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Molecular Interactions of Pyrimidines, Purines, and Some Other Heteroaromatic Compounds in Aqueous Media*

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ABSTRACT: Interactions of mixed purines, pyrimidines, and other heteroaromatic compounds (quinoxaline and chloroquine) were examined in aqueous media by the phase-solubility method. Association constants at 25° are reported for 18 adenines, 10 deoxyguanosines, and 5 other complexes. These data confirm the fact that there is no specific interaction of bases in aqueous media in the Watson–Crick sense, and support base stacking as being primarily responsible for the interaction. Although the base stacking appears to depend primarily upon the size of the π-electron systems, substituents modify the association tendency considerably. The present study suggests a possibility that some structural specificity does exist to discriminate the interaction of a certain pair of heteroaromatic compounds from that of another pair, although base stacking is generally considered to be nonspecific.

Specific hydrogen-bond formation between purines and pyrimidines is believed to be involved in the molecular basis of information transfer in biological systems. Much attention has, therefore, been focused on the molecular interaction of these heteroaromatic compounds. Several groups have been attempting to gain insight into the mechanism of the basic recognition processes as well as into the source of stabilizing energy for the structure of nucleic acids (Felsenfeld and Miles, 1967; Pullman, 1968).

Extensive studies on the molecular interactions of purine and pyrimidine derivatives have shown that these molecules interact with specific complementarity between purines and pyrimidines in such organic solvents as carbon tetrachloride (Küchler and Derkosch, 1966), chloroform (Hamlin *et al.*, 1965; Kyogoku *et al.*, 1966; Kyogoku *et al.*, 1967a,b; Miller and Sobell, 1967; Pitha *et al.*, 1966), and dimethyl sulfoxide (Katz and Penman, 1966; Shoup *et al.*, 1966; Newmark and Cantor, 1968). In aqueous solution, however, their interactions exhibit no such specificity (Ts'o 1968; Solie and Schellman, 1968; Lord and Thomas, 1967). These observations have led a number of investigators to consider a possibility that the basic recognition process may take place in a hydrophobic environment formed by exclusion of water in the presence of enzyme (Tinoco *et al.*, 1968). However, it is not known how enzymes, the polynucleotide back-bone structure, and other factors interplay to provide such an environment. In order to approach this problem, basic information about the association tendencies between mixed monomeric constituents of nucleic acids in aqueous media is needed so that effects of other factors can be individually ascertained.

Although a considerable amount of quantitative information is available for the self-association of monomers in aqueous solution (Ts'o, 1968), similar information regarding the interactions of mixed monomers is very limited (Solie and Schellman, 1968; Ts'o *et al.*, 1963). Little quantitative data concerning the association tendency of the guanine residue in water is available in the literature, although the association is often assumed to be substantial because of a strong tendency of guanosine monophosphate to form a gel in concentrated solutions under appropriate conditions (Gellert *et al.*, 1962).

We have, therefore, undertaken a quantitative study of the association tendencies of the adenine and guanine residues toward a wide variety of structurally modified purines and pyrimidines as well as toward some other heteroaromatic compounds. The phase-solubility method extensively used for studies of molecular interaction by Higuchi and his associates (for review, see Higuchi and Connors, 1965) was employed with the aid of radioactive materials for some systems. The same technique was used by Ts'o *et al.* (1963) for the systems similar to those investigated in the present study. Equilibrium association constants at 25° were calculated from solubility data on the assumption that the forma-

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tion of a 1:1 soluble complex is responsible for the increase in the solubility of one component in the presence of another.

The results obtained support the theory that base stacking is predominantly responsible for the interaction of these heteroaromatic compounds. Although the stacking interaction in aqueous media is generally considered to be nonspecific, this study indicates the presence of some structural specificity which discriminates the interaction between a certain pair of compounds from that of another pair.

