Thermochimica Acta, 173 (1990) 161–169
Elsevier Science Publishers B.V., Amsterdam

COMPUTATIONAL THERMODYNAMIC STUDY OF TWO SPECIES USED FOR MODELLING THE ANAESTHETIC ACTIVITY OF NITROUS OXIDE: THE N_2O–H_2O ASSOCIATES *,**

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(Received 16 April 1990)

ABSTRACT

Hydrogen-bond formation and perturbation have played an important role in the understanding of anaesthetic activity; the associating system N_2O–H_2O has been used for this purpose in the molecular modelling of the physiological effects of nitrous oxide. The associate of nitrous oxide and water is formed by a hydrogen bond directed to either the O or the N atom. Using recent computational data, partition functions of both species were constructed and applied to the evaluation of the system thermodynamics. It was found that, in spite of being favoured by the potential-energy term, the H–O bonded species becomes less stable than the H–N bonded structure in the region of medium and higher temperatures, co-existence of the two structures being predicted for a wide temperature interval. A substantial enhancement of the heat-capacity term by the isomeric interplay is indicated, with a maximum value of about 19 J K^{-1} mol^{-1}. The found extremum in the temperature-related behaviour of the heat-capacity terms is analysed and discussed.

INTRODUCTION

The understanding of anaesthetic activity at the molecular level is based on intermolecular interactions [2] and a pertinent classification based on the interactions has been proposed by Sandorfy [3]. In the approach an important role is attributed to the formation, perturbation or breaking of hydrogen bonds. Molecular complexes, in the simplest case dimers, serve as models of the systems and recently the usefulness of evaluating the model thermodynamics has been pointed out [4]. There is coincidence with a

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* Dedicated to Professor Camille Sandorfy on the occasion of his 70th birthday.

** Part LV in the series Multimolecular Clusters and Their Isomerism; for part LIV, see Ref. 1.

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considerable research interest in gas-phase molecular complexes or clusters in general, see, for example, Refs. 5–7. Structural isomerism represents one of the cluster topical features, and has been studied by both experimental and theoretical means. The phenomenon has been, inter alia, observed using nitrous oxide in an anaesthetic activity molecular model, viz. the associating system N_2O–H_2O [4]. However, probably the most comprehensively studied cluster isomerism is the case of N_2O–HF [8–23]. The isomerism of clusters has several consequences concerning both the observational and the computational sides of cluster studies. In connection with an ever encreasing interest in cluster thermodynamics [24–33] cluster-isomerism manifestation in thermodynamical characteristics has become a subject of investigation, too [34–43]. The cluster manifestation in the behaviour of thermodynamic quantities could help in extending the range of systems in which isomerism has so far been observed [44–54].

In the present study we treated the thermodynamics of the N_2O–H_2O associating system with due respect being paid to its two-fold isomerism. Attention was given both to physiologically relevant situations and to the wider thermochemical connections.

DESCRIPTION OF THE N_2O–H_2O SYSTEM

The computations [4] revealed and characterized two local energy minima on the interaction-potential hypersurface of nitrous oxide and water: one possessing H–O ($N_2O \cdot HOH$) and the other H–N ($ON_2 \cdot HOH$) hydrogen bonds. The computations were carried out within the SCF approach using two different atomic-orbital basis sets denoted [4] as MINI-1 and 4-31G. In both treatments the H–O and H–N bonded species were planar, the former lying lower in the potential-energy term as indicated in Table 1. In addition to structure and energetics, harmonic vibrational frequencies were also evaluated in Ref. 4. Thus, potential-energy changes, ΔE_i (where i denotes 1

TABLE 1

Energetics [4] of formation of the $N_2O \cdot HOH$ and $ON_2 \cdot HOH$ complexes

Complex	ΔE_i [a] (kJ mol^{-1})		$\Delta H_{0,i}^{\circ}$ [b] (kJ mol^{-1})	
	MINI-1	4-31G	MINI-1	4-31G
$N_2O \cdot HOH$	−11.84	−23.36	−5.51	−17.30
$ON_2 \cdot HOH$	−5.46	−5.87	−1.23	−1.97

[a] Potential-energy change.

