

## CONFORMATIONAL ANALYSIS OF BICYCLIC PHOSPHATE DERIVATIVES BY COMPUTATIONAL METHODS

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### ABSTRACT

Trimethylolpropane phosphate is an ethyl bicyclic phosphate produced during the partial pyrolysis of certain synthetic, ester-based turbine lubricants supplemented with phosphate-based lubricity additives, being considered as having high toxicity. In this paper its structure was simulated by molecular mechanics methods using the OPLS, AMBER and MMFF94s force fields by the AM1 semiempirical approach and the Hartree-Fock Self-Consistent Field (RHF) method and results were compared with X-ray structure. Generally the generated structures obtained by these methods reproduced with accuracy the experimental data. The structure obtained by the RHF approach was closer to experimental data.

### INTRODUCTION

Trimethylolpropane phosphate (TMPP, 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-oxide (fig. 1) [1] is an ethyl bicyclic phosphate produced during the partial pyrolysis of certain synthetic, ester-based turbine lubricants supplemented with phosphate-based lubricity additives [2]. TMPP has also been demonstrated to be formed through the partial pyrolysis of certain fire-retardant-treated urethane foams [3]. TMPP induces epileptiform activities in hippocampal CA1 neurons, and binds to the GABAA-benzodiazepine receptors [4]. It shows very low binding affinity for GABAB, nonadrenergic, dopaminergic, or cholinergic receptors [5].

The oral rat LD50 value of 3.08 mg/kg [6] includes TMPP in the category of highly toxic bicyclic phosphorus esters, according to the Hodge and Sterner scale [7].

In this paper the structure of TMPP was simulated by conformational analysis using molecular mechanics and quantum methods, in vacuum. The conformations of minimum energy thus obtained were compared to X-ray crystallography structure [8] of the same compound. The chosen method could be used further in structure-toxicity studies.

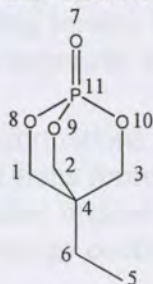


Fig. 1. Structure of 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-oxide



## METHODS

### **Bicyclic phosphate structure simulation by OMEGA software**

The molecular structure of the title bicyclic phosphate was modelled by the conformational search ability of the Omega v.2.3.2 (OMEGA (version 2.3.2), OpenEye Science Software, 3600 Cerrillos Road, Suite 1107, Santa Fe, USA, 2008.) program. SMILES notation was used as program input. For the structure generation of conformers, following parameters were used: a maximum of 400 conformers per compound, an energy cutoff of 10 kcal/mol relative to global minimum identified from the search. The force field used was the 94s variant of the MMFF (Merck Molecular force field) with coulomb interactions and the attractive part of the van der Waals interactions. The RMSD fit value 0.1 Å was used to avoid redundant conformers.

### **Bicyclic phosphate structure simulation by HYPERCHEM**

Bicyclic phosphate structure were built by the Hyperchem software (HyperChem 7.52 release for Windows; HyperCube, Inc., Gainesville, Florida, USA, <http://www.hyper.com>.) and conformational analysis was performed by molecular mechanics calculations, using the OPLS and AMBER force fields, with the RMS gradient value of 0.01 kcal/Å·mol as criterion to choose an optimized conformation, an acceptance energy cutoff of 20 kcal/mol above the minimum energy. Conformational analysis was, also, performed by the semiempirical AM1 method [9] with the RMS gradient value of 0.01 kcal/Å·mol, as criterion to choose an optimized conformation and Polak-Ribiere as conjugate gradient, an acceptance energy cutoff of 10 kcal/mol above the minimum energy, SCF convergence of  $10^{-5}$ .

### **Bicyclic phosphate structure simulation by Gaussian**

Gaussian 03W (Gaussian 03, Gaussian, Inc., Wallingford CT, 2004.) was used to model the structure of the 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-oxide. The Hartree-Fock Self-Consistent Field method was employed, with 3-21G basis set for geometry optimization and frequency calculation.

## RESULTS AND DISCUSSION

One conformation was obtained by each method. The respective optimized structures were superimposed on the corresponding unmodified X-ray structure [8] by a least-squares superimposition procedure (root-mean-square-deviation (RMSD) values are presented in Table 1). Only non-hydrogen atoms were matched.

Averages were calculated for each type of bond and angle, for each minimum energy structure, as well as for the X-ray one. Standard deviations were computed in each case, with respect to the experimental data. Results are presented in Table 1 (bold values indicate the method with lowest standard deviation between average and experimental values).



**Table 1.** Experimental and calculated bond lengths and angles of the optimized compound obtained by molecular mechanics and quantum chemical calculations

	AM1	AMBER	RHF	MMFF94s	OPLS	X-RAY
P11-O8*	1.61	1.60	1.63	1.62	1.60	1.56
P11-O9*	1.61	1.60	1.63	1.62	1.60	1.56
P11-O10*	1.61	1.60	1.63	1.62	1.60	1.57
Average	1.61	1.60	1.63	1.63	1.60	1.56
Standard deviation	0.03	0.03	0.05	0.05	0.03	
O8-P11-O9**	100.86	101.72	99.76	102.12	101.72	104.12
O9-P11-O10**	101.32	102.23	99.93	102.12	102.23	103.95
O10-P11-O8**	100.86	101.72	99.76	102.12	101.72	104.46
Average	101.01	101.89	99.82	102.12	101.89	104.18
Standard deviation	2.24	1.62	3.09	1.46	1.62	
O8-C1*	1.41	1.43	1.46	1.43	1.43	1.46
O9-C2*	1.41	1.43	1.46	1.43	1.43	1.46
O10-C3*	1.41	1.43	1.46	1.43	1.43	1.46
Average	1.41	1.43	1.46	1.46	1.43	1.46
Standard deviation	0.04	0.02	0.00	0.00	0.02	
O7-P11-O8*	117.07	116.23	117.99	116.08	116.23	114.36
O7-P11-O9*	116.95	116.30	117.93	116.09	116.30	114.67
O7-P11-O10*	116.95	116.30	117.93	116.09	116.30	114.03
Average	116.99	116.28	117.95	117.95	116.28	114.35
Standard deviation	1.87	1.36	2.54	2.54	1.36	
P11-O7*	1.44	1.48	1.50	1.50	1.48	1.45
Standard deviation	0.00	0.02	0.05	0.04	0.02	
RMSD	0.061	0.057	0.080	0.084	0.056	

\* bond length (in Å); \*\* bond angle (in degrees)

Calculated bond lengths and angles were in good agreement with the experimental ones. The obtained RMSD values obtained by the least-squares superimposition procedure of the optimized structure derived from the above mentioned methods over the experimental X-ray one indicated that the optimized structure modelled by the Amber, OPLS and AM1 methods was in good agreement with the experimental one.

## CONCLUSIONS

- Several optimization procedures were studied to obtain a consistent molecular structure of 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-oxide.
- Conformational analysis was performed by molecular mechanics calculations employing the OPLS, Amber and MMFF94s force fields, the semiempirical AM1 approach and the *ab initio* RHF method.
- Generally the employed methods reproduced with accuracy the experimental X-ray data. Amber, OPLS and AM1 methods modelled better the the TMPP structure.
- The above presented results are useful for structure-toxicity relationships modeling.



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