Materials and Methods

Materials. [^{3}H]Adenine (specific activity 7 Ci/mmole) and 8-[^{3}H]deoxyguanosine (specific activity 5 Ci/mmole) were obtained from Schwarz BioResearch Inc., as were adenine, adenosine, inosine, and 5-iodouridine. Deoxyguanosine was obtained from Calbiochem. The following compounds were purchased from Sigma Chemical Co.: uridine, thymine, cytosine, purine, hypoxanthine, guanosine, and chloroquine diphosphate. Uracil, 5-bromouracil, and 1,3-dimethyluracil were obtained from Nutritional Biochemical Co. 5-Fluorouracil was a gift from Hoffman–La Roche, Inc. 5-Chlorouracil was purchased from K & K Laboratories, Inc. Caffeine was from British Drug Houses. 8-Methoxycaffeine, 3,3-dimethylglutaric acid, and naphthalene were from Eastman Organic, Inc. Theophylline was obtained from Mallinckrodt Co. Quinoxaline from Aldrich Chemical Co. was vacuum distilled before use. PPO[1] and POPOP were from New England Nuclear Co. All other chemicals used were of Fisher Certified reagent grade.

Radioactive adenine and deoxyguanosine suitable for solubility studies were prepared by appropriate dilution of [^{3}H]adenine and 8-[^{3}H]deoxyguanosine with the corresponding nonradioactive materials at elevated temperatures, around 90° for adenine and 60–65° for deoxyguanosine. The solutions were quickly cooled on ice and allowed to stand in a refrigerator overnight. The precipitates were collected by filtration. The specific activities of the final preparations were about 14.7 and 22.2 μCi per mmole for adenine and deoxyguanosine, respectively.

Solubility Measurements. GENERAL PROCEDURE. In the present solubility studies, the component whose solubility is measured is referred to as a "solute," and the second component added to the system is referred to as a "complexing agent." An excess amount (10–20 mg) of a radioactive or nonradioactive solute was placed in each of several 10-ml screw-capped vials. A constant volume (2–4 ml) of solutions of varying concentrations of complexing agent was placed into each of the vials containing a solute. The vials were closed and shaken in the dark in a constant-temperature water bath maintained at 25 ± 0.5° until equilibrium was attained. The waxed paper lining of the caps was satisfactory for the present purpose as it leached out only a negligible amount of ultraviolet-absorbing materials. After equilibration, the contents of the vials were filtered through sintered glass filters (medium porosity) or, as in the case of deoxyguanosine systems, through Millipore filters (PHWP-02500). An aliquot of filtrate was withdrawn for determination of the total concentration of the solute by spectrophotometry and/or by radioactivity measurement. For spectrophotometric measurements, a Cary Model 15 spectrophotometer was used to determine absorbance at the wavelength of maximum absorption of the solutes. Since the concentration of complexing agent was known, the absorbance due to complexing agents at the wavelength was subtracted from the total value to give correct absorbance of solute. For radioactivity measurements, a 0.1-ml aliquot of filtrate was added to 10 ml of a scintillation fluid consisting of 60 g of napththalene, 4 g of POP, 0.2 g of POPOP, 100 ml of methanol, and dioxane to give a total volume of 1 l. Radioactivity was measured in a Beckman LS-200B liquid scintillation system.

ADENINE COMPLEXES. Equilibration periods varied from 3 to 7 days, depending upon the preparation of adenine. Anhydrous adenine formed supersaturated solutions before approaching its equilibrium solubility. The saturated solution of adenine at 25° has a pH of around 6.2–6.4, so that adenine exists predominantly in a molecular form at saturation. Thus, most of the interactions of adenine with nonionizable or weakly acidic complexing agents were studied without added buffer. The pH of filtrates was measured to ensure that it was between 5.9 and 6.5. With more acidic complexing agents such as 5-halouracils, 0.02 M DMGA buffer (pH 6.2) was used to ensure that adenine as well as the complexing agents were present predominantly in molecular form. With chloroquine, 0.05 M DMGA buffer (pH 6.1) was employed. At this pH chloroquine exists predominantly as divalent cation since its pK_{a2} is 7.8 (Parker and Irvin, 1952).