[b] The enthalpy change at absolute zero or the ground-state energy change, i.e. ΔE_i corrected for zero-point vibrations.

or 2, i.e. $N_2O \cdot HOH$ or $ON_2 \cdot HOH$, respectively), upon the associate formations

$$N_2O(g) + H_2O(g) = N_2O \cdot HOH(g) \tag{1}$$

and

$$N_2O(g) + H_2O(g) = ON_2 \cdot HOH(g) \tag{2}$$

can be corrected for zero-point vibrational contribution yielding the ground-state energy change (or, in other words, the standard enthalpy change at the absolute zero temperature), $\Delta H^\circ_{0,i}$ (Table 1).

In the present study the treatment was carried out on two parallel data sets: (i) MINI-1, which uses the MINI-1 energetics and harmonic vibrational frequences for both monomers and dimers in eqns. (1) and (2); and (ii) 4-31G, which employs the data from the latter approximation [4]. For both treatments the 4-31G structural parameters [4] were adopted.

COMPUTATIONAL TREATMENT

An isomeric mixture is characterized by the values of the mole fractions, w_i, of the individual isomers. The isomers are primarily described by their potential-energy terms, ΔE_i. However, if the rotational–vibrational motions are considered then the relevant quantities are the standard enthalpy changes at absolute zero, $\Delta H^\circ_{0,i}$, and the isomeric partition functions, q_i. Under conditions of inter-isomer thermodynamic equilibrium the mole fractions are given [39–43] in molecular terms as follows:

$$w_i = \frac{q_i \exp[-\Delta H^\circ_{0,i}/(RT)]}{\sum\limits_{j=1}^{n} q_j \exp\left[-\Delta H^\circ_{0,j}/(RT)\right]} \tag{3}$$

where n stands for the number of isomers. Equation (3) was primarily designed for gas-phase conditions, however, it can be applied [55] to other environments, too, if the partition functions are adjusted accordingly. It is useful to mention a critical difference from the rather generally used treatments based on the so-called simple Boltzmann, configurational or steric factors [5,56–59]:

$$w_i' = \frac{\exp[-\Delta E_i/(RT)]}{\sum\limits_{j=1}^{n} \exp\left[-\Delta E_j/(RT)\right]} \tag{4}$$

In eqn. (4) no information on the rotational–vibrational motions is employed.

With the help of partition functions and energetics, the entire thermodynamics of the species under study can be described. For an isomeric system it has become customary to distinguish [39–43] two categories of quantities: (i) the standard partial terms, ΔX_i°, involving the individual isomers, e.g. in our case the terms connected with either process (1) or (2); and (ii) practical applications require the standard overall terms, ΔX_T°, too, into which all the isomers contribute accordingly, i.e. according to their mole fractions or weighting factors w_i. In our case the overall terms are connected with a summary, total process

$$N_2O(g) + H_2O(g) = N_2O - H_2O(g) \tag{5}$$

where the formula $N_2O–H_2O$ denotes a pseudospecies formed by the equilibrium mixture of both isomers. In addition to the partial and overall terms, a third quantity has been introduced [39–43], viz. the isomerism contributions to the thermodynamic terms $\delta X_1^{(\mathrm{iso})}$ defined as

$$\delta X_1^{(\mathrm{iso})} = \Delta X_T^\circ - \Delta X_1^\circ \tag{6}$$

Clearly, the values of $\delta X_1^{(\mathrm{iso})}$ generally depend on the choice of the reference isomer labelled as $i = 1$. It is convenient to choose the most stable species (in the low-temperature region) as the reference structure.

RESULTS AND DISCUSSION

The H–O bonded isomer is preferred to the H–N one, not only in terms of the ΔE_i values, but also in terms of the $\Delta H_{0,i}^\circ$ values (Table 1). However, the temperature course of the weight factors evaluated according to eqn. (3) (see Table 2), demonstrates how such conclusions can be misleading. In both the MINI-1 and 4-31G approximations of energy, the w_1 and w_2 terms not only approach each other with increasing temperature, but they finally cross. Thus, after reaching the equimolar point the relative stability of both species is reversed and the $ON_2 \cdot HOH$ isomer becomes the more important component of the equilibrium mixture. However, over a wide temperature interval both structures exhibit the same order of magnitude of equilibrium concentrations and, hence, they coexist. The equimolar point lies considerably lower in the MINI-1 approach when the isomeric coexistence is certainly significant for physiological conditions also. Thus, if the MINI-1 approach is chosen as the basis for molecular modelling of the N_2O anaesthetic activity, then the model–complex isomerism must be taken into account accordingly. However, within the 4-31G treatment at room temperature, the $N_2O \cdot HOH$ structure is still the predominant one.

It is evident from Table 2 that the simple Boltzmann factors w_i' do not work well for the $N_2O–H_2O$ system. Owing to the nature (eqn. (4)) of these factors they are unable to exhibit any temperature crossing. Moreover, the

TABLE 2

Temperature evolution of the mole fraction (w_1 and w_1') [a] of the $N_2O \cdot HOH$ species in its equilibrium mixture with $ON_2 \cdot HOH$

T (K)	w_1 [b] (%)	
	MINI-1 [c]	4-31G
100	99.4 (100.0)	100.0 (100.0)
200	89.2 (97.9)	100.0 (100.0)
298.15	72.9 (92.9)	99.0 (99.9)
400	59.5 (87.2)	94.5 (99.5)
500	50.4 (82.3)	85.9 (98.5)
506.1 [d]	50.0 (82.0)	85.3 (98.5)
878.5 [d]	34.8 (70.5)	50.0 (91.6)
1000	32.5 (68.3)	42.8 (89.1)
1500	27.2 (62.5)	27.1 (80.3)
2000	24.7 (59.5)	20.7 (74.1)

[a] The simple Boltzmann factors w_1' are given in parentheses.

[b] The mole fraction w_2 of $ON_2 \cdot HOH$ $w_2 = 100.0 - w_1$.

[c] The MINI-1 energetics and vibrational frequencies; 4-31G geometry.

[d] The equimolar point in one of the energy approximations.

TABLE 3

Temperature evolution of the isomerism contributions [a] $\delta X_1^{(iso)}$ to the thermodynamic functions [b] of the N_2O–$H_2O(g)$ system

T (K)	$\delta H_1^{(iso)}$ (kJ mol^{-1})	$\delta S_1^{(iso)}$ (J K^{-1} mol^{-1})	$\delta C_{p,1}^{(iso)}$ (J K^{-1} mol^{-1})
MINI-1			
100	0.027	0.316	1.61
200	0.594	3.92	9.22
298.15	1.58	7.91	9.73
400	2.44	10.4	7.12
500	3.03	11.8	4.95
1000	4.28	13.6	1.18
1500	4.65	13.9	0.472
2000	4.82	14.0	0.241
4-31G			
100	3×10^{-7}	3×10^{-6}	5×10^{-5}
200	0.006	0.032	0.293
298.15	0.168	0.645	3.88
400	0.948	2.84	11.7
500	2.45	6.17	17.7
1000	9.99	17.1	9.03
1500	12.8	19.4	3.25
2000	13.9	20.0	1.52

[a] Related to the $N_2O \cdot HOH$ species as reference structure.

[b] $X = H$, S or C_p for enthalpy, entropy or heat capacity at constant pressure, respectively.

decrease with temperature of the w_1' term is considerably slower than that of the w_1 weighting factor, especially in the 4-31G approach. Overall, the simple Boltzmann factors prove to be rather useless in the particular case studied here.

The temperature evolution of the isomerism contributions $\delta X_1^{(\mathrm{iso})}$ to the thermodynamic functions is presented in Table 3 for enthalpy (X = H), entropy (X = S) and heat capacity at constant pressure (X = C_p). The isomerism contributions are related to the $N_2O \cdot HOH$ isomer as reference structure. It is clear that the isomerism contributions to the thermodynamic

TABLE 4

Temperature evolution of the standard,[a] partial,[b] ΔX_i°, and overall,[c] ΔX_T°, thermodynamic terms[d] for the $N_2O(g)$ and $H_2O(g)$ association evaluated within the 4-31G approximation

T (K)	ΔX_1°	ΔX_2°	ΔX_T°
$X = H$ (kJ mol^{-1})			
100	−19.3	−3.00	−19.3
200	−19.1	−2.24	−19.1
298.15	−18.4	−1.19	−18.2
400	−17.3	−0.029	−16.4
500	−16.2	1.15	−13.8
1000	−10.3	7.18	−0.295
1500	−4.19	13.3	8.57
2000	1.95	19.5	15.8
$X = S$ (J K^{-1} mol^{-1})			
100	−94.2	−80.8	−94.2
200	−93.8	−75.8	−93.8
298.15	−90.7	−71.6	−90.1
400	−87.8	−68.2	−84.9
500	−85.3	−65.6	−79.2
1000	−77.1	−57.2	−60.1
1500	−72.2	−52.3	−52.8
2000	−68.7	−48.7	−48.6
$X = C_p$ (J K^{-1} mol^{-1})			
100	−5.89	3.48	−5.89
200	5.86	9.89	6.16
298.15	9.31	11.2	13.2
400	10.7	11.6	22.4
500	11.3	11.8	29.0
1000	12.1	12.2	21.1
1500	12.3	12.3	15.5
2000	12.3	12.3	13.8

