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COMPARATIVE MO INVESTIGATION OF HINDERED ROTATION AND THERMAL DECOMPOSITION OF CARBAMATES AND THIOCARBAMATES

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Investigation of hindered rotation in carbamates reveals the high flexibility and ionic character of the C-N bond as compared to common amides. This flexibility decreases in the case of thiocarbamates. The mechanism of activation of carbamates has been explored. Computations have proven the possibility of formation of an intramolecular H-bond in carbamates and thiocarbamates. This intramolecular H-bond is formed immediately after protonation of the carbamate. The possibility of formation of zwitterions as intermediates in the decomposition of carbamic and dithiocarbamic acids is discussed.

1. Introduction

The potent carcinogen urethan (ethyl carbamate) and its derivatives are some of the most widely studied chemical carcinogens [1]. It is generally considered that urethan, in vivo, is activated and forms covalent adducts with macromolecules [2]. The N-C(O) moiety is the characteristic link in the adduct formation. It has been widely accepted [3,4] that an understanding of the orientation of an amide carcinogen can be approached from an investigation of the conformation and dynamics associated with the peptide linkage. This together with the surprising difference in biological activity between carbamates and thiocarbamates makes a detailed structural investigation of the electronic properties of the N-C(O) linkage in these systems a logical step in understanding their activity.

The phenomenon of restricted rotation about amide bonds is well known [5] and is believed to be of particular importance in determining the dynamic properties of the host molecule [6]. Mathematical models that have been proposed to treat conformational transitions in biomolecules, e.g., helix-coil transitions, depend on the knowledge of the electronic properties of the peptide linkage in these systems [7]. Furthermore, it has been shown [8] that intramolecular interactions involving peptides may be predicted from a knowledge of the dynamics of the skeletal peptide linkage. Information such as amide bond sequence [9], specific site of binding to nucleic acids [10], flexibility [11], etc., may be deduced from a knowledge of the dynamic properties of the peptide link. NMR spectroscopy and quantum-mechanical calculations are the main tools in this area of investigation.

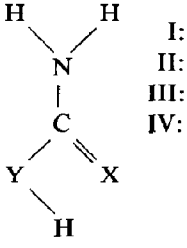
One of the very important reactions of the peptide link, that takes place in vivo, is protonation. This H^+-transfer reaction has been extensively studied [12] in order to propose a fundamental model of proton transfer in biochemical systems [13]. For a proton-transfer reaction of the form

$$AH \ldots B^- \rightleftharpoons A^- \ldots HB$$

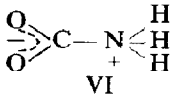
the equilibrium is determined [14] by the H-bond donor property of AH and the acceptor property (proton affinity) of B^-. Furthermore, it is governed by its environment [15]. The importance of the above-mentioned dynamical properties of the peptide link has been detailed elsewhere [16].

In the present paper, some dynamic properties of carbamates are discussed, viz., the hindered rotation about the C–N bond and the effect of protonation and H-bond formation on their electronic properties.

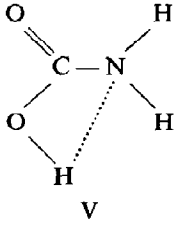
Hindered rotation in *N,N'*-disubstituted carbamates has been reported by several authors using NMR techniques [17–19]. The kinetic profiles for the decomposition of carbamates indicate that only the acid form of the molecule decomposes into carbon dioxide (disulphide) and an amine [20]. The zwitterion (VI) [21] and the intramolecular H-bonded structure [20] (V) were proposed to represent carbamic acids in solution and the reactive form for their decomposition. However no experimental evidence was given.



I: X = Y = O
II: X = O; Y = S
III: X = S; Y = O
IV: X = Y = S



VI



V

In the present comparative theoretical treatment the energetics and mechanism of the decomposition of carbamates are investigated in an effort to explore the process of their activation. Barriers to internal rotation, as a measure of the extent of π-delocalization in the C–N bond region, have been estimated both experimentally and theoretically. Forces that give rise to hindered rotation are analyzed on a comparative basis.

2. Method of calculation

All calculations reported here were carried out within the INDO-MO framework. Details of the method have been published elsewhere [22] and the energy partitioning scheme has been detailed before [23].