DEOXYGUANOSINE COMPLEXES. Unlike the dissolution characteristics of adenine, those of deoxyguanosine varied widely from vial to vial. Therefore, to ensure uniform dissolution behavior the solutes were solubilized by warming prior to equilibration at 25°. An equilibrium period of 4 days was then necessary. The saturated solution of deoxyguanosine becomes pink on standing for 1 or 2 weeks. This discoloration was retarded in the presence of complexing agents. After 4-days equilibration, the filtrates were all colorless. Solubility study was done in water in the absence of added buffer, except the system involving chloroquine in which 0.05 M DMGA buffer (pH 6.1) was used.

OTHER COMPLEXES. Hypoxanthine, guanosine, and adenosine complexes were equilibrated in water at 25°. Concentration of these solutes was determined spectrophotometrically at 250 mμ for hypoxanthine, 252 mμ for guanosine, and 260 mμ for adenosine. Appropriate corrections were made for absorbance due to the complexing agents at the corresponding wavelength as mentioned earlier.

Calculation of Stability Constants. Association constants were calculated from the phase-solubility diagram obtained by plotting the total concentration of dissolved solute against the total concentration of complexing agent (Higuchi and Connors, 1965). The indication of a linear relation in such phase-solubility diagrams does not necessarily mean that only a 1:1 complex is formed. However, for practical purposes this assumption is usually made, and apparent 1:1 stability constant ($K_{app\ 1:1}$) can be calculated from the slope and intercept by using the equation

$$K_{app\ 1:1} = \frac{\text{slope}}{\text{intercept } (1 - \text{slope})}.$$

[1] Abbreviations used are: POP, 2,5-diphenyloxazole; POPOP, 1,4-bis[2-(5-phenyloxazoyl)]benzene; DMGA buffer, 3,3-dimethylglutaric acid–NaOH buffer.

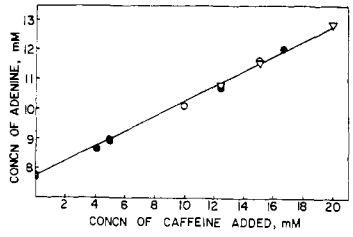


FIGURE 1: Phase-solubility diagram for the interaction of adenine with caffeine at 25°. Keys: (▽) by radioactivity measurements in 0.02 M DMGA buffer (pH 6.2); (○) by absorbance measurements in 0.02 M DMGA buffer (pH 6.2); (●) by absorbance measurements in water.

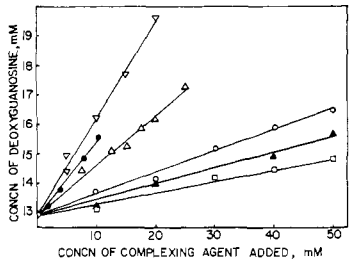


FIGURE 3: Phase-solubility diagrams for the interactions of deoxyguanosine at 25° with chloroquine (▽), 8-methoxycaffeine (●), theophylline (△), inosine (○), 1,3-dimethyluracil (▲), and cytosine (□).

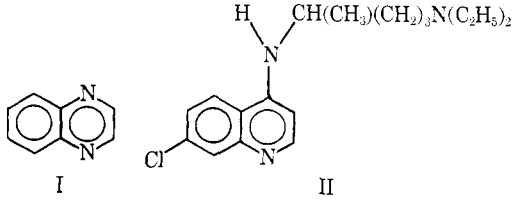
Results

Evaluation of the Use of Radioactive Materials. The solubility diagram obtained by radioactivity measurements using radioactive materials was compared with that obtained by absorbance measurements employing a nonradioactive solute. The former method has particular advantage, if applicable, when both solute and complexing agent possess maximum absorption at similar wavelengths.