[a] Standard state: an ideal gas at 1 atm = 101 325 Pa pressure.
[b] Association to $N_2O \cdot HOH$ ($i = 1$) or to $ON_2 \cdot HOH$ ($i = 2$).
[c] Association to the equilibrium mixture of both isomers (see footnote b).
[d] Enthalpy ($X = H$), entropy ($X = S$), or heat capacity at constant pressure ($X = C_p$).

TABLE 5

Temperature maxima ($J\ K^{-1}\ mol^{-1}$) of the $\delta C_{p,1}^{(iso)}$ and $\Delta C_{p,T}^{\circ}$ terms

T (K)	$\Delta C_{p,1}^{\circ}$	$\Delta C_{p,2}^{\circ}$	$\delta C_{p,1}^{(iso)}$	$\Delta C_{p,T}^{\circ}$
MINI-1				
251.4 [a]	6.06	9.42	10.3	16.3
317.1 [b]	8.15	10.4	9.30	17.5
4-31G				
579.6 [a]	11.6	11.9	19.0	30.6
586.9 [b]	11.6	12.0	19.0	30.7

[a] Maximum in the $\delta C_{p,1}^{(iso)}$ term.

[b] Maximum in the $\Delta C_{p,T}^{\circ}$ term.

functions of the associating system N_2O–H_2O are important at medium and higher temperatures for a proper evaluation of any of the three characteristics considered. It is noteworthy that, while the $\delta H_1^{(iso)}$ and $\delta S_1^{(iso)}$ terms systematically increase with increasing temperature, the third quantity, i.e. $\delta C_{p,1}^{(iso)}$, exhibits a temperature maximum in both energy approximations studied.

Table 4 transfers from the level of the isomerism contributions to complete reaction terms, i.e. to standard partial and overall enthalpy, entropy and heat capacity at constant pressure changes for the associate formations, namely within the 4-31G approach. The overall $\Delta C_{p,T}^{\circ}$ term conserves the extremum behaviour indicated by the $\delta C_{p,1}^{(iso)}$ contribution. Conversely, the partial $\Delta C_{p,1}^{\circ}$ and $\Delta C_{p,2}^{\circ}$ terms increase smoothly with increasing temperature. Let us mention for completeness that this report is not the first evaluation of the thermodynamics of this system. There are some data available [4] on the partial terms of process (1) (however, no treatment of the system isomerism is given). In the latter paper, the approach of quasi-linear species was applied to N_2O, nevertheless qualitative features of the related data for reaction (1) are essentially the same in both reports.

The extremum behaviour of the $\delta C_{p,1}^{(iso)}$ and, particularly, $\Delta C_{p,T}^{\circ}$ terms deserves attention not only from the thermodynamical but also from the physiological point of view. The temperature extrema are specified in Table 5 for both these terms and for both energy treatments. In fact, the isomeric interplay causes the standard heat-capacity change to increase more than two-fold in the temperature region of the extrema. However, the regions are not far from physiological conditions, especially in the MINI-1 case. Hence, the isomerism effects stabilize the associates in two ways: (i) by increasing the association equilibrium constant (the overall equilibrium constant can be as much as twice the case without isomerism); and (ii) the increase in heat capacity effectively means that an energy addition to the system will cause a lower temperature increase as compared with the situation where isomerism would not be present.

From a more general point of view and in conclusion, for weak molecular complexes (and for hydrogen-bonded species in particular) this type of isomerism appears to be a quite frequent event. This observation has consequences for both the preparation and the understanding and interpretation of computational and experimental studies, including applications in molecular biology.

ACKNOWLEDGEMENTS

This study was carried out during a research stay at the Max-Planck-Institut für Chemie (Otto-Hahn-Institut) supported by the Alexander von Humboldt-Stiftung. The support of and valuable discussions with Professor Karl Heinzinger and the kind hospitality extended by him and his group are gratefully acknowledged.

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