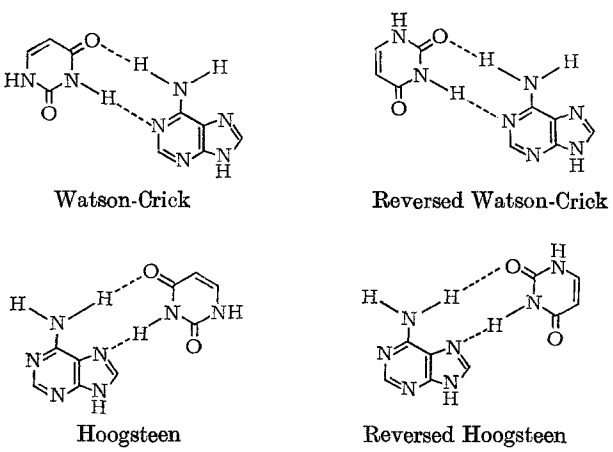


Fig. 1. Different configurations of the adenine-uracil dimer

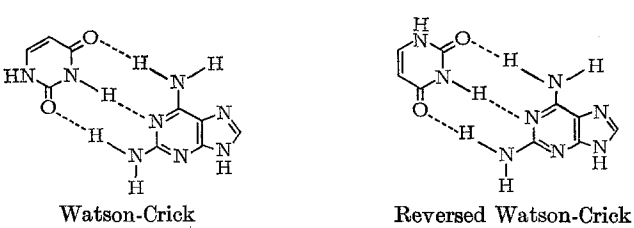


Fig. 2. The three hydrogen bonds in the Watson-Crick and reversed Watson-Crick 2,6-diaminopurine-uracil dimers

associations of 2,6-DAP with uracil, with the difference, illustrated in Fig. 2, that the "Watson-Crick" and "reversed Watson-Crick" dimers contain in this case three hydrogen bonds.

In the case of the trimers, four possibilities occur again for each group A + 2U or 2,6-DAP + 2U, corresponding to the four possible simultaneous arrangements of the two uracils, linked one with the pyrimidine and the other with the imidazole ring of the central purine. These arrangements can be denoted as:

1. Watson-Crick—Hoogsteen,
2. Watson-Crick—reversed Hoogsteen,
3. Reversed Watson-Crick—Hoogsteen,
4. Reversed Watsen-Crick—reversed Hoogsteen.

## Results and Discussion

We have carried out calculations on the Van der Waals-London interaction energies in these different associations. The method used has been described in details for the dimers in Ref. [*1*] and for the trimers in Ref. [*4*] and will therefore not be repeated here. We would just like to emphasize that we are utilizing the monopole approximation and that the total interaction energies ($E_M$) are the sums of the monopole-monopole component ($E_{qq}$), the monopole induced-dipole component ($E_{q\alpha}$) and the dispersion or London component ($E_L$).

The results are indicated in Tabs. 1 and 2. In these tables $U_1$ indicates the uracil hydrogen-bonded to the pyrimidine ring of the purine and $U_2$ the uracil hydrogen-bonded to the imidazole ring of the purine. Following the technical details discussed in Ref. [*4*] the interactions purine-$U_1$ or purine-$U_2$ give a measure of the energies corresponding to the isolated dimers while the interactions $U_1 - U_2$ measure the repulsive component due to the formation of the trimer; the interactions purine + 2U give the total interaction energies in the trimers.

The principal conclusions which can be drawn from the examination of Tabs. 1 and 2 are:

1. The most stable configuration for the A–U dimer is the Hoogsteen one. As already stated this is the one observed upon cocrystallization of alkylated derivatives of adenine and uracil [*11, 12*].

2. The most stable configuration for the 2,6-DAP–U dimer is the reversed Watson-Crick one.

3. The most stable configuration for the A + 2U trimer is the Watson-Crick—reversed Hoogsteen one. This curious result is due to some extent to the effect of repulsion between the two uracils. If this repulsion would be neglected the most stable configuration would be the Watson-Crick—Hoogsteen one. It is the somewhat lower repulsion observed in the Watson-Crick—reversed Hoogsteen model that ensures the overall greater stability of this model over the Watson-Crick—Hoogsteen one.

4. The most stable configuration for the 2,6-DAP–2U trimer is the reversed Watson-Crick—Hoogsteen one, followed closely by the reversed Watson-Crick—reversed Hoogsteen one.

It is most striking to remark that experimental studies on the structure of observed trimers seem to confirm the theoretical predictions. Thus a careful

Table 1. *Energies of Van der Waals-London interactions in complexes of adenine with uracil* (kcal/mole)

| Configuration | Interaction | $E_{QQ}$ | $E_{Q\alpha}$ | $E_L$ | $E_M$ |
|---|---|---|---|---|---|
| Watson-Crick— | A – $U_1$ | −4.64 | −0.25 | −0.69 | − 5.58 |
| Hoogsteen | A – $U_2$ | −5.86 | −0.22 | −0.88 | − 6.96 |
| | $U_1$ – $U_2$ | +0.96 | −0.02 | −0.03 | + 0.91 |
| | A + 2U | −9.54 | −0.49 | −1.60 | −11.63 |
| Watson-Crick | A – $U_1$ | −4.64 | −0.25 | −0.69 | − 5.58 |
| —reversed Hoogsteen | A – $U_2$ | −5.63 | −0.17 | −0.94 | − 6.74 |
| | $U_1$ – $U_2$ | +0.57 | −0.01 | −0.03 | + 0.53 |
| | A + 2U | −9.70 | −0.43 | −1.66 | −11.79 |
| reversed Watson-Crick | A – $U_1$ | −3.98 | −0.25 | −0.71 | − 4.94 |
| —Hoogsteen | A – $U_2$ | −5.86 | −0.22 | −0.88 | − 6.96 |
| | $U_1$ – $U_2$ | +0.60 | −0.02 | −0.03 | + 0.55 |
| | A + 2U | −9.24 | −0.49 | −1.62 | −11.35 |
| reversed Watson-Crick | A – $U_1$ | −3.98 | −0.25 | −0.71 | − 4.94 |
| —reversed Hoogsteen | A – $U_2$ | −5.63 | −0.17 | −0.94 | − 6.74 |
| | $U_1$ – $U_2$ | +0.42 | −0.01 | −0.03 | + 0.38 |
| | A + 2U | −9.19 | −0.43 | −1.68 | −11.30 |