A typical phase-solubility diagram obtained for the interaction of adenine with caffeine at 25° is presented in Figure 1. Within the concentration range of caffeine investigated (4.14–20 mM), only a soluble complex (or complexes) was formed. The figure shows that the same solubility diagram is obtained whether the assay for total adenine solubilized is done by absorbance measurements or by radioactivity measurements. Thus, the use of tritiated compounds for this type of experiments is justified. Further, for a nonionizable complexing agent such as caffeine, the use of DMGA buffer (pH 6.2) did not modify the solubility diagram in water.

Association Constants for Various Complexes. Similar phase-solubility diagrams for some adenine, deoxyguanosine, and guanosine complexes are presented in Figures 2, 3, and 4, respectively. In all cases only soluble complexes were obtained. Based on such solubility diagrams, the apparent 1:1 association constants for the adenine and deoxyguanosine complexes calculated from the equation are presented in Tables I and II, respectively. Those of the guanosine and other complexes are presented in Table III. The slope and intercept values obtained by the method of least squares were used for computation of these $K_{app\ 1:1}$ values.

Comparison of Association Tendency of the Adenine and Guanine Residues. The interactions of adenine and deoxyguanosine with pyrimidines, purines, and other heteroaromatic compounds (see Tables I and II) show that in both series the purines, quinoxaline (I) and chloroquine (II), generally have a higher tendency to interact than the pyrimidines. Because of the retarding effect of the sugar moiety,



the tendency of deoxyguanosine to associate with the pyrimidines and purines is apparently half as much as that of adenine. However, it is noteworthy that other classes of heteroaromatic compounds, *i.e.*, quinoxaline and quinoline, interact to a similar extent with both deoxyguanosine and adenine. Chloroquine has been reported to bind polyadenylate and polyguanylate equaly well (Blodgett and Yielding, 1968). Although the ring nitrogen of chloroquine is predominantly charged under the present experimental conditions, the association tendency is substantial.

Effect of Substituents on Association Tendency of Parent Compounds. Methylation of the purine and pyrimidine residues enhances association tendencies. 5-Methyl substitution in uracil has the same enhancing effect as N methylation at both positions 1 and 3 of uracil (1,3-dimethyluracil). This observation agrees with the findings of Helmkamp and Kondo (1968) that the enhanced stacking association of purines caused by alkyl substitution is dependent upon the nature and position of the substituent. Comparison of the

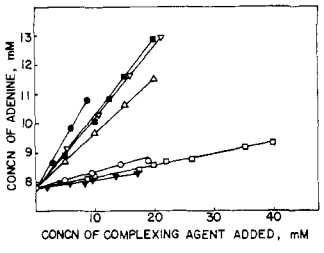


FIGURE 2: Phase-solubility diagrams for the interaction of adenine at 25° with 8-methoxycaffeine (●), caffeine (■), chloroquine (▽), theophylline (△), thymine (○), cytosine (□), and uracil (▼).

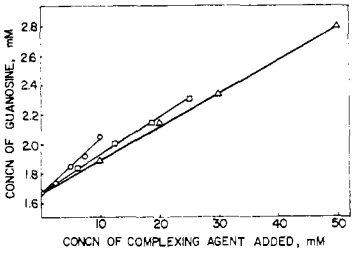


FIGURE 4: Phase-solubility diagrams for the interactions of guanosine at 25° with 8-methoxycaffeine (○), caffeine (□), and quinoxaline (△).

