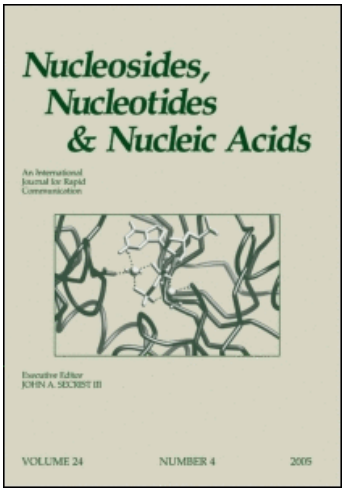

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Experimental and Theoretical Volumes of Nucleic Acids

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EXPERIMENTAL AND THEORETICAL VOLUMES OF NUCLEIC ACIDS

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ABSTRACT: Further evidence of the need to incorporate both experimental and theoretical results in estimates of the volumes of molecules is presented. The volumes of a series of alkyllated purines and pyrimidines, with experimentally known volumes, were estimated by van der Waals and Semi-empirical quantum mechanical methods. In all instances, the van der Waals methods failed to reproduce the experimental volumes. The Semi-empircal methods were able to reproduce the experimental volumes consistentally.

Molecular volume is fundamental to understanding of molecular structure and physical properties of biological systems. Molecular volume can be correlated to experimentally observable factors such as surface accessibility, heat capacity, and chemical reactivity. The accuracy of their determination limits their useful application. Traditional methods employing Van der Waals radii contain inconsistencies and arbitrary assumptions which result in significant differences between calculated and experimental values. Volumes calculated by semiempirical methods, with reference to experimentally determined values, lead to improved accuracy and hence usefulness. We previously reported results for small molecules, amino acids, and proteins. The current study examines nucleic acid alkylated and unmodified base volumes using the same techniques.

Experimental volumes for the pyridines range from 94 $Å^3$/ molecule for uracile to 265 $Å^3$/ molecule for 1, 3 Diethyl thymine. Using two different methods which employ Van der Waals radii to calculate volume, the experimental volumes were either underpredicted by 8% or overpredicted by 15%. It was possible, using semi-empirical molecular orbital calculations, to reproduce the experimental volumes by including 99.7% of the total electron density in each instance

Experimental volumes for the purines range from 160 $Å^3$/ molecule for adenosine to 235 $Å^3$/ molecule for 9-Methyl-8-ethyl adenosine. The methods employing Van der Waals radii incorrectly predict the volumes as was found for the pyridines. Using semi-empirical molecular

orbital calculations, it was again possible to systematically reproduce the experimental volumes by including 99.7% of the total electron charge.

These studies indicate that it is possible to accurately reproduce the molecular volumes of nucleic acids by use of molecular orbital calculations. This is true for both naturally occurring and chemically modified bases. Since the volume, and attendant surface area, of nucleic acids plays an essentially role in understanding the nature of their interaction with other molecules, this more accurate prediction offers a superior means of assessing the effect of chemical modification of the bases.

Semiempirical Volume Calculations

Compound	Included[a]	Volume[b]	Volume[c]	Error[d]
1,3-Dimethyl-U	99.96	181.3	187.8	3.6
1,3,6-Trimethyl-U	99.85	206.2	208.1	1.0
1,3,5,6-Tetramethyl-U	99.86	231.8	233.8	0.9
1,3-Dimethyl-6-ethyl-U	99.88	233.0	230.0	-1.3
1,6-Dimethyl-3-ethyl-U	99.85	234.8	234.1	-0.3
1,3-Diethyl-T	99.85	265.0	264.5	0.0
1,5,N-Trimethyl-C	99.87	210.0	212.9	1.4
9-Methyl-A	99.80	186.0	186.3	0.2
8,9-Dimethyl-A	99.76	206.9	205.5	-0.7
2,9-Dimethyl-A	99.66	211.2	211.5	0.1
9-Methyl-2-ethyl-A	99.76	231.3	230.3	-0.4
9-Ethyl-G	99.84	213.7	214.9	0.6

a. Percentage of total, calculated electron density included.
b. Experimentally determined volumes from reference 3.
c. Volume calculated from an average, total included electron density of 99.8%
d. Percentage error $(V^c - V^b)/V^b$. The average error is 1.0%.

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