Table 2. *Energies of Van der Waals-London interactions in complexes of 2,6-diaminopurine with uracil* (kcal/mole)

| Configuration | Interaction | $E_{QQ}$ | $E_{Q\alpha}$ | $E_L$ | $E_M$ |
|---|---|---|---|---|---|
| Watson-Crick— | 2,6-DAP – $U_1$ | − 6.49 | −0.22 | −1.16 | − 7.87 |
| Hoogsteen | 2,6-DAP – $U_2$ | − 5.80 | −0.24 | −0.48 | − 6.52 |
| | $U_1$ – $U_2$ | + 0.96 | −0.02 | −0.03 | + 0.91 |
| | 2,6-DAP + 2U | −11.33 | −0.48 | −1.67 | −13.48 |
| Watson-Crick— | 2,6-DAP – $U_1$ | − 6.49 | −0.22 | −1.16 | − 7.87 |
| reversed Hoogsteen | 2,6-DAP – $U_2$ | − 5.55 | −0.21 | −0.51 | − 6.27 |
| | $U_1$ – $U_2$ | + 0.57 | −0.01 | −0.03 | + 0.53 |
| | 2,6-DAP + 2U | −11.47 | −0.44 | −1.70 | −13.61 |
| Reversed Watson-Crick | 2,6-DAP – $U_1$ | − 6.69 | −0.21 | −1.16 | − 8.06 |
| —Hoogsteen | 2,6-DAP – $U_2$ | − 5.80 | −0.24 | −0.48 | − 6.52 |
| | $U_1$ – $U_2$ | + 0.60 | −0.02 | −0.03 | + 0.55 |
| | 2,6-DAP + 2U | −11.89 | −0.47 | −1.67 | −14.03 |
| Reversed Watson-Crick | 2,6-DAP – $U_1$ | − 6.69 | −0.21 | −1.16 | − 8.06 |
| —reversed Hoogsteen | 2,6-DAP – $U_2$ | − 5.55 | −0.21 | −0.51 | − 6.27 |
| | $U_1$ – $U_2$ | + 0.42 | −0.01 | −0.03 | + 0.38 |
| | 2,6-DAP + 2U | −11.82 | −0.43 | −1.70 | −13.95 |

investigation of the shifts of infra-red frequencies upon helix formation led MILES [*9*] to the conclusion that in poly-(A + 2U) the configuration of the triplet is Watson-Crick—reversed Hoogsteen. Although results concerning a polynucleotide in solution cannot be considered as confirming calculations on an isolated trimer, the agreement between the two may be considered as significant. As concerns the structure predicted for the 2,6 DAP + 2U trimers it corresponds to the one observed in a 2:1 cocrystalline complex containing 1-methyl-5-iodouracil and 9-ethyl-2,6-diaminopurine [*10*]. This agreement between the theoretical calculations and experiment seems to indicate, among others, that the solid state configuration reflects probably the most stable configuration formed in solution

prior to crystallization, and that this factor is therefore more important, in the present case at least, than the crystal lattice forces for the selection of the observed configuration. Truly, the theoretical differences between the possible configurations are, however, small and the crystal lattice forces could play a role in reinforcing the preferential stabilization.

As concerns the occurence of the cross-associations themselves, they can be accounted for, in the complexes involving 2,6-DAP, by extending to them the rule which we have previously established [*1*, *2*] for complexes involving the bases of the nucleic acids and which states that for cross-associations to occur the Van der Waals-London energy of such an interaction must be greater than the mean of the corresponding energies of the two autoassociations of the constituents of the complex. As shown before [*1*] the energy of autoassociation of two uracils is of the order of −4 kcal/mole. The energy of autoassociation of two 2,6-diaminopurines by hydrogen-bonding involving one of the amino groups and $N_1$ may amount to −6 kcal/mole for the most favorable association. The two energies of autoassociation appear therefore smaller than the energy of the cross-association 2,6-DAP–U which, as found above, amounts to −8 kcal/mole. On the other hand, in agreement with experiment, both the energies of the autoassociation 2,6-DAP − 2,6-DAP and of the cross-association 2,6-DAP–U are greater than the corresponding energies involving adenine (−5,8 and −7 kcal/mole respectively). It may also be worth stressing, that, as indicated already previously [*3*], the Watson-Crick or reversed Watson-Crick arrangements of the 2,6-DAP–U dimers correspond to much smaller interaction energies than that of the Watson-Crick guanine-cytosine dimer (−19,2 kcal/mole), although both contain three hydrogen bonds. This calculation is in agreement with the experimental results concerning the relative stabilities of the corresponding polynucleotide helices [*15*]. Finally, it may be observed that it is the contribution of the electrostatic $E_{qq}$ component that predominates in this type of associations.

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Prof. Dr. Bernard Pullman
Institut de Biologie Physico-chimique
Laboratoire de Chimie Quantique
Université de Paris
13, Rue Pierre Curie
Paris-V$^e$, France