The NMR spectra were run on a Varian XL-400 spectrometer equipped with a variable temperature probe.

3. Results and discussion

3.1. Internal rotation characteristics

Fig. 1 presents the NMR spectrum of ethyl carbamate at room temperature (20.0 ± 0.1°C). The spectrum is composed of the methyl group triplet centred at 1.3 ppm and the methylene quartet at 4.2 ppm. A low-intensity broad signal appears at 4.85 ppm and is due to the NH_2 protons. This last signal is the only one that shows a temperature dependence.

Thus, below the coalescence temperature (−10°C; solvent dependent) the NH signal splits into two sharp peaks. The positions and intensities of these peaks are solvent and temperature depen-

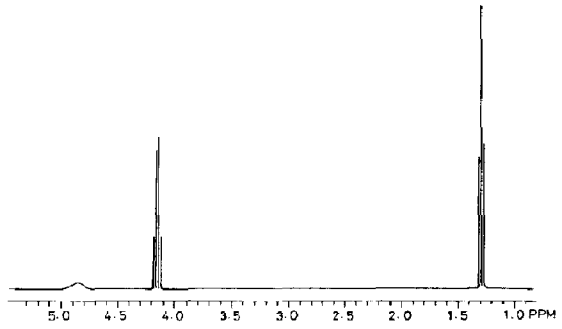


Fig. 1. NMR spectrum of ethylcarbamate at 20°C in C^2HCl_3.

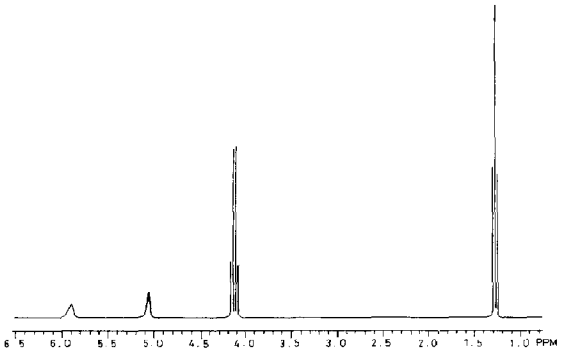


Fig. 2. NMR spectrum of ethylcarbamate at -60 °c in C^2HCl_3.

dent. Fig. 2 presents the NMR spectrum of ethyl carbamate at -60°C, whereas fig. 3 illustrates the variation of the NH signal with temperature.

The case one encounters here is termed 'uncoupled AB case' with unequal population. The enthalpy of activation, $\Delta G^{\ddagger}$, is estimated [24] using eqs. 1 and 2.

$$K_c = \pi \Delta W/\sqrt{2} \quad (1)$$

$$\Delta G^{\ddagger} = 4.57 T_c (10.32 + \log T_c/K_c) \quad (2)$$

where K_c is the rate constant of the exchange at the coalescence temperature T_c. The value of $\Delta G^{\ddagger}$ so calculated is 13.3 kcal/mol. This is considerably lower than the approx. 20 kcal/mol barrier found in common amides [24]. The significance of $\Delta G^{\ddagger}$ will be discussed below (vida infra).

Table 1

NMR characteristics (in ppm) of the N–H signal in ethylcarbamate at different temperatures

T (K)	δ_1	δ_2	Δw [a]
293	4.85	–	–
273	4.87	–	–
253	4.84	5.23	0.39
233	4.88	5.46	0.58
213	5.03	5.84	0.81

[a] Chemical shift difference.

Table 2 lists the barriers to internal rotation, $\Delta E^{\ddagger}$, computed theoretically for the studied molecules.

These barriers are overestimated relative to what is expected based on experimental data of similar molecules. The barrier to internal rotation in amides ranges [24] between 20 and 25 kcal/mol.

The barrier height increases as the number of sulphur atoms in the molecule increases. The behavior of the two isomeric thiocarbamates II and III, upon rotation is interesting. Thus, the barrier height calculated for III is 45% greater than that

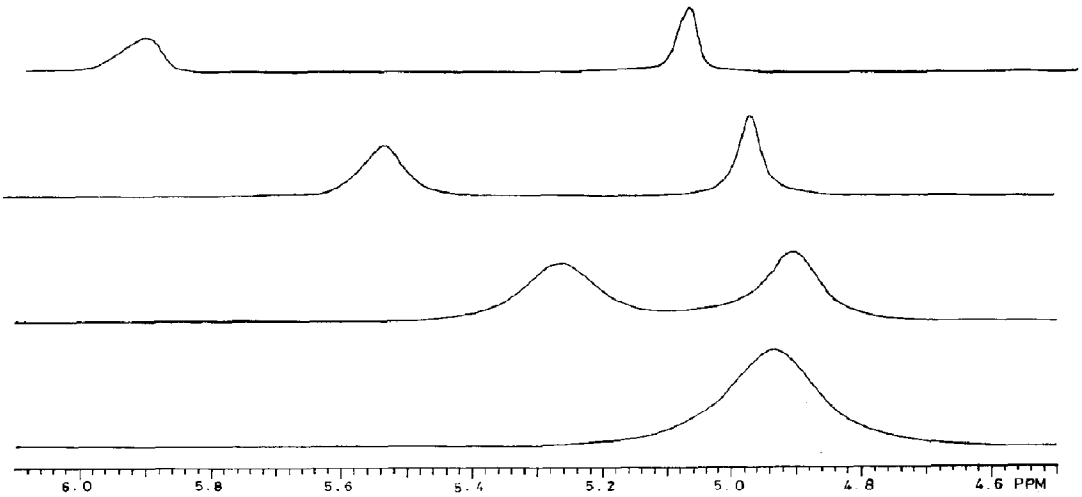


Fig. 3. Temperature dependence of the NH signal in the NMR spectrum of ethylcarbamate.

Table 2

Variations in the one- and two-atom energy (eV) components and their bonded and non-bonded contributions upon rotation about the C–N bond of the carbamates studied

Energy	I	IA[a]	II	IIA[a]	III	IV	IVA[a]
$\Delta E^{\ddagger}$	1.197	1.261	1.207	1.531	1.621	1.987	2.361
ΔE_A	0.608	1.180	0.234	1.033	0.802	0.606	3.316
ΔE_{AB}	0.599	0.086	0.997	0.678	0.988	1.448	−0.735
ΔE_T^1	0.1751	0.046	0.494	0.158	0.340	0.342	0.046
ΔE_b^1	0.063	−0.83	0.191	−0.056	0.230	0.362	−0.113
ΔE_n^1	0.111	0.129	0.303	0.214	0.111	−0.021	0.159
ΔE_T^2	0.980	0.700	1.374	1.279	1.903	2.020	1.172
ΔE_b^2	0.786	0.035	1.069	1.064	1.965	1.905	0.799
ΔE_n^2	0.204	0.665	0.305	0.215	−0.062	0.115	0.373
ΔE_T^3	1.700	0.787	0.844	0.799	0.360	0.726	0.712
ΔE_b^3	−0.309	−0.177	−0.429	−0.229	−0.425	−0.538	−0.438
ΔE_n^3	2.010	1.055	1.273	1.028	0.785	1.264	1.151
ΔE_T^4	2.256	1.538	1.716	1.558	1.616	1.640	2.665

[a] A denotes the corresponding anion.

of II. This indicates that the delocalization of the π-density of the C=S group into the C–N region is much greater than that of the C=O group.

Table 2 presents the changes in the one- and two-atom energy components upon rotation, for the studied compounds and anions.

It is clear that the process of internal rotation in carbamates is opposed by the bonded exchange, overlap and electrostatic attraction interactions and is only enhanced by electrostatic nuclear repulsion. On the other hand, the corresponding non-bonded contributions are repulsive and favor non-planar conformation.

Table 3 presents the interference energy differences ΔE^2_{C-N} ($E^2_{C-N}(\theta = 0°) - E^2_{C-N}(\theta = 90°)$), its σ- and π-components, the difference in the total two-atom energy, ΔE_{C-N}, and the ratio of interference, to the total interaction in the C–N bond region. The values in table 3 are very illustrative. Thus, the process of internal rotation causes very small variations in the σ-components of E^2_{C-N}. That is, the σ-binding density in the C–N region is not affected by rotation. On the other hand, a considerable decrease in the π-interference energy takes place upon rotation. The total variation in the C–N interaction energy is dominated by the E^2_{C-N} component as reflected by the 0.85 ± 0.09 ratio.

Table 3

Partitioned two-centre overlap energies (in eV) of C–N bonds in the carbamates studied

Species	ΔE^2_{C-N}			E_{C-N}	E^2_{C-N}/E_{C-N}
	σ-	π-	Total		
I	−0.14	2.08	1.94	2.18	0.89
II	−0.34	2.50	2.16	2.33	0.93
III	0.25	2.91	3.16	4.16	0.76
IV	−0.15	3.23	3.08	3.88	0.79
IA	−0.42	2.16	1.74	1.84	0.94
IIA	0.33	3.32	2.99	3.52	0.85
IVA	−0.44	4.79	4.35	5.48	0.80
					mean = 0.85 ± 0.09

3.2. Thermal decomposition of carbamates

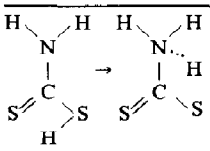
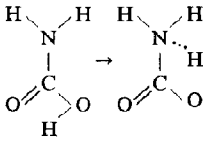
In this section, we restrict our discussion to the decomposition of carbamic and dithiocarbamic acids in an effort to explore the role of intramolecular H-bonding, protonation and zwitterion formation in their activation mechanism.

3.2.1. Intramolecular H-bonding

The structures of the chain and ring conformers of carbamic and dithiocarbamic acids are set out on the left in table 4. On the right-hand side, the changes in bond lengths and bond angles which accompany the conversion of the chain into the

Table 4

Changes in bond lengths (Å) and bond angles (°) accompanying H-bond formation in carbamic and dithiocarbamic acids

	X	ΔR_{C-N}	ΔR_{X-H}	$\Delta <$ NCX	$\Delta <$ XCX	$R_{N...H}$
	S	−0.010	0.08	2.7	1.0	2.18
	O	0.008	0.02	2.1	1.2	1.92

ring conformer are outlined. Analysis of the data in table 4 reveals the following:

(i) H-bond formation introduces very little variation in the skeletal structures of the molecules. The main effect is in the increase of the N–C–X (X = O or S) angle which may be regarded as a response by the heavy-atom backbone to accommodate the H atom in an optimal position for hydrogen-bond formation, namely, as close as possible to a line joining the centres of the heavy atoms of the donor and acceptor groups. The conversion reaction of nitrous acid shows the same feature [26].

(ii) Neither of the two ring conformers has a symmetrical H-bond. The O–H and H...N distances are 1.03 and 1.92 Å, respectively, and the S–H and H...N distances are 1.11 and 2.2 Å, for carbamic and dithiocarbamic acids, respectively. The O...N and S...N distances are 2.38 and 2.55 Å, respectively. Both are greater than any of the values which have been proposed for a symmetrical bond. Isaacson and Morokuma [27] and Donohue [28] have put the limit at 2.3 Å.

(iii) The hydrogen-bond lengths $R_{N...H}$ calculated for the two molecules seem to be in line with other values reported for amides [24].

The energetics of H-bond formation for carbamic and dithiocarbamic acids, as well as the changes in the one- and two-atom energy components, are given in table 5. The conversion of dithiocarbamic acid from the chain to the ring conformer is energetically favorable and the corresponding stabilization energy (8.4 kcal/mol) is considerable. On the other hand, the hydrogen-bond formation is repulsive in the case of carbamic acid. This destabilization effect reflects a considerable strain in the ring conformer.

In conclusion, intramolecular H-bonding is energetically favorable for dithiocarbamic acid only. The stabilization energy (8.4 kcal/mol) is comparable to that calculated for other four-membered H-bridged rings, e.g., thiol formic acid.

3.2.2. *Effect of protonation*

Table 6 presents the protonation reactions considered for carbamic and dithiocarbamic acids. The protonation reactions were considered for both the H-bonded and chain structures of the

Table 5

Energetics (energies in eV) of the H-bond formation of carbamic and dithiocarbamic acids

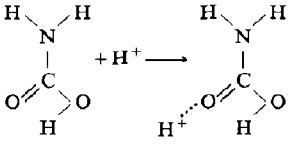
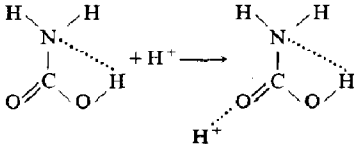
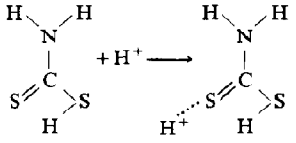
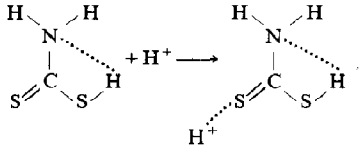
A negative sign indicates a more stable chain conformer.

Energy component	Carbamic acid (X = O)	Dithiocarbamic acid (X = S)
ΔE	−2.624	0.364
ΔE_C	−0.414	0.135
ΔE_N	0.175	−0.077
ΔE_X	0.203	0.117
ΔE_H	0.422	0.458
ΔE_{CN}	−0.642	0.633
ΔE_{CX}	−0.138	−0.168
ΔE_{XH}	−0.639	3.381

Table 6

Characteristics of the protonation reactions considered for carbamic and dithiocarbamic acids

ϕ, angle (°) of the approached proton; Δq_N, amount of charge transfered from the nitrogen atom upon protonation.

Protonation reaction	Proton affinity	$R_{X\ldots H^+}$	ϕ	Δq_N
	189.13	1.30	7	0.051
	196.98	1.32	7	0.042
	92.11	1.51	5	0.052
	91.75	1.50	5	0.049

two acids. For each conformer, the distance of the approaching proton ($=X\ldots H^+$) and the angle of approach,relative to the C=X bond, were optimized. Protonation energies, $X\ldots H^+$ distances, angles and the change in net charge on the nitrogen are listed in table 6.

The calculated proton affinity of carbamic acid is much greater than that of dithiocarbamic acid. This is due to the greater electronegativity and the smaller size of oxygen as compared to sulphur. This is further evidence that the polarizability (which takes into account the above two factors) is a good criterion to account for the different behaviour of oxygen and sulphur.

Protonation of the chain or ring conformers of dithiocarbamic acid shows more or less the same affinity. This indicates that H-bond formation has no influence on the protonation process. The situation is completely different in the case of carbamic acid. The intramolecular H-bond stabilizes the protonated species by 7.85 kcal/mol over the non-hydrogen-bonded one.

3.2.3. Stability of zwitterions

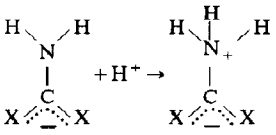
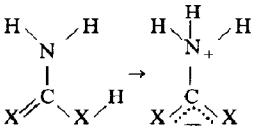
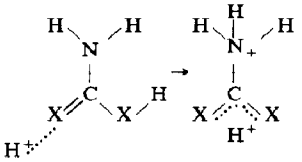
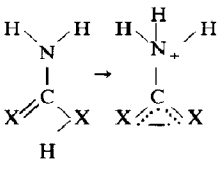
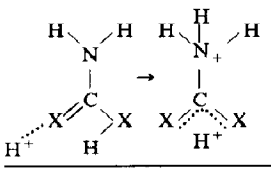
The energetics of formation of the zwitterions of carbamic and dithiocarbamic acids from the chain, ring and protonated conformers are given in table 7. The first row in table 7 presents the theoretical proton affinities of the anions protonated at the nitrogen site. These proton affinities may be considered to be that of nitrogen base in the specific environment.

The conclusions drawn from table 7 may be summarized as:

(i) The formation of the zwitterion for carbamic acid is prohibited, in the gas phase, by an energy

Table 7

Relative stabilities (energies in eV) of the zwitterions of carbamic and dithiocarbamic acids

Reaction	Carbamic acid (X = O)	Dithiocarbamic acid (X = S)
	3.979	5.738
	7.889	1.451
	11.04	2.594
	10.513	1.087
	13.343	2.245

destabilization of approx. 200 kcal/mol. H-bond formation decreases the stability of the zwitterion.

(ii) The formation of the dithiocarbamic acid zwitterion is feasible since it is only 32.27 kcal/mol above the acid itself. The energy gap increases with protonation according to the conclusions drawn in the last two sections, namely, the predominance of the ring protonated acid, then the actual energy gap between the acid and its zwitterion is 60 kcal/mol.

(iii) For a zwitterion to be formed from the H-bonded conformer, a complete transfer of the H atom should take place from the oxygen

Table 8

Calculated proton affinities (kcal/mol) and normalized proton affinity difference for donor and acceptor groups of carbamic and dithiocarbamic acids

Group	Carbamic acid (X = O)	Dithiocarbamic acid (X = S)
Acceptor (A) ($-NH_2$)	−91.71	−132.26
Donor (D) (X = C–X)	−334.05	−170.443
Δ	−0.569	−0.128

Normalized proton affinity (PA) difference $\Delta = [PA(A) - PA(D)]/[PA(A) + PA(D)]$.

(sulphur) to the nitrogen atom. If we assume that the criteria used by Pimental et al. [29] for intermolecular H-bonds are valid in the present case, then this transfer of the H atom would depend on the difference in proton affinity between the donor (D) and acceptor (A) groups. The donor group in our case X = C–X (X = O or S) and the acceptor is the $-NH_2$ group. The calculated values for the proton affinities of these two groups in the two acids are given in table 8 along with the normalized proton-affinity difference Δ [19]. According to the scale of Pimental et al. [29], the process of H transfer is feasible in the case of the two acids.

4. Conclusions

The results of the present work would lead to the following conclusions:

(1) The nature of the hindered rotation about the C–N bond of carbamates has been established both experimentally and theoretically. The experimentally determined enthalpy of activation, $\Delta G^{\ddagger}$, indicates that the presence of an electron-donating group ($-OC_2H_5$) directly attached to the carbon atom of the peptide link would considerably lower the barrier to internal rotation around the C–N bond and pinpoint a major difference between carbamates on the one hand and common amide on the other. This falls in line with previously published trends [24,30].

(2) The theoretically computed barriers, $\Delta E^{\ddagger}$ ($= E_a - RT$), are overestimated due to the following reasons: (a) Inherent incapability of the theoretical model. The INDO method, like any other semi-empirical single-determinant method, is parameterized to reproduce the energies of equilibrium structures. Rotation around one of the bonds would involve electron correlation effects which are absent in the equilibrium structure and it is not obvious as to how to estimate their magnitude. (b) Calculations correspond to the free acid in the gas phase. Electron-donor substituents (e.g., $-C_2H_5$ group) would have the effect of lowering the barrier height by 5 kcal/mol (for 1,1-dimethylamide, $\Delta G^{\ddagger} = 21.7$ kcal/mol, whereas for its 2-ethyl derivative, $\Delta G^{\ddagger} = 16.7$ kcal/mol) [24].

(3) On a comparative basis, replacement of oxygen by sulphur increases delocalization of the charge density and increases the partial π-bond character in the C–N region which lead to almost doubling of the rotational barrier on going from carbamic to dithiocarbamic acids. This latter is predicted to have a rotational barrier comparable to that of common amides.

(4) Conclusion (3) indicates a major difference between carbamic and dithiocarbamic acids. That is, the extent of ionic character in the N–C bond. This ionic character is maximum in carbamic acid and decreases as the number of sulphur atoms increases. The ionic character of the N–C bond underlies the biological activity of amide bonds in forming adducts with biomolecules.

(5) Large proton affinity values calculated for the studied compounds suggest an increased tendency for formation of inter- or intramolecular H-bonding. Recent results [31] show that activation of biological type species via protonation would lead to the formation of such H-bonds. For example, protonated alanine derivatives

$$CH_3\overset{\cdots\cdots}{C}OH^{+}NH(CH_3)COOCH_3$$

where the geometry of the interacting groups is similar to the geometry of adjacent amide links in a peptide. In contrast to the case of dithiocarbamic acid, intramolecular H-bonding is energetically unfavorable in carbamic acid. The process of activation of carbamates may thus be assumed to be intermolecular protonation that may be followed by intramolecular H-bonding.

(6) Although zwitterion formation is energetically prohibited for carbamic acid, its formation is feasible in the case of its dithio derivative, indicating different routes for their behaviour in solution. This conclusion elaborates upon the previous thermal analysis carried out on dithiocarbamates [21].

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