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Abstract

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On the Reactivity of Five- and Six-Membered Heterocyclic Compounds

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Many examples are known in which five-membered heterocyclic compounds prove to be considerably more reactive than six-membered compounds of the same series. Thus, tetrahydrofuran is more reactive than tetrahydropyran; five-membered glycosides prove to be many times more reactive than six-membered ones; and five-membered γ-monosaccharides, in contrast to six-membered ones, are so unstable that they have not even been isolated in the free state, and only their derivatives exist.

The reasons for such a difference in the reactivity of compounds in a given homologous series should naturally be sought in thermodynamics. To substantiate this assertion it would be necessary to determine the magnitudes of the change in the isobaric-isothermal potential in the corresponding reactions. Unfortunately, at present this is difficult mainly because data on entropies are lacking. However, from the examples of lactams and formals ([1,2]) it has been shown that the capacity of these compounds for polymerization changes in parallel with their so-called enthalpy of cyclization, i.e., the difference between the enthalpy of the given cyclic compound and the additively calculated enthalpy of the unit of the corresponding polymer. It follows from this that the enthalpy of cyclization can to a certain extent characterize the reactivity of a given cyclic compound in its transformations into linear compounds.

The main question of the present work was the extension of this conclusion to the γ- and δ-forms of monosaccharides, the polymerization of which may play a significant role in the biosynthesis of natural compounds. In passing, the work also made it possible to clarify certain other questions which, in our view, are of substantial interest.

The calculation of the enthalpy of cyclization of a given cyclic compound can be carried out in two ways: 1) by comparing the experimentally determined heat of combustion of this compound with its heat of combustion calculated additively from the increments of the corresponding groups; 2) by comparing the heats of combustion of the five- and six-membered compounds of a given series.

If, as has been shown in many cases, the enthalpy of cyclization of a six-membered ring is taken to be equal to zero, then the enthalpy of cyclization of a five-membered ring can be determined from the formula:

$$-\Delta H = (-\Delta H_{5-} + A) - (-\Delta H_{6-}),$$

where A is the increment of the heat of combustion of the group by which the 6- and 5-membered rings differ.

Thus, the experimentally determined quantities were the heats of combustion of the corresponding compounds. In all cases where this proved possible, the heats of combustion were reduced to the gaseous state. The heats of vaporization were calculated from empirical and semiempirical relationships ([3–5]).

The calorimetric apparatus and the method for measuring heats of combustion have been described in detail previously ([6]). The heats of combustion of the substances studied, both solid and liquid, with the exception of *n*-dibutyl ether, were obtained with an accuracy of 0.02–0.03% (mean deviation from the arithmetic mean). Liquid substances were burned in thin-walled glass ampoules weighing 0.15–0.25 g. Some of the objects of study, namely: αd- and βd-CH_3-glucopyranosides (δ-form), βd-CH_3-glucofuranoside (γ-form), and 2-methoxytetrahydropyran, were synthesized by us. The methods for obtaining these substances are described in the literature ([7–10]). The remaining substances were available in finished form and were only subjected to thorough purification. For all the substances studied, physicochemical constants were determined, which agreed well with the literature data. Table 1 gives the heats of combustion of all the substances we studied.

In the second column of Table 1 are given, in kcal_{15}, the changes in enthalpy upon isothermal (20°) combustion of the substances studied in the solid or liquid state at a pressure of 1 atm, and with formation as reaction products of gaseous CO_2 and liquid H_2O—also at a pressure of 1 atm. In the third column are given the calculated heats of vaporization, and in the last column—the heats of combustion for the gaseous state.

Table 1

Substance	$-\Delta H_c^{20}$, kcal/mol	Heat of vaporization, kcal/mol	$-\Delta H_c^{20}$(g), kcal/mol
Tetrahydrofuran (l)	598.0 ± 0.1	7.8	605.8
Tetrahydropyran (l)	750.1 ± 0.2	8.5	758.6
n-Dibutyl ether (l)	1277.5 ± 0.8	11.2	1288.7
αd-Glucose (s)	670.3 ± 0.1	–	–

Substance	$-\Delta H_c^{20}$, kcal/mol	Heat of vaporization, kcal/mol	$-\Delta H_c^{20}$(g), kcal/mol
2-Methoxytetrahydropyran (l)	868.8 ± 0.3	10.2	879.0
δ-Oxyvaleraldehyde (l)	697.2 ± 0.2	–	–
αd-Xylose (s)	559.2 ± 0.2	–	–
αd-CH_3-methylglucopyranoside (s)	842.1 ± 0.2	–	–
βd-CH_3-methylglucopyranoside (s)	841.1 ± 0.1	–	–
βd-CH_3-methylglucofuranoside (l)	849.4 ± 0.2	–	–

The data obtained by us make it possible to draw a number of conclusions.

1. Using the simplest oxygen-containing heterocycles—tetrahydropyran and tetrahydrofuran—as an example, by comparing experimental and additively calculated heats of combustion it was possible to show that the enthalpy of cyclization of a six-membered ring is close to zero, while that of a five-membered ring is about 5 kcal (this was previously shown for cyclanes and cyclic formals ([2])). From the difference between the heats of combustion of *n*-dibutyl ether and *n*-octane ([11]), the oxygen-atom increment necessary for additive calculation was calculated (−28.8 kcal/mol). The increment of the $-CH_2-$group was taken as 157.4 kcal/mol ([11]). The calculation was carried out in the two ways indicated above for the gaseous state.

a. The enthalpy of cyclization is

$$-\Delta H_\text{c} = -\Delta H_\text{comb. exp} - (-\Delta H_\text{comb. add}),$$

where

$$-\Delta H_\text{comb. add} = 157.4\, n + (-28.8),$$

n is the number of $-CH_2-$groups. With such a calculation, the value $-\Delta H_\text{c}$ for tetrahydropyran proves to be equal to 0.4 kcal/mol ($758.6_\text{exp} - 758.2_\text{add}$), and for tetrahydrofuran 5 kcal/mol ($605.8 - 600.8$).

b. For a five-membered ring, the enthalpy of cyclization can also be calculated from the following relation:

$$-\Delta H_{\mathrm{c}} = (-\Delta H_{\mathrm{comb.\,5-membered}}+157.4)-(-\Delta H_{\mathrm{comb.\,6-membered}}) = (605.8+157.4)-758.6 = 4.6\ \mathrm{kcal/mol}$$

The results obtained in both cases are close, since the heats of comb-

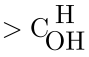
of tetrahydropyran, the experimental and calculated values almost coincide.

2. In proceeding to the determination of the heats of combustion of carbohydrates and substances close to them in structure, we considered it necessary to check the method using some pure substance of this class. As such a substance, αd-glucose was taken. The heat of its combustion according to our measurements (see Table 1) is $-\Delta H_c^{20} = 670.3$ kcal/mole, and according to the data of Huffman and Fox ([12]), reduced to our conditions, $-\Delta H_c^{20} = 670.18$ kcal/mole. The difference is 0.02%.

3. It was further necessary to show the validity of the simplest additive calculation being carried out for carbohydrates whose molecules contain a large number of polar functional groups. For this purpose the heats of combustion of 2-methoxytetrahydropyran, δ-oxyvaleraldehyde, αd-CH_3-glucopyranoside, and αd-xylose were determined, and the following calculations were carried out:

a. The increment for replacement of a hydrogen atom at the first carbon atom by a methyl radical was calculated from comparison of the heats of combustion of 2-methoxytetrahydropyran and δ-oxyvaleraldehyde: $868.8-697.2 = 171.6$ kcal/mole, and of αd-CH_3-glucopyranoside and αd-glucose: $842.1 - 670.3 = 171.8$ kcal/mole. A change in the structure of the ring in this case does not affect the magnitude of this increment.

b. On the basis of the data on the heat of combustion of αd-xylose, the heat of combustion of αd-glucose was calculated. The increment of the group



$$> C^{H}_{OH}$$

(111.8 kcal/mole) was estimated from comparison of the heats of combustion of n-hexanol (950.6 kcal/mole) and n-pentane (838.8 kcal/mole) in the liquid state ([11,13]). The calculated value proved to be 671.0 kcal/mole, the experimental value 670.3 kcal/mole.

Similar calculations showed the possibility of applying the simplest additive calculations to the class of carbohydrates.

4. Thus, it may be considered that also in the case of carbohydrates the enthalpy of cyclization of a six-membered ring will be close to zero. This makes it possible to estimate the enthalpy of cyclization of the

five-membered ring of βd-CH_3-glucofuranoside by comparing its heat of combustion with the heat of combustion of the six-membered ring of βd-CH_3-glucopyranoside ($849.4 - 841.1 = 8.3$ kcal/mole). However, the difference obtained cannot be regarded as the enthalpy of cyclization of βd-CH_3-glucofuranoside because of the difference in the state of aggregation of the substances compared. One may take the enthalpy of crystallization of βd-CH_3-glucopyranoside as equal to the enthalpy of crystallization of αd-CH_3-glucopyranoside, which according to the literature data is about 3 kcal/mole ([14]). Then the enthalpy of cyclization of the five-membered ring (γ-form) will be about 5 kcal/mole. This makes it possible to explain the increased reactivity of the five-membered ring, for example in the hydrolysis of these compounds, the impossibility of isolating γ-monosaccharides (furanoses) in the free state, and makes to some degree justified the supposition of the possibility of formation in nature of higher carbohydrates by polymerization of the corresponding low-molecular-weight cyclic compounds.

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named after M. V. Lomonosov

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