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RESEARCH ON 1-AZABICYCLIC SYSTEMS

XIV.* DIFFERENCE IN THE ENTHALPIES OF THE cis- AND trans-FUSED FORMS OF QUINOLIZIDINE

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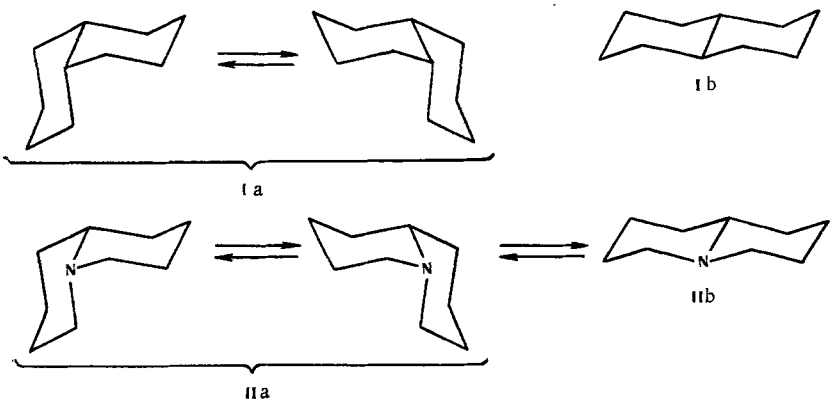
The enthalpy of the cis–trans conversion of quinolizidine was calculated by two independent methods on the basis of the literature data on the heat content of decalins, the difference in the enthalpies of the N–H-axial and N–H-equatorial conformations of piperidine, and the hydrogen bond energies in the quinuclidine–phenol and quinolizidine–phenol systems. The calculations yielded ΔH values of 3.7 and 4.3 kcal/mole for gaseous quinolizidine and 3.3 kcal/mole in favor of the trans-fused form for the liquid.

The differences in the thermodynamic properties of cis- (Ia) and trans-decalin (Ib) [2-6] have been the starting point and basis for comparisons and calculations [3, 7, 8] of the parameters of the conformational equilibrium between the cis- (IIa) and trans-fused (IIb) conformations of quinolizidine.



The results of a determination of the difference in the thermodynamic parameters that characterize the Ia⇌Ib and IIa⇌IIb equilibria are presented in Table 1. Except for [11], all of the determinations of the ΔH° or ΔG° values of the cis-trans conversion of quinolizidine presented in Table 1 are indirect, and their results deviate considerably from one another. Data on the entropy of the process under consideration has not been obtained in any of the studies. If one takes into account the fact that IIa is an unseparable d,l-pair, the cis-fused conformation is preferred from an entropy point of view by no more than R ln 2, i.e., 1.38 cal·deg^{-1}·mole^{-1}. Relative to the conclusions drawn in [7], it has been noted that the calculations were based on erroneous notions of the dimensions of the unshared electron pair of nitrogen [8, 12]. The data of [8, 9] met with disapproval [13, 14], but Aaron subsequently [10] rejected his previously obtained ΔG° value of −4.6 kcal/mole [8] and proposed a new ΔG° value of −2.6 kcal/mole. The latter determination found support in a communication by Crabb and Newton, who made an attempt to explain the unexpected closeness of the free energies of cis-trans conversion of quinolizidine (II) and indolizidine (III) [15].

*See [1] for communication XIII.

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TABLE 1. Difference in the Thermodynamic Functions of cis- and trans-Decalins and the cis- and trans-fused Conformations of Quinolizidine

Equilibrium*	$-\Delta H^\circ$, kcal/mole	ΔS°, cal/mole·deg	$-\Delta G^\circ$, kcal/mole	Method	Conditions	Literature
IIa⇌IIb	3,19—3,13	0,76—0,66	2,96	Calculation from thermochemical data and vibrational spectral data	Gas phase	2
	2.55	1.38		Calculation of the butanelike gauche interactions	Liquid phase	3
	2,85	1,38		Calculation of the butanelike gauche interactions	Gas phase	3
	2,72±0,20	0,55±0.3		Study of the palladium-catalyzed equilibrium	Liquid phase	4
	2,69±0,31			Thermochemical	Liquid phase	5
	3,09±0,77			Thermochemical	Gas phase	5
		~0		Thermochemical	Liquid phase	6
Ia⇌Ib	1,9			Calculation of the energy of nonbonded interactions		7
	≥4.6†		4,6	Calculation of the energy of nonbonded interactions		8
	2,6					3
	≥4,4†		4,4	Kinetic	Solution in CH_3CN	9
	≥2,6†		2,6‡	IR spectroscopy	Solution in CCl_4	10
	>3.3			IR spectroscopy	Liquid and gas phase	11
	3,3			Calculation from data in [4, 5, 26, 27]	Liquid phase	This research
	3,7			Calculation from data in [5, 26, 27]	Gas phase	This research
	4.3			Calculation from data in [5, 29]	Gas phase	This research

* In a number of cases the equilibrium as such was not studied and should be considered to be arbitrary and introduced for convenience in the comparison and designation of the energically preferred isomers or conformations.

† Under the assumption that $\Delta S \leq 0$.

‡ At room temperature.

The contradictory character of the experimental data on the thermodynamic parameters of the IIa⇌IIb equilibrium compelled us to find at least the upper boundary of the ΔH° values by conducting experiments directly with II. For this, we investigated the ratio of the intensities of the Bohlmann bands to the intensities of the principal C−H stretching vibrations in the IR spectrum of II as the temperature was varied from 20 to 300° [11]. It was established that this ratio is independent of the temperature, whereas distinct changes were observed for indolizine (III) [16]. The ΔH° value presented in Table 1 was found from the expression

$K = e^{\frac{-\Delta G^\circ}{RT}}$ and the assumption that $\Delta S^\circ \approx 0$ and that a 5% change in the IIa⇌IIb equilibrium could be detected from the IR spectra [11]. If the ΔS° value of −0.55 cal/mole·deg found for decalins [4] is assumed for quinolizidine (II), $\Delta H^\circ < -3.7$ kcal/mole.

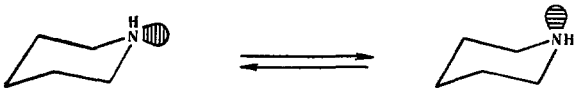
A fundamental question is important in the discussion of the thermodynamic stabilities of isomers IIa and IIb: Is the difference in the enthalpies for isomers IIa and IIb more profound than for the Ia and Ib pair? Does trans-fused quinolizidine (IIb) experience additional stabilization as compared with trans-decalin (Ib)? The set of data available in the literature makes it possible to not only give a positive response to these questions but also to make an approximate calculation of the ΔH° value of the cis-trans conversion of II.

An electronic interaction exists between the unshared electron pair of the heteroatom and the α-C−H bonds that are anticoplanar to it; this interaction evidently is of universal character, and its partial appearance in IR spectra has been described, for example, for II]17], ethers [18], acyclic amines [19], and piperidines [20, 21]. The probable mechanism of the effect has been examined [14, 22, 23].

In [9] the additional stabilization of IIb was conjecturally linked with weakening of the steric interactions of the unshared electron pair of nitrogen as compared with the 10-C−H bond in Ib because of its smaller dimensions than in the case of the hydrogen atom. In this case, the three-dimensional packing of the unshared electron pair of nitrogen was not set up as a function of the conformations. Presently it can be asserted with a high degree of definiteness that the steric effect plays a role in the stabilization of IIb, since the electronic interaction of three axial α-C−H bonds with the antiparallel (with respect to them) unshared electron pair of nitrogen is accompanied by its delocalization [14, 22, 24, 25] and consequently by a decrease in the effective volume and weakening of the nonbonded interactions.

A second contribution to the stabilization of quinolizidine IIb is created as a result of the above-described electronic interaction, as a consequence of which the C−N bonds acquire partially unsaturated character [19, 22].

Let us dissolve two conformations of piperidine (IV) – one with an axial N−H bond (IVa) and one with an equatorial N−H bond (IVb) –



IVa IVb

for the difference in enthalpies of which from the results of numerous determinations, critically examined in [26], and the data in [27] one can assume a ΔH° value of −0.6 kcal/mole, which is practically equal for solutions and the gas phase.

In conformations IVa and IVb the nonbonded interactions of the hydrogen atom attached to nitrogen with the closest hydrogen atoms are weak and approximately equal in both conformers [26]. The energy difference between IVa and IVb is therefore determined primarily by the difference in the orientation of the unshared electron pair of nitrogen. The lower enthalpy of IVb is due to electronic and steric effects associated with delocalization of the unshared electron pair of nitrogen.

Quinolizidine IIb has three axial α-C−H bonds, whereas IIa has only one such bond. Conformations IIa and IIb consequently differ with respect to the number of axial α-C−H bonds in the same way as conformations IVa and IVb, and the additional stabilization of IIb can, within a first approximation, be assumed to be equal to the difference in the enthalpies of IVa and IVb. Hence, taking the data on decalins [4, 5] as our foundation, we obtain $\Delta H^\circ \approx -3.3$ and −3.7 kcal/mole, respectively, for the liquid and gas phases for the cis−trans conversion of II.

In the above calculation of the enthalpy of the cis−trans conversion of II it is assumed that the contribution of each transoid fragment made up of the unshared pair of electrons of nitrogen and the α-C−H bond is equivalent, whereas it is known, for example, that the energy of stabilization of α-deuteroisopropylamine in the conformation with a transoid orientation of the unshared electron pair of nitrogen and the C−D bond is −0.12 kcal/mole [19], as compared with $\Delta H \approx -0.6$ kcal/mole for IV [26, 27]. These values indicate that the calculation of the stabilization energy in which the energy necessary in any system per single transoid fragment made up of the unshared electron pair of nitrogen and the α-C−H bond is taken as a constant and is used for the determination of the stabilization energy in a system with a different number of such fragments is a relatively rough calculation. In addition, there are indications that delocalization of the unshared electron pair of nitrogen is realized more effectively in compounds with a fixed configuration than in systems with labile conformations [24]. Quinolizidine IIb has a rigid skeleton, and IIa is a conformationally labile formation, the interconversion of the mirror-image forms of which is possible without inversion of the nitrogen atom.

In connection with the noted inadequacy of the calculation presented above, it seems of interest to search for different methods for the determination of the enthalpy of the cis−trans conversion of II. The energy of the additional stabilization of IIb evidently can be determined as the difference in the heat effects that take place at nitrogen and are not accompanied by a configurational rearrangement and conformational changes in the reaction of quinolizidine and any other model compound that meets the series of conditions. The nature of this sort of model compound should be close to that of quinolizidine, and it should contain a tertiary nitrogen atom, should not have other reaction centers that compete with nitrogen, and should have a geometry that excludes the pos-

sibility of delocalization of the unshared pair of nitrogen. Quinuclidine (V) satisfactorily meets requirements of this sort [28].

The heats of formation of a hydrogen bond between phenol and bases II and V, which were found to be 7.4* and 8.6 kcal/mole, respectively, were presented in [29]. Hence, the additional stabilization energy of IIb is −1.2 kcal/mole. Since the determinations were made in the same solvent, the effects associated with weak interactions of perchloroethylene at nitrogen and the hydroxyl group that also somewhat affect the value of the enthalpy of the hydrogen bond obtained in each case are cancelled by substraction, and the value obtained can be related to the gas phase. Then, again using data on Ia and Ib [5] as our basis, we find $\Delta H^\circ \approx -3.1 + (-1.2) \approx -4.3$ kcal/mole for the cis−trans conversion of II in the gas phase.

On the background of the above-presented contradictory literature data on the thermodynamics of the IIa⇌IIb equilibrium, the ΔH° values of the cis−trans conversion of II obtained in the present research by two independent methods are in satisfactory agreement. They are close to the results described by Katritzky and co-workers [9].

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*A ΔH value of 9.8 kcal/mole is presented in [30] for the hydrogen bond between phenol and II. Data [29] on the hydrogen bonds of II and V with phenol obtained by the same authors under the same conditions were used for the calculations in the present communication.