TABLE I: Adenine Complexes.[a]

Complexing Agent	Concn (mM) Range	n[b]	I (mM)[c]	Slope ($\times 10^2$)	Std Error[d] ($\times 10^2$)	$K_{app\ 1:1}$ M^{-1} at 25°
Uracil	2.09–17.33	10	7.77	3.13	0.35	4.16
5-Fluorouracil	7.80–23.40	5	7.76	4.05	0.31	5.44
5-Chlorouracil	6.68–13.35	4	7.77	4.69	0.26	6.33
5-Bromouracil	4.36–7.85	4	7.76	5.18	0.20	7.04
Uridine	12.5–50.0	4	7.85	3.07	0.22	4.03
5-Iodouridine	5.00–20.0	5	7.84	7.02	0.33	9.63
1,3-Dimethyluracil	10.0–50.0	10	7.82	5.29	0.29	7.14
Thymine	4.75–19.0	5	7.78	5.18	0.41	7.00
Cytosine	8.80–40.0	10	7.85	3.71	0.13	4.89
Caffeine	4.14–20.0	13	7.63	26.1	0.40	45.1
8-Methoxycaffeine	2.39–8.78	4	7.68	35.9	1.03	80.2
Theophylline	5.00–20.0	5	7.74	19.3	0.29	31.1
Purine	8.00–40.0	9	7.99	8.30	0.51	11.3
Adenosine	2.89–19.30	13	7.83	14.1	0.59	21.0
Deoxyguanosine	2.6–13.0	4	7.80	12.8	0.17	18.8
Inosine	10.0–50.0	6	7.86	6.09	0.48	8.25
Quinoxaline	15.0–50.0	5	7.82	12.2	0.29	17.8
Chloroquine	5.40–21.4	5	7.84	23.5	0.63	39.2

[a] Average solubility of adenine in water at 25° = (7.80 ± 0.078) × 10^{-3} M. [b] n = number of experimental values for the concentration of complexing agents within the specified ranges. [c] I = intercept = S_0. [d] Standard error of slope.

TABLE II: Deoxyguanosine Complexes.[a]

Complexing Agent	Concn (mM) range	n	I (mM)	Slope ($\times 10^2$)	Std Error ($\times 10^2$)	$K_{app\ 1:1}$ M^{-1} at 25°
Cytosine	10.0–50.0	7	12.78	4.07	0.41	3.32
1,3-Dimethyluracil	10.0–50.0	5	12.76	5.69	0.28	4.73
Caffeine	4.0–20.0	10	13.00	25.6	0.86	26.5
8-Methoxycaffeine	2.0–10.0	5	12.69	28.0	1.03	30.7
Theophylline	7.5–25.0	7	13.06	16.2	0.85	14.0
Purine	10.0–50.0	8	13.00	9.0	0.33	7.61
Adenosine	3.86–19.3	5	12.60	10.4	1.13	9.21
Inosine	10.0–50.0	6	12.96	7.13	0.40	5.92
Quinoxaline	15.0–50.0	10	13.27	15.9	0.32	14.3
Chloroquine	5.0–20.0	7	12.91	32.9	0.91	38.0

[a] Average solubility of deoxyguanosine in water at 25° = (12.90 ± 0.35) × 10^{-3} M. The other specifications are the same as in Table I.

association tendencies of caffeine and theophylline toward adenine and deoxyguanosine (Table IV) also indicates that the high interactive tendency of the alkylxanthines (III) is attributable to the presence of *N*-methyl substituents. The enhancing effect of 8-methoxy substitution is observed also in adenine, guanosine, and deoxyguanosine complexes.

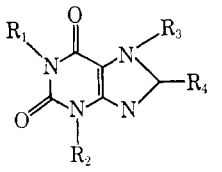
5-Halogen substitution exhibits a marked effect on the association tendency of the uracil residue. The interactions of a series of 5-halogenated uracils with adenine indicated that the order of enhancing effect is the same as the order of increasing van der Waal's radii for the substituents (see Table I). Ts'o and Chan (1964) have also reported that 5-bromouridine self-associates more extensively than does uridine.

The sugar moiety apparently causes some reduction of association tendency. The interaction of caffeine with adenosine was less than that with adenine (Table IV). The binding tendency of uridine toward adenine was also slightly less than that of uracil (Table I). This retarding effect of the ribose moiety is expected to be of steric origin (Broom *et al.*, 1967). Further, the effect of the 2′-hydroxyl group on the association tendency of the guanosine residue is illustrated

TABLE III: Hypoxanthine, Adenosine, and Guanosine Complexes.[a]

Solute–Complexing Agent	Concn (mM) Range	n	I (mM)	Slope ($\times 10^2$)	Std Error ($\times 10^2$)	$K_{app\ 1:1}$ M^{-1} at 25°
Hypoxanthine–caffeine	5.0–20.0	5	5.11	4.92	0.08	10.1
Adenosine–caffeine	5.0–20.0	5	19.2	43.0	1.58	39.4
Guanosine–caffeine	6.25–25.0	5	1.67	2.61	0.08	15.6
Guanosine–8-methoxycaffeine	2.5–10.0	5	1.66	3.68	0.26	23.0
Guanosine–quinoxaline	10.0–50.0	5	1.68	2.27	0.06	13.8

[a] All specifications are the same as in Table I.



III

theophylline, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
caffeine, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
8-methoxycaffeine, $R_1 = R_2 = R_3 = CH_3$; $R_4 = OCH_3$

in Table V. Quinoxaline interacts to a similar extent with both guanosine and deoxyguanosine. The alkylxanthines, on the other hand, definitely formed more stable complexes with deoxyguanosine than with guanosine. The self-association tendency of 2′-deoxyadenosine has also been observed to be larger than that of adenosine (Broom *et al.*, 1967).

The amino group also appears to have an enhancing effect. Despite the retarding effect of the ribose group, adenosine forms a more stable complex with adenine than does purine. Inosine, which lacks the amino group of the guanine residue, interacts less strongly with adenine than does deoxyguanosine. The association tendencies of hypoxanthine, guanosine, and deoxyguanosine toward caffeine are also in accord with this view (Table IV).

Discussion

It is now well established that planar aromatic molecules interact in water by way of vertical stacking of one molecule on top of another (Jardetzky, 1964; Chan *et al.*, 1964). The presence of a large mobile π-electron system, therefore particularly favors this type of interaction. Thus, purines are expected to have a higher tendency to associate than pyrimidines (Ts'o *et al.*, 1963). The data summarized in Tables I and II generally support this view and clearly indicate the absence of Watson–Crick-type specificity in these interactions, as has previously been reported from Raman studies (Lord and Thomas, 1967).

Although the size of the interacting molecules appears to be of prime importance in deciding the association tendency of these molecules in aqueous media, various substituents markedly modify the association tendencies of parent compounds (see Tables IV, V, and VI), for example, alkylation, hydroxylation, and halogenation. Although these results agree with those reported earlier (for review, see Ts'o, 1968), it should be emphasized that the effect of 5-halogen substitution in the uracil residue may shed light on the nature of these interactions. The order of association tendency of 5-halouracils follows the order of the wavelength of maximum absorption of the monomers at pH 5, and also of the refractivity of the substituents which is related to polarizability (Table VI). These facts indicate the importance of the contribution of electronic effects as well as of London dispersion forces in stabilizing complexes in aqueous media.

In the present study, however, a few controversial points were noticed. Many of the differences in physical properties between ribosides and 2′-deoxyribosides have been explained on the basis of the presence of an intramolecular hydrogen bond between N-3 and the 2′-OH group (Ts'o *et al.*, 1966). Since the presence of such a hydrogen bond would reduce the free rotation about the glycosidic bond, the retarding steric effect of the sugar moiety would be expected to be less in the presence of the intramolecular hydrogen bond than

TABLE IV: Apparent 1:1 Stability Constants (M^{-1}) of Alkylxanthine Complexes at 25°.

	Caffeine	8-Methoxy-caffeine	Theophylline
Adenine	45.1	80.2	31.2
Adenosine	39.4		
Guanosine	15.6	23.0	
Deoxyguanosine	26.5	30.7	14.0
Hypoxanthine	10.1		

TABLE V: Effect of 2′-Hydroxyl Group on the Interactive Tendency of Guanine Nucleosides, $K_{app\ 1:1}$ (M^{-1}) at 25°.

	Guanosine	Deoxy-guanosine
Caffeine	15.6	26.5
8-Methoxycaffeine	23.0	30.7
Quinoxaline	13.8	14.3

TABLE VI: Interactions of 5-Halogenated Uracils with Adenine.

Complexing Agent	$K_{app\ 1:1}$ M^{-1} at 25°	λ_{max} at pH 5 (mμ)[a]	R_D[b]
Uracil	4.16	260	1.028
5-Fluorouracil	5.44	268	0.81
5-Chlorouracil	6.33	275	5.844
5-Bromouracil	7.04	278	8.741
Uridine	4.03	262[c]	
5-Iodouridine	9.63	291	13.954

[a] Berens and Shugar (1963). [b] Vogel (1948). [c] Beaven *et al.* (1955).

in its absence. According to this simple expectation, the association tendency of guanosine would be higher than that of deoxyguanosine. This, however, is not the case (see Tables II and III). The contribution of the 2′-OH group is much more complex than is indicated by the simple expectation mentioned above. In order to assess the effect of the glycosidic moiety on the interaction of heteroaromatic compounds, many more studies on the nature of the complexing agent itself are needed.

Extension of the study of purine and pyrimidine base interactions in aqueous media to other classes of heteroaromatic compounds has provided entirely new information which may have some bearing on the nature of molecular interaction. Namely, the order of association tendencies of a series of complexing agents of similar size, including those which do not belong to the same homologous series, toward a given solute is not necessarily the same as that toward another solute. The order of association tendencies among some purines, a quinoline derivative and a quinoxaline toward adenine is: 8-methoxycaffeine > caffeine > chloroquine > theophylline > adenosine > quinoxaline. The order toward deoxyguanosine is: chloroquine > 8-methoxycaffeine > caffeine > quinoxaline > theophylline > adenosine. This discrepancy in the order may indicate the presence of some structural features which discriminate the interaction of a certain pair of compounds from that of another pair, although stacking interaction in aqueous media is generally considered to be nonspecific.

In view of current interest in the secondary structure and conformation of polynucleotides in water (Tinoco *et al.*, 1968; Chan and Nelson, 1969; Ts'o and Kondo, 1969), it may be pointed out that many characteristics of monomer interactions in aqueous media revealed in the present study are reflected in the properties of the secondary structure of homopolymers and their complexes with complementary homopolymers. For example, polythymidylate (poly T) has a higher T_m (36°) than polyuridylate (poly U) (Shugar and Szer, 1962), and similarly methyl substitution in polycytidylate (poly C) increases the T_m value by about 19° (Szer, 1965). The stability of a triple-stranded complex, poly(T_2-A), as judged by the T_m value, is much higher than that of the corresponding complex formed between poly U and poly A (Barszcz and Shugar, 1968). Analogous with 5-methyl substitution, 5-bromo-substituted pyrimidine polymers also form more stable complexes with complementary polymers than the corresponding unsubstituted polymers do (Pochon and Michelson, 1965; Inman and Baldwin, 1964; Howard *et al.*, 1969). This trend would not be unreasonable if base-stacking interaction plays a more important role in stabilizing the single- and double-stranded helical structures of nucleic acids than hydrogen-bonding interaction (Herskovits *et al.*, 1961; DeVoe and Tinoco, 1962; Crothers and Zimm, 1964; Fasman *et al.*, 1964; Hanlon, 1966). The order of the stability of the 2:1 complexes of a series of poly 5-halouridylates is, however, not in complete agreement with that of the association tendencies of the constituent monomers toward adenine investigated in the present study (Massoulie *et al.*, 1966). Lack of strict correlation between the interactions of the monomer and polymer series likely indicates that many factors are involved in these interactions, particularly in the polymer series. Geometric constraint which is absent in monomer interactions will undoubtedly have an influence on the polymer interactions.

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