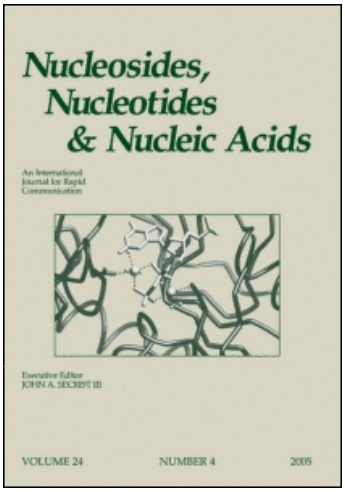

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Partial Molar Volumes of mRNA 5′ Cap Analogues

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ABSTRACT

Partial molar volumes in aqueous solution of eleven selected 7-methylguanine cap-analogues and their guanine counterparts were determined by means of density measurements. Hydrophobicity of the investigated compounds regarding their structural features was analysed within the framework of the solute-solvent interaction model, based on the relative density of the molecular solvation shell.

INTRODUCTION

Eukaryotic mRNAs are distinguished by the presence of a 5′-terminal cap structure, m^7GpppN (N = G, A C or U), which consists of 7-methylguanosine linked by a 5′-to-5′ triphosphate bridge to the first transcribed nucleoside and

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is specifically recognized by the eukaryotic translation initiation factor eIF4E. 7-Methylguanine is stabilized in the eIF4E-cap complex by cation-π sandwich stacking between two tryptophans and three Watson-Crick type hydrogen bonds.[1] The triphosphate chain of the bound cap forms hydrogen bonds and salt bridges with the arginines and lysins of the protein. A deeper insight into thermodynamics of eIF4E binding to the cap[2] requires analysis of both the hydrophobic and electrostatic effects.

RESULTS AND DISCUSSION

Partial molar volumes at infinite dilution in aqueous solution of $\overline{V_2^0}$ 11 selected guanine nucleotides and nucleosides including cap-analogues were determined by density measurements (Table 1). The nucleotides are available as sodium salts and the Na^+ ions, in the amounts as indicated in Table 1, also contribute to $\overline{V_2^0}$. Introduction of the methyl group at N(7) of GMP and GTP resulted in a decrease of the partial molar volumes by $15\,cm^3{\cdot}mol^{-1}$ and $4\,cm^3{\cdot}mol^{-1}$, respectively. This indicates that the volume increase caused by the methyl group at N(7) is surpassed by the volume decrease due to reorganization of the water molecules in the solvation shell around the positively charged nitrogen. The hydrophobic parameter $\alpha = (V_2^M - \overline{V_2^0})/V_{1,solv}$, defined as relative density of water in the molecular solvation shell,[3,4] was

Table 1. Structural parameters of 7-methylguanine and guanine analogues. For syntheses see Cai et al.[6]

		Volume [$cm^3{\cdot}mol^{-1}$]					Surface [$Å^2$]		
Compound	Na^+ content[d]	$\overline{V_2^0}$	V_2^M	$V_{1,solv}$	S_{polar}	S^M	$S^{(C8H8)}$	α	P
m^7G	0	189.0 ± 2.3	124.0	801.8	130.9	258.4	15.0	−0.081	0.56
GMP	2	220 ± 14	137.5	879.6	184.7	287.0		−0.062	0.66
GMPme[a]	1	234.4 ± 2.1	147.9	922.0	179.5	303.5		−0.076	0.60
m^7GMP	2	205.0 ± 1.6	148.8	848.5	167.9	287.8	15.3	−0.042	0.66
bz^7GMP [b]	2	280.3 ± 2.5	184.4	1002.5	166.3	353.7	16.2	−0.066	0.54
m^7GMPme[a]	0.5	259.1 ± 2.3	155.9	953.7	161.6	320.5	16.6	−0.097	0.56
GTP	4	290 ± 22	183.1	1051.5	259.0	356.9		−0.054	0.75
m^7GTP	3.5	286 ± 5	196.1	1093.4	254.2	383.4	15.4	−0.047	0.72
et^7GTP[c]	3.5	305 ± 7	203.0	1074.9	246.5	393.1	14.2	−0.054	0.69
bz^7GTP [b]	3.5	395 ± 4	235.3	1155.7	244.6	439.8	15.6	−0.083	0.62
m^7GpppG	3	415 ± 10	304.6	1511.1	364.6	586.2	14.1	−0.050	0.66
Na^+	1		2.1	193.3	8.0	8.0			

[a]P^1-methyl ester.
[b]7-benzyl.
[c]7-ethyl.
[d]Na^+ content measured by Flame Atomic Absorption Spectroscopy.

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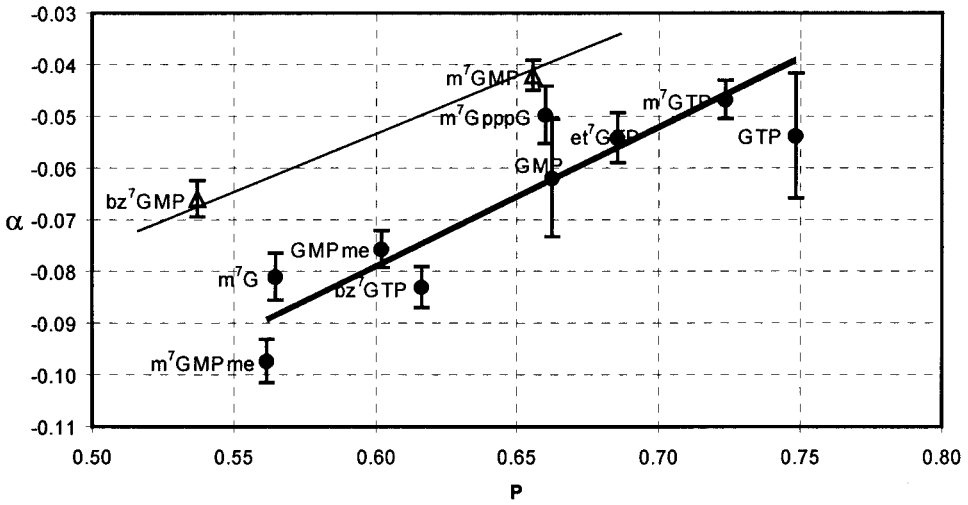

Figure 1. Dependence of α on polarity P for the investigated analogues. $\alpha = bP + \alpha_0$, $b = 0.27(\pm 0.04)$.

calculated using the molecular volume V_2^M and the volume of the solvation shell $V_{1,solv}$ (Table 1) determined by the program GEPOL, version 12.1.[5] Generally, for hydrophobic compounds α becomes more negative with decreasing polarity, $P = S_{polar}/S^M$, where S_{polar} and S^M are the polar and the total surfaces of the molecule (calculated by GEPOL), respectively.[3,4] A decrease of α points to reduction of the density of the solvation water; and hence to structural arrangement of the water molecules in the solvation shell. It was assumed that each sodium cation contributes to the V_2^M, $V_{1,solv}$, and S_{polar}. Substitution at N(7) introduces a positive charge in the imidazole ring, therefore the polar surface was extended by the surface of the C(8) and H(8).

Correlation between α and P is observed for almost all the analogues (Fig. 1), except for m^7GMP and bz^7GMP. In the case of m^7GTP, et^7GTP, and bz^7GTP the elevation of the hydrophobic character may be attributed to introduction of the bulky substituents of increasing diameter. In the series of GMP, GMPme, and m^7GMPme introduction of the subsequent methyl groups increases the hydrophobic character of the compounds. It can be also observed that the phosphates in principle decrease the hydrophobicity. The partial hydrophobic partial hydrophilic character of the molecular surface of the cap provides the molecule with the unique features for specific recognition in the eIF4E cap-binding centre based on cooperativity of cation-π stacking and hydrogen bonding.[7]

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