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Bioorganic & Medicinal Chemistry 13 (2005) 5826–5829
Bioorganic & Medicinal Chemistry

Calorimetric and computational study of enthalpy of formation of 3,6-dibutanoic-1,2,4,5-tetroxane

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Received 30 April 2005; accepted 24 May 2005
Available online 28 June 2005

Abstract—A thermochemical method, a rather simple experimental technique, is used to determine the enthalpy of the formation of 3,6-dibutanoic-1,2,4,5-tetroxane. The study is complemented with suitable theoretical calculations at the semiempirical and ab initio levels. A particular satisfactory agreement between both ways is found for the ab initio calculation at the 6-311G basis set level. Some possible extensions of the present procedure are pointed out.

1. Introduction

The devastating consequence of malaria is a cause of wide international concern.[1] A promising approach for treating malaria deriving from chloroquine-resistant parasites is based on the development of new drugs which incorporate in their molecule structure a peroxide functionality.[2–5] As a result of an apparent association between the peroxide functional group and antimalarial activity, a substantial effort has been devoted to developing new peroxide antimalarials.[3–5] Of these, we have been particularly interested in the 3,6-dibutanoic-1,2,4,5-tetroxane (DAPG), which is easily prepared by the acid-catalyzed condensation of glutaraldehyde and hydrogen peroxide, speculating that this peroxide could have antimalarial activity.

In this study, we report the synthesis and the experimental enthalpy of the formation of DPAG, as well as the theoretical results calculated from semiempirical and ab initio Hartree–Fock methods.

2. Theoretical calculations

Among the most important purposes of the calorimetric studies is to find out the molecular energy of a set of structurally and functionally related molecules to establish the corresponding structure–activity relationships and to be able to discuss the main electronic features determining the chemical reactivity.

It is well known that to make theoretical calculations of molecular enthalpy of formation, it is necessary to find a suitable isodesmic chemical reaction to optimize the corresponding molecular structure and to perform the frequency calculations from the optimized equilibrium molecular geometries, applying the corresponding theoretical method to obtain the total electronic energy at 298 K. Here, we have chosen the Gaussian 94 package[9] to perform the theoretical calculations at the semiempirical and ab initio levels.

To get the equilibrium molecular geometries, it is necessary to localize the absolute minimum at the potential energy hypersurface, which is not a trivial task. The

Keywords: 3,6-Dibutanoic-1,2,4,5-tetroxane; Calorimetric study; Theorectical calculations; Semiempirical and ab intio calculations.
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doi:10.1016/j.bmc.2005.05.046

optimization procedure is complete when the numerical process converges, i.e., when the forces are null and all the frequencies are real.

3. Results and discussion

3.1. Experimental enthalpy of formation

Table 1 gives the results for a typical combustion experiment on compound DPAG. Table 2 gives the standard molar energy and enthalpy of combustion and formation of DPAG, in the crystalline state at $T = 298.15$ K and corresponding to the reaction

$$C_{10}H_{16}O_8\,(c) + 10O_2\,(g) \rightarrow 10CO_2\,(g) + 8H_2O\,(l). \quad (1)$$

The uncertainties of the standard molar energy is four times the final overall standard deviation of the mean and they were estimated as outlined by statistical methods. Vapor pressure was determined at different temperatures and the enthalpy of sublimation was calculated as pointed out before.

The standard molar enthalpies of formation for both crystalline and gaseous states of the DPAG at $T = 298.15$ K are also given in Table 2. No combustion enthalpy and enthalpy of sublimation have been found in the standard literature for comparison purposes.

3.2. Theoretical enthalpy of formation

In the case of the DPAG, the isodesmic reaction is $2H_3C–CH_2–O–O–CH_2CH_3$ (DEP) (g) + $2CH_3–COOH$ (g) + $H_3C–CH_3$ (g) → DPAG (g) + $6CH_4$ (g).

To calculate enthalpy values at 298 K, the difference between the enthalpy at temperature T and 0 K can be evaluated according to the standard thermodynamic formulae. The sum of electronic and enthalpy energies at 298 K at the Hartree–Fock level using the semiempirical and ab initio procedures with different basis sets for the studied compounds are also summarized in Table 3. We have resorted to the semiempirical calculations at the AM1 and PM3 levels since it is well known that in these procedures, a suitable adjustment of the elements of the F matrix is used to bring the calculated results into the best possible agreement with standard thermochemical results, largely enthalpy of formation.[10] Semiempirical methods like AM1[11] and PM3[12–14] provide a quite effective compromise between the accuracy of the results and the expense of computer time required. A calculation performed with AM1 and PM3 is able to reflect the experiment as effectively as an ab initio calculation using a small basis set.[15] Regarding the ab initio calculations, we have made enthalpy computations using several basis sets of molecular orbitals (i.e. 3-21G, 3-21+G, 6-31G, 6-31+G, 6-311G, and 6-311+G)

Table 1. Results from typical combustion experiments at 298.15 K

	1	2	3	4	5	6	7	8
M_{DPAG} (g)	0.0004	0.0003	0.0005	0.0006	0.0005	0.0004	0.0007	0.0005
m_{gel} (g)	0.0339	0.0039	0.0373	0.0385	0.0213	0.0366	0.0360	0.0377
m_{Fe} (g)	0.0120	0.0125	0.0121	0.0132	0.0118	0.0096	0.0111	0.0018
ΔT (K)	0.049570	0.012991	0.053924	0.056209	0.034127	0.051374	0.051954	0.048443
$(m_{water} + E)\Delta T$ (cal)[a]	176.28	46.20	191.76	199.89	121.36	182.69	184.76	172.27
$m_{gel}\Delta U_{gel}$ (cal)[b]	147.75	16.99	162.56	167.79	92.83	159.51	156.89	166.03
$m_{Fe}\Delta U_{Fe}$ (cal)[c]	26.76	27.88	26.98	29.44	26.31	21.41	24.75	4.01
ΔU_c (cal/g)[d]	4432.44	4431.18	4430.50	4429.16	4433.38	4432.24	4439.92	4439.26
ΔH_c (kcal/mol)	−1171.18	−1170.85	−1170.67	−1170.32	−1171.43	−1171.13	−1173.16	−1172.99

[a] $m_{water} = 2700$ g.
[b] ΔU_{gel} (heat of combustion of gelatine capsules) = 4358.30 ± 0.65 (cal/g).
[c] ΔU_{Fe} (heat of combustion of iron wire) = 2230.00 ± 0.70 (cal/g).
[d] ΔU_c standard specific heats of combustion.

Table 2. Summary of experimental specific heats of combustion and standard molar thermodynamic function of DPAG at $T = 298.15$ K

Experiment number	ΔU_c^0(c)[a] (cal/mol)	$-(\Delta H_c^0$(c)[b] (kcal/mol)	$-\Delta H_f^0$(c)[c] (kcal/mol)	$-\Delta H_f^0$(g)[d] (kcal/mol)
1	4432.44	1171.18	317.26	262.76
2	4431.18	1170.85	317.59	263.09
3	4430.50	1170.67	317.77	263.27
4	4429.16	1170.32	318.12	263.62
5	4433.38	1171.43	317.01	262.51
6	4432.24	1171.13	317.31	262.81
7	4439.92	1173.16	315.28	260.78
8	4439.27	1172.99	315.45	260.95
Average value	4434.26	1171.47	316.98	262.47
Standard deviation	3.87	1.05	1.05	1.05

[a] Standard molar heat of combustion.
[b] Standard enthalpy of combustion.
[c] Standard enthalpy of formation in crystalline state.
[d] Standard enthalpy of formation in gas phase obtained from the sublimation molar enthalpy ($\Delta H_S = 54.5$ kcal/mol).

Table 3. Calculated electronic energy and heat of reaction (in Hartree units)

	$-(\varepsilon_0 + H_{corr})$[a] Hartree							
	AM1	PM3	RHF 3-21G	RHF 3-21+G	RHF 6-31G	RHF 6-31+G	RHF 6-311G	RHF 6-311+G
DPAG	0.107652	0.121523	980.970905	981.118240	985.968213	985.99755	986.249282	986.246318
DEP	0.088909	0.127295	305.069212	305.112382	306.622051	306.631078	306.698948	306.704826
CH_4	0.034185	0.028432	39.925067	39.927109	40.128804	40.129575	40.136938	40.137280
Acetic acid	0.097462	0.095528	226.462966	226.506267	227.629449	227.637306	227.690399	227.69586
Ethane	0.051104	0.049756	78.709545	78.712647	79.113214	79.114248	79.128130	79.128657
ΔH_r[b]	0.012356	0.113977	0.048479	0.018302	0.011609	0.009736	0.035956	0.011312

[a] Sum of electronic and thermal enthalpies at semiempirical and Hartree–Fock ab initio techniques with different basis sets levels.
[b] Heat of reaction obtained with semiempirical and Hartree–Fock ab initio techniques at different basis sets levels: $\Delta H_r = \sum(\varepsilon_0 + H_{corr})_{products} - \sum(\varepsilon_0 + H_{corr})_{reactants}$.

Table 4. Enthalpy of formation of DPAG

$-\Delta H_f^0(g)$[a] (kcal/mol)							
AM1	PM3	RHF 3-21G	RHF 3-21+G	RHF 6-31G	RHF 6-31+G	RHF 6-311G	RHF 6-311+G
236.955	316.231	268.467	256.194	251.994	250.818	267.272	251.807

[a] Standard enthalpy of formation in gas phase at the semiempirical and Hartree–Fock ab initio technique levels and with different basis sets.

to test their relative capabilities to predict accurately the enthalpy of formation of the DPAG.

The heats of formation calculated through atomization reaction are given in Table 4. The analysis of theoretical results shows that ab initio procedures yield better results than semiempirical methods. Moreover, the best agreement among experimental data and theoretical predictions happens for the 6-311G basis set.

4. Conclusions

We have reported a rather simple and accurate enough experimental method to determine the enthalpy of the formation of the title compound and we have complemented it with the theoretical calculation of the property under study via semiempirical and ab initio molecular orbital methods. The theoretical value of the enthalpy of formation of DPAG, 276.27 kcal/mol, evaluated at the Hartree–Fock at the 6-311G basis set level, is in very good agreement with the experimental value, 262.47 kcal/mol. This methodology, consisting of the experimental determination of the thermochemical property and its complementation with theoretical procedures, represents a quite sensible way to study similar oxane derivative molecules, and at present, further studies along this line are under development. Results will be published elsewhere in the near future.

5. Experimental procedure

5.1. Synthesis of glutaraldehyde acid diperoxide

The DPAG is synthesized by the oxidation of glutaraldehyde with oxygen peroxide in the presence of concentrated sulfuric acid, following the Bayer and Viller method modified by Jorge et al.[6]

Sixty-eight percent of H_2O_2 (0.04 mol, 1.36 g) and glutaraldehyde (0.0762 mmol, 7.62 g) were added by consecutive dropwise addition to a stirred solution of water (12 ml), EtOH (12 ml), and H_2SO_4 (12 ml) at −10 °C. Stirring was continued for 4 h at −20 °C. The resulting white precipitate was filtered, washed with water, and air-dried. The precipitate was recrystallized in methanol and carefully dried under vacuum conditions. Melting points were determined with a electrothermal capillary melting point apparatus and we obtained a melting point of 90 °C.

5.2. Thermochemical measurements

The measurement of the heat of combustion of DPAG was made with an isoperibol macrocalorimeter fitted with a stirred water bath. The substance was burned in oxygen at $p = 25$ atm. The current of ignition was determined to be 2 A. The heat capacity of the calorimeter (E) was determined with a standard reference sample of benzoic acid (Sample SRM 39i, NIST) for all experiments, E was measured to be (856.17 ± 1.5) cal/K. The crystalline compounds were pressed into gelatine capsules of masses approximately 5×10^{-4} g. The reduction of the data to standard conditions was made through conventional procedures. [7] The atomic weights used were those recommended by the IUPAC Commission. [8]

The vapor pressures as a function of temperature of DPAG were measured by a mercury manometer through a Bodestein differential equipment, and the enthalpy of sublimation was deduced from the temperature dependence of the vapor pressures (Clausius–Clapeyron equation).

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