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PARABOLIC RELATIONSHIP BETWEEN FREE ENERGIES OF CONFORMATIONAL AND ISOMERIZATIONAL EQUILIBRIA AND THE POLARITY OF SOLVENTS

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Summary: The empirical parabolic function is devised for the determination of ΔG^o values in the solvents of various polarity and in vapour phase.

Numerous investigations have shown that the solvent effect on conformational equilibria is often much more important than the intramolecular interactions [1,2]. Hence the vapour phase energy difference between two conformers, ΔG^o_v, should be used to evaluate intramolecular factors dominating conformational equilibria. However the direct experimental determination of ΔG^o_v values meets with essential technical difficulties [1,3]. Several approaches are known for the estimation of these values. For example, a simple linear extrapolation of ΔG^o_{sol} values vs. a function $(\varepsilon - 1)/(2\varepsilon + 1)\cdot a^3$ (where a is the solvent molecular radius and ε is the dielectric constant of the particular solvent) to the value $\varepsilon = 1$ (vapour) has been suggested [3]. However this method has been shown to give unreliable results [1,4]. A quantitative approach elaborated by R.J.Abraham [1,4,5] takes into account dipole, quadrupole and higher order terms. Though this method gives satisfactory results the calculations are rather intricate and cumbersome and require a knowledge of a number of molecular parameters. Hence one still needs a simple but rather accurate method of evaluation of ΔG^o_v values and in this communication we present an approach to the solution of this problem.

In the course of various treatments of a large body of experimental data on conformational equilibria we have finally found that the parabolic function (1)

$$(1) \qquad \Delta G^o = A + B\sqrt{C - X}$$

(X is a function $(\varepsilon - 1)/(2\varepsilon + 1)$ and A, B and C are empirical parameters) *is the adequate representation of the dependence of energy difference between conformers upon the dielectric constant of the solvents*. This equation permits estimation of both (a) ΔG^o for some particular solvent and (b) the vapour phase value, ΔG^o_v, by extrapolation to X = 0 (the parabolic extrapolation method, PEM). The parameters A, B and C, correlation coefficients r, standard error of approximation ($S = \sqrt{\sum_i \Delta G_i^2/(n-1)}$), PEM and literature data of ΔG^o_v for several conformational equilibria are given in Table 1. The entries 9 and 10 of Table 1 demonstrate the application of our method to the description of *cis*-*trans* isomerizational equilibria. The data collected in Table 1 clearly indicate the statistical validity of the proposed parabolic expression (1).

In the course of exploration of this method we have noticed the important feature that in the majority of the examples studied the dependence of ΔG^o values on the solvent polarity could be approximated with reliable accuracy by the use of the simplified expression (2):

$$\Delta G^o = A + B\sqrt{0.5 - X} \quad , \qquad (2)$$

i.e. C = 0.5. The corresponding data are also included in Table 1. Fig.1 exemplifies this dependence for the data on the conformational equilibrium of *trans*-1,2-dibromocyclohexane. The data of Table 1 demonstrate the high reliability of equation (2). At present it is not quite clear whether the deviations of the optimized values of C from 0.5 are essential in principle or are due to uncertainties involved in experimental ΔG^o and ε values. We feel intuitively that C should be equal to 0.5 since $\lim_{\varepsilon \to \infty} X = 0.5$. In this case the A parameter should be regarded as the extremal ΔG^o value for the solvent with infinitely large polarity and the B parameter could be considered as the measure of the susceptibility of the equilibrium to the change of solvent polarity.

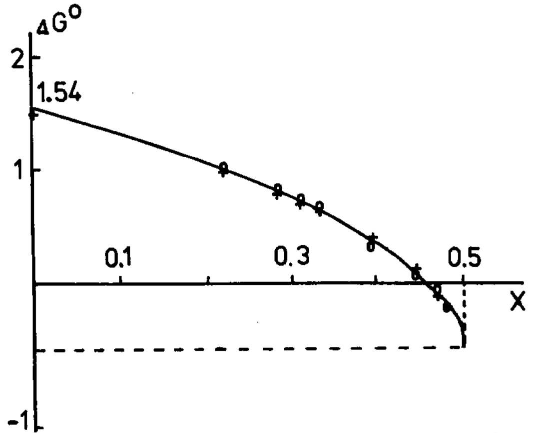

Fig.1. Parabolic correlation of the data for the conformational equilibrium of *trans*-1,2-dibromocyclohexane (Ref.5; o - experimental values, + - calculated data using Abraham method).

Table 1. Data of parabolic approximation.

No	Compounds, equilibria and references	eq	n	A	B	C	r	S	ΔG_v^o ($\frac{kcal}{mol}$)	
									PEM	Lit*
1	trans-1,2-dibromocyclohexane(aa $\rightleftarrows$ ee)(Ref.5)	1	9	-0.78	3.29	0.513	0.9925	0.058	1.58	1.50
		2	9	-0.62	3.05	0.5	0.9922	0.059	1.54	
2	trans-1,4-dibromocyclohexane(aa $\rightleftarrows$ ee)(Ref.5)	1	8	-0.48	1.54	0.485	0.9772	0.057	0.59	0.88
		2	8	-0.63	1.84	0.5	0.9651	0.071	0.67	
3	4-methoxycyclohexanone (a $\rightleftarrows$ e)(Ref.6)	1	15	0.14	0.78	0.494	0.9308	0.055	0.69	-
		2	15	0.11	0.82	0.5	0.9227	0.058	0.69	
4	2-bromocyclohexanone (a $\rightleftarrows$ e)(Ref.7)	1	4	-0.63	3.32	0.515	0.9973	0.042	1.76	-
		2	4	-0.44	3.06	0.5	0.9971	0.043	1.72	
5	1,2-dichloroethane$^+$ (ap $\rightleftarrows$ sc)(Ref.1)	1	9	-0.24	2.12	0.517	0.9610	0.083	1.28	1.20
		2	9	-0.13	1.95	0.5	0.9608	0.083	1.25	
		1	10§	-0.08	1.85	0.495	0.9743	0.079	1.22	
		2	10§	-0.11	1.89	0.5	0.9742	0.079	1.23	
6	1,1,2,2-tetrachloroethane$^+$ (sc $\rightleftarrows$ ap)(Ref.1)	1	9	-1.55	2.00	0.595	0.9777	0.052	-0.01	0.0
		2	9	-1.08	1.42	0.5	0.9748	0.055	-0.08	
7	dichloroacetaldehyde$^+$ (sp $\rightleftarrows$ ac)(Ref.8)	1	11	-1.06	2.81	0.485	0.9613	0.166	0.90	-
		2	11	-1.29	3.18	0.5	0.9400	0.206	0.96	
8	bromoacetaldehyde$^+$ (ac $\rightleftarrows$ sp)(Ref.9)	1	11	-0.72	1.48	0.494	0.9787	0.058	0.32	-
		2	11	-0.77	1.57	0.5	0.9731	0.066	0.34	
9	2-isopropyl-5-methoxy-1,3-dioxane(trans $\rightleftarrows$ cis) (Ref.10)	1	8	0.06	1.86	0.480	0.9796	0.074	1.35	1.25
		2	8	-0.13	2.17	0.5	0.9578	0.105	1.40	
10	2-isopropyl-5-bromo-1,3-dioxane(trans $\rightleftarrows$ cis) (Ref.10)	1	4	0.60	2.21	0.481	0.9980	0.028	2.13	2.5
		2	4	0.31	2.75	0.5	0.9952	0.043	2.25	

* data from Refs. 1,5; $^+$ ap - anti-periplanar, ac - anti-clynal, sp - syn-periplanar, sc - syn-clynal; § including the experimental ΔG_v^o value.

Using the described PEM approach one should keep in mind the following: (a) The range of polarity of the solvents used has to be as wide as possible, (b) The specific interactions in solution should be eliminated. In particular, hydrogen bonding solvents (alcohols, water) and aromatic ones must be excluded (cf. Refs. 1,5), (c) The use of a single solvent is preferred to the use of mixed solvents, because the preferable solvation of a solute by the polar component of the medium may lead to a systematic error (cf. Ref.1), (d) The perturbation of medium polarity by the solute should be taken into account, especially for the solvents of low polarity (cf. Refs.1,3-5), (e) The dielectric constant values used must correspond to the temperature of measurement (*cf*. Ref. 5).

In principle, one can calculate the parameters of equation (2) and hence the PEM value of ΔG^o_v from only two measurements of high accuracy in the solvents with sufficiently different polarity using the equations (3) and (4):

$$B = (\Delta G_1 - \Delta G_2)/(\sqrt{0.5 - X_1} - \sqrt{0.5 - X_2}) \quad (3)$$

$$A = \Delta G_1 - B\sqrt{0.5 - X_1} = \Delta G_2 - B\sqrt{0.5 - X_2} \quad (4)$$

For example we calculated the following ΔG^o_v values for *trans*-1,2-dibromocyclohexane [5]: 1,48(pentane-acetone), 1.53(CS_2-acetone) and 1.53 kcal/mol (hexane-CH_2Cl_2)(*cf*. ΔG^o_v = 1.5 kcal/mol [5]).

Scope and applications of the parabolic approximation are now under active study.

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