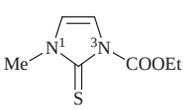
# Structure and molecular interactions of anti-thyroid drugs. Part 1. Dipole moments of carbimazole and methimazole, and conformation of carbimazole

**Christian Laurence,*[a] Mohamed J. El Ghomari[b] and Maryvonne Luçon[a]**

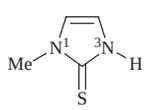
[a] *Laboratoire de Spectrochimie, Faculté des Sciences et des Techniques, Université de Nantes, 2, rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France*
[b] *Laboratoire de Spectroscopie, Faculté des Sciences Semlalia, Université Cadi Ayyad, Marrakech, Morocco*

**The dipole moments of carbimazole and methimazole are respectively 4.30 D (in benzene) and 5.43 D (in dioxane). The 4.30 D value and the solvent variation of the two carbonyl bands of carbimazole in the IR spectrum are consistent with a *Z*⇌*E* conformational equilibrium. Polar solvents stabilize the more polar *Z* conformer and, whereas carbimazole exists about 90% in the *E* form in heptane and $CCl_4$, it is almost entirely in the *Z* form in water. In $CCl_4$ the energy difference between the *Z* and *E* isomers, determined from the ratio of the intensities of the two carbonyl bands, is found to be 9.6 kJ mol$^{-1}$, and is in good agreement with 6-31G** calculations.**

Carbimazole **1** (3-ethoxycarbonyl-1-methyl-2,3-dihydro-1*H*-imidazole-2-thione) and methimazole **2** (1-methyl-2,3-dihydro-1*H*-imidazole-2-thione) are anti-thyroid agents which depress the formation of thyroid hormones and, for this reason, are major drugs currently used for the treatment of hyperthyroidism.[1] These two drugs, and other anti-thyroid agents bearing the thiourea pharmacophore, inhibit the first step in the pathway of thyroid hormone biosynthesis which is the incorporation of oxidized iodide into tyrosine residues in the large thyroid hormone precursor molecule, thyroglobulin. This process is catalyzed by the heme-containing enzyme thyroid peroxidase.[2]




**1**




**2**

Although anti-thyroid drugs have been in use for over 50 years, their mechanisms of action are still poorly understood at the molecular level.[3] This is not surprising since the crystal structures of thyroglobulin and thyroid peroxidase have not yet been determined,[3] and most physico-chemical properties of carbimazole and methimazole are unknown. Only a crystal structure has been found[4] in a literature survey on carbimazole. We have therefore undertaken studies on the structure and molecular interactions of carbimazole and methimazole. This paper reports their dipole moments and the conformational isomerism of carbimazole in various solvents from heptane to water.

## Experimental

### Materials

Methimazole is an Aldrich compound crystallized from $CCl_4$. Carbimazole was generously given by the laboratoires Roche Nicholas (Gaillard, France) with the following characteristics: white microcrystalline powder, mp 124 °C, assay = 99.44%, heavy metals ⩽10 ppm, drying loss = 0.000%, and $\lambda_{max}$ (0.1 M HCl) 291 nm. Heptane, carbon tetrachloride, benzene, chloroform, 1,4-dioxane, methyl sulfoxide and acetonitrile are Aldrich solvents of spectroscopic grade.

### Electro-optical measurements

Relative permittivity, $\varepsilon$ was measured by the superheterodyne beat method on a DM 01 dipolmeter from WTW, refractive indexes, $n$, on an Abbé refractometer from Zeiss and densities, $d$, on a DMA 48 densimeter from Anton Paar. Solutions were made up inside a dry glove-box in the mass fraction range 0.009–0.003 for carbimazole in benzene and 0.0008–0.0002 for methimazole in dioxane. All $\varepsilon$, $d$ and $n$ measurements were performed at 293 K.

### Vibration spectra

IR spectra of carbimazole in KBr pellets, Nujol mull and in various solvents were recorded over the range 1700–1800 cm$^{-1}$ with a Fourier transform spectrometer (Bruker 48) by selecting 1 cm$^{-1}$ resolution. Measurements of overlapping bands were performed by a mathematical decomposition programme included in the Opus™ Bruker software. In the variable temperature experiments, the temperature of the 0.5 mm $CaF_2$ cell was varied from 7 to 52 °C. Raman spectral measurements were carried out with a Bruker RFS 100 spectrometer.

### Calculations

The energies and dipole moments were obtained from semi-empirical and *ab initio* methods (SPARTAN 4.0 programme)[5] by single point calculations (*vide infra*).

## Results and discussion

### Experimental dipole moments

The dipole moments $\mu$ were determined by the Guggenheim–Smith (G.S.) [eqn. (1)] and Halverstadt–Kumler (H.K.) [eqns. (2) and (3)] methods, reviewed by Exner,[6] where $P_{2\infty}$ = polariz-

$$P_{or,2\infty} = \frac{4\pi N}{9kT}\mu^2 = \frac{3M_2}{d_1}\left[\frac{a}{(\varepsilon_1+2)^2} - \frac{\gamma}{(n_1^2+2)^2}\right] \quad (1)$$

$$P_{2\infty} = P_E + P_A + \frac{4\pi N}{9kT}\mu^2 = \frac{3aM_2}{d_1(\varepsilon_1+2)^2} + M_2\frac{\varepsilon_1-1}{\varepsilon_1+2}\left(\frac{1}{d_1}+\beta\right) \quad (2)$$

$$\mu^2 = 1.642\times10^{-4}\,T\,(P_{2\infty} - aR_D) \text{ with } a = 1.05 \text{ or } 1.15 \quad (3)$$

**Table 1** Polarization, refraction[a] and dipole moments for carbimazole **1**(benzene) and methimazole **2** (dioxane)[c] at 20 °C

| Compound | Method | $a$ | $\beta$ | $\gamma$ | $P_{2\infty}$/cm$^3$ mol$^{-1}$ | $R_D$/cm$^3$ mol$^{-1}$ | $P_{or,2\infty}$/cm$^3$ mol$^{-1}$ | $\mu$/D[b] |
|---|---|---|---|---|---|---|---|---|
| Carbimazole | G.S. | 11.27 | | 0.201 | | | 383.6 | 4.30 |
| | H.K.[d] | 11.27 | −0.362 | | 433.9 | 44.2 | | 4.32 |
| | H.K.[e] | 11.27 | −0.362 | | 433.9 | 44.2 | | 4.29 |
| Methimazole | G.S. | 33.13 | | 0 | | | 620.2 | 5.45 |
| | H.K.[d] | 33.13 | −0.226 | | 641.7 | 31.3 | | 5.41 |

[a] Calculated from Vogel's increments. [b] 1 Debye = 3.334 × 10$^{-30}$ C m. [c] Dioxane was selected because of insolubility in benzene. [d] Atomic polarization taken as 5% of the $R_D$ value. [e] Atomic polarization taken as 15% of the $R_D$ value.

**Table 2** Theoretical calculations of the dipole moments of the $Z$ and $E$ conformers of carbimazole, and of their energy difference. Mole fraction of conformer $Z$ ($x$), $Z \rightleftharpoons E$ equilibrium constant ($K$) and Gibbs energy of the isomerisation process ($\Delta G$) in benzene at 20 °C

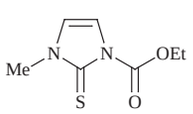
| Method | $\mu_Z$/D | $\mu_E$/D | $-\Delta E_o$[a]/kJ mol$^{-1}$ | $x$ | $K$ | $-\Delta G^\circ_{293}$/kJ mol$^{-1}$ |
|---|---|---|---|---|---|---|
| AM1 | 6.07 | 3.08 | 3.51 | 0.33 | 2.0 | 1.72 |
| HF-4-31G | 7.68 | 3.22 | 3.60 | 0.17 | 5.0 | 3.93 |
| HF-6-31G** | 7.21 | 3.25 | 11.92 | 0.19 | 4.2 | 3.51 |
| Bond moments | 6.24 | 3.48 | | 0.24 | 3.2 | 2.85 |
| IR intensities | | | | 0.20[b] | 4.0[b] | 3.43[b] |

[a] $-\Delta H^\circ_{298}$ for semi-empirical calculations. [b] At the temperature of the cell in the IR beam.

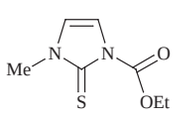
ation of solute 2 at infinite dilution, $P_{or,2\infty}$ = orientation polarization of solute 2 at infinite dilution, $P_E$, $P_A$ = electronic, atomic polarization, $R_D$ = refraction at the sodium D line, $N$ = Avogadro number, $k$ = Boltzmann constant, $T$ = temperature (in K), $M_2$ = molar mass of solute 2, $\varepsilon$ = relative permittivity, $n_1$ = refractive index, $d_1$ = density of solvent 1, $a$, $\beta$, $\gamma$ = slopes of the plots of $\varepsilon_{12}$, $d_{12}^{-1}$, $n_{12}^2$ *versus* the solute mass fraction, $\varepsilon_{12}$ = relative permittivity, $n_{12}$ = refractive index, $d_{12}$ = density of solutions. The polarisation data and dipole moments are listed in Table 1. The mean values selected for the discussion are 4.30 D for carbimazole and 5.43 D for methimazole.

**Dipole moment conformational study of carbimazole**

In the solid state[4] carbimazole adopts a quasi-planar conformation $Z$. With this geometry semi-empirical and *ab initio* Hartree–Fock calculations give $\mu_Z$ values ranging from 6.07 to 7.21 D (Table 2), all greater than the experimental value. On the contrary if we suppose that carbimazole adopts an $E$ planar conformation in benzene solution and calculate $\mu_E$ values (for the solid state geometry after a 180° rotation of the ester group around the C–N bond), we find values between 3.08 and 3.25 D




*Z* (s-*cis*)




*E* (s-*trans*)

(Table 2), lower than the experimental value. The simplest explanation of an experimental value intermediate between values calculated for the $E$ and $Z$ conformations, is the existence of a $Z \rightleftharpoons E$ conformational equilibrium in benzene solution. Since the polarisation, proportional to $(\mu/M_2)^2$, is an additive property, we can calculate the mole fraction $x$ of conformer $Z$, the equilibrium constant $K$ and the Gibbs energy $\Delta G^\circ$ by means of eqns. (4)–(6). The values listed in Table 2 show

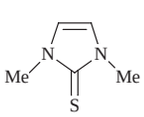
$$\mu^2_{exp} = x\mu^2_z + (1 - x)\mu^2_E \quad (4)$$

$$K_{293} = (1 - x)/x \quad (5)$$

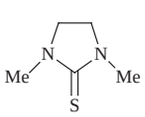
$$\Delta G^\circ_{293}/\text{kJ mol}^{-1} = -2.436 \ln K_{293} \quad (6)$$

that carbimazole is mainly in the $E$ conformation in benzene solution. The greater stability of conformer $E$ in this apolar solvent agrees with the energy differences calculated *in vacuo* at various levels which are listed in Table 2 (in so far that thermal corrections, zero-point vibrational corrections and entropy contribution can be neglected).

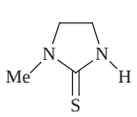
We have also calculated $\mu_Z$ and $\mu_E$ by vector addition of bond and mesomeric moments.[6] The simplest method consists of (i) starting with the dipole moment of **3** directed along the CS bond, (ii) subtracting the methyl group (0.3 D)[6] at 75.1° (the direction between CS and N–CO),[4] (iii) adding the COOEt group moment (1.86 D)[7] at 64°,[7] and (iv) taking into account the conjugation between CO and N by a mesomeric moment. A mesomeric moment of 0.6 D has been derived[8] for simple amides, but the conjugation should be somewhat smaller for carbamates and we therefore reduce it to 0.4 D. Unfortunately the dipole moment of the starting molecule **3** is unknown. We have calculated it from the dipole moment of methimazole **2** in dioxane (5.43 D), by taking into account the dioxane effect (−0.79 D, from the difference between the dipole moments of **5** in benzene and dioxane)[9] and by substituting the nitrogen N$^3$ with a methyl group (−0.50 D, from the difference between the dipole moments of **4** and **5**).[9] This procedure gives $\mu$(**3**) = 4.14 D, in good agreement with the value[9] of 4.04 D for the similar compound **6**. Finally we get the result shown in Fig. 1 and the



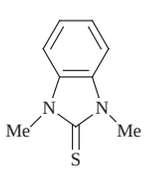

**3**




**4**




**5**




**6**

values $\mu_Z$ = 6.24 D and $\mu_E$ = 3.48 D. Table 2 shows that this vector addition method gives a population of conformer $Z$ (24%) intermediate between the AM1 (33%) and 6-31G** (20%) calculations.

**Vibrational study of the carbimazole conformers**

As the carbonyl stretching vibration is rather sensitive to conformation,[10–12] we have undertaken an IR and Raman study of the carbimazole conformation.

**Solid state and benzene solution.** In the solid state we observe (Fig. 2) one IR carbonyl band at 1758 cm$^{-1}$ (with a shoulder at 1754 cm$^{-1}$ for the KBr pellet as well as for the Nujol mull). The Raman powder spectrum also shows (Fig. 2) one carbonyl band, but now at 1771 cm$^{-1}$ and with a symmetrical profile. We

**Table 3** Carbonyl frequencies, $\nu_Z$ and $\nu_E$, of the $Z$ and $E$ conformers of carbimazole; mole fraction, $x$, of the $Z$ conformer; $Z \rightleftharpoons E$ equilibrium constant, $K$; Reichardt $E_T$ parameter

| Solvent | $\nu_Z$/cm$^{-1}$ | $\nu_E$[a]/cm$^{-1}$ | $x$ | log $K$[b] | $E_T$/kcal mol$^{-1}$ |
|---|---|---|---|---|---|
| Heptane | 1789.3 | 1750 | 0.089 | 1.01 | 30.9 |
| $CCl_4$ | 1786.0 | 1747 | 0.094 | 0.98 | 32.4 |
| $C_6H_6$ | 1782.3 | 1743 | 0.198 | 0.61 | 34.3 |
| $CHCl_3$ | 1778.1 | 1749 | 0.362 | 0.25 | 39.1 |
| DMSO | 1773.4 | 1744 | 0.565 | −0.11 | 45.1 |
| MeCN[c] | 1777.1 | 1749 | 0.588 | −0.15 | 45.6 |
| $D_2O$ | 1765.2 | | | | 63.1 |
| Solid state | 1771 (R)<br>1754.5 (IR)[a] | | | | |

[a] Disymmetrical band. [b] At the temperature of the cell in the IR beam. [c] Raman spectroscopy gives similar results in this solvent.

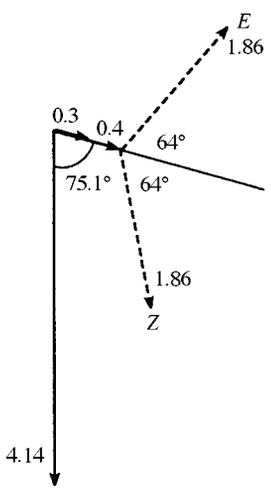



**Fig. 1** Vector addition of group and mesomeric moments contributing to the dipole moments of the $Z$ and $E$ conformers of carbimazole

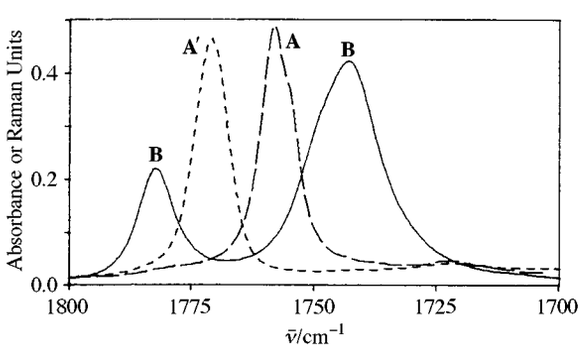



**Fig. 2** Carbonyl band(s) of carbimazole in the solid state (A, IR and A′, Raman) and in benzene (B)

have found no explanation for these frequency and shape differences, but, clearly, the X-ray finding[4] of a $Z$ conformation in the crystalline state allows the attribution of this unique band to the $Z$ conformer carbonyl stretching vibration.

In benzene solution two carbonyl bands appear, the less intense at 1782.3 cm$^{-1}$ and the more intense at 1743.1 cm$^{-1}$ (Fig. 2). This confirms the co-existence of both $E$ and $Z$ isomers in benzene. Since the carbonyl stretching wavenumber is higher as substituents are more electron-withdrawing,[13] and since the electron-withdrawing field effect of the thiocarbonyl group must be more efficient on the carbonyl group in the $Z$ conformer, the high wavenumber band is attributed to the $Z$ conformer.

The carbonyl band integrated intensity is generally not sensitive to substituent field effects.[14] So we can assume equal carbonyl intensities for the $E$ and $Z$ conformers. Then the ratio of band areas gives $K = 4.0$ and $x = 0.20$. These values agree well with those already reported in Table 2.

**Influence of solvent polarity on the conformational equilibrium.** Two carbonyl bands also appear, with various intensities, in the IR spectra of carbimazole in heptane, $CCl_4$, DMSO, $CHCl_3$ and MeCN. We have measured their intensity ratio and see, in Table 3, that the population of conformer $Z$ regularly increases with the solvent polarity. This confirms the well-established rule[15] that the polar solvents stabilize the more polar conformers (here $Z$).

A simple relationship [eqn. (4)], where $n$ is the number of

$$\log K = 3.45 - 0.080\ E_T \qquad (4)$$

$$n = 6 \quad r = 0.987 \quad s = 0.10$$

solvents, $r$ the correlation coefficient and $s$ the standard deviation, exists between log $K$ and the Reichardt $E_T$ solvent parameter.[16] This relation allows the calculation of the conformer populations in water, the solvent with the highest $E_T$ value (63.1).[16] We obtain $K = 0.02$ and a $Z$ conformer mole fraction of 0.98. We indeed observe in the IR spectrum of an aqueous solution of carbimazole one (broad because of hydrogen bonding) carbonyl band in the region absorption of $Z$ conformers. In water, the polarity and hydrogen-bonding donor property displace almost entirely the $Z \rightleftharpoons E$ equilibrium towards the $Z$ form.

**IR determination of the $Z \rightleftharpoons E$ reaction enthalpy.** Finally we have determined the enthalpy of the $Z \rightleftharpoons E$ reaction in $CCl_4$ from the variation of the ratio $A_E/A_Z$ of the carbonyl band areas with temperature, in the range 7–52 °C. The relation is given in eqn. (5). If the ratio $I_E/I_Z$ of integrated intensities

$$\mathrm{d} \ln (A_E/A_Z)/\mathrm{d}T = 1170 \pm 104 \qquad (5)$$

remains constant with temperature, we can derive eqn. (6), and

$$\mathrm{d} \ln (A_E/A_Z)/\mathrm{d}T = \mathrm{d} (\ln K)/\mathrm{d}T = -\Delta H^\circ/R \qquad (6)$$

thus eqn. (7). This value confirms the greater stability of the $E$

$$\Delta H^\circ = -9.6 \pm 0.8 \text{ kJ mol}^{-1} \qquad (7)$$

conformer in $CCl_4$ and agrees satisfactorily with the energy differences calculated *in vacuo* by the 6-31G** method.

## Acknowledgements

We thank the laboratoires Roche Nicholas for providing us with carbimazole. The aid of Professor Exner (Praha) in the vector addition method is gratefully acknowledged. We also thank Dr J. Y. Le Questel (Nantes) for theoretical calculations, Dr A. Chardin (Nantes) for dipole moment measurements under the guidance of Professor A. Proutière and Dr M. Hérail (Nantes), and Dr M. Helbert for some IR measurements.

## References


1 J. Buxeraud, in *Traité de chimie thérapeutique*, Tec et Doc Lavoisier, Paris, 1995, vol. 4, ch. 18.
2 D. S. Cooper, *N. Engl. J. Med.*, 1984, **311**, 1353.
3 J. Leclerc, J. Orgiazzi, B. Rousser, J. L. Schlienger and J. L. Wemeau, *La thyