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SOLVATION EFFECTS AND THE MECHANISM OF DRUG-DNA BINDING

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Many experimental and theoretical papers describing drug binding to nucleic acids have appeared in the last two decades but in spite of numerous efforts the basic mechanisms involved in the process presently are not clearly understood. Here the attention will be given to the more general aspects of dye-binding (non specific) which are common to most interacting systems, leaving aside specific interactions which are peculiar of particular dyes and/or particular DNA sequences. From the literature on non-specific binding it is found that the attention has been given essentially to the role of electrostatic interactions,[1] whereas solvation effects have been generally neglected.

Cornerstone of the electrostatic models is the presence of the dielectric constant ε which appears both in the so called linear charge density expressed by means of the dimensionless parameter $\xi = e^2/\varepsilon\, bkT \simeq 7.14/b$ (b in A) at 25°C and in the Debye screening parameter $\kappa = (8\pi e^2 I/100\ kT)^{1/2} \simeq 0.33\ I^{1/2}$ in A^{-1} at 25°C where e is the charge, k is Boltzmann's constant, T is the absolute temperature and I is the ionic strength. Since the dependence upon ionic strength has been widely considered (1) our attention has been centred mainly on the role of the dielectric constant which can be changed by employing various cosolvents.

In this communication we report on the binding of a few drugs (ethidium bromide, propidium di-iodide, proflavine and actinomycin D) to calf thymus DNA water solutions in the presence of alcohols (methanol, ethanol, propanols) which lower the dielectric constant, and in the presence of amides (formamide and N-methyl formamide) which increase the dielectric constant of the solutions. The log of the ethidium to DNA binding constant when plotted versus the dielectric constant of the solution, with alcohols as cosolvents, shows a linear fall independent of the alcohol employed.[2] The results, as recently shown, cannot be described in terms of electrostatic effects which are between one and two orders of magnitudes smaller than those observed and, furthermore, of opposite trend. A thermodynamic analysis has shown instead that solvation effects have a dominant role in the process.[2]

When extending the analysis to other dyes such as propidium, proflavine and actinomycin in alcohol water solutions, it is found the trend is again that

displayed by ethidium but when amides are used as cosolvents then the log K vs ε trend becomes opposite to that displayed by alcohols. However the data both for alcohols and amides, can be brought together if log K is plotted versus the co-solvent volume fraction as shown in the figure.

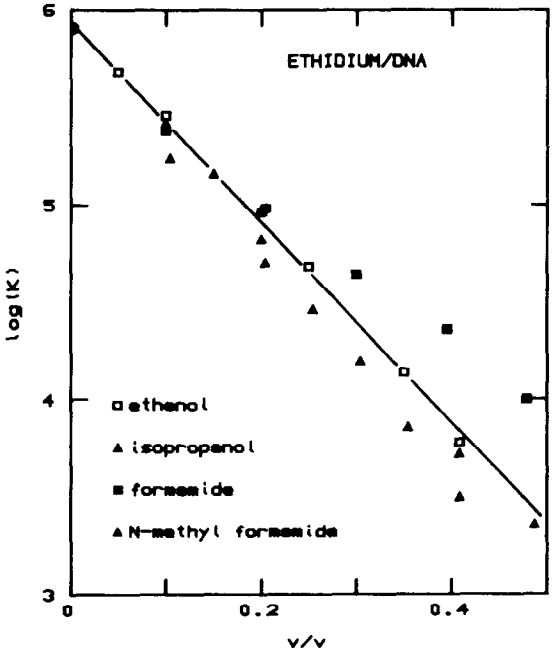

Fig.1 - Logarithm of the binding constant K of ethidium to DNA versus cosolvent volume fraction.

The conclusions first reached for the ethidium/DNA/water/alcohol system, exhibiting a marginal role of the electrostatic interactions, are confirmed by the use of other dyes and, above all, by the results obtained employing amides as cosolvents.[3] In terms of electrostatic interactions addition of amides would lead to effects opposite to those observed for alcohols, since ε is lower for alcohols and higher for amides, and this is contrary to our findings. When comparing the binding energy $-\Delta G=RT \ln K$ a large change in ΔG, of the order of 0.7 kcal/10% cosolvent volume, is found for several dyes and cosolvents thereby strongly suggesting that solvation effects largely account for the free energy of intercalation. To be noted that also other interactions, e.g. solute-solute, are strongly influenced by the presence of cosolvents. In conclusion the above results can be understood in terms of drug solvent interactions which are more favourable in the presence of cosolvents and therefore lead to more unfavourable DNA drug interaction. Since this effect is quite large its presence can be an obstacle to accurate determinations of the strength of specific interactions. Finally, a close correlation to "in vivo" interactions is expected since in living systems water is certainly accompanied by a high percentage of other molecules which are likely to produce effects similar to those described in this paper.

References

1. See, e.g. R.A.G. Friedman and G.S. Manning, Biopolymers 23, 2671 (1984) and references quoted therein.
2. G. Baldini and G. Varani, Biopolymers 25, 2187 (1986).
3. G. Varani, L. Della Torre and G. Baldini, Biophysical Chemistry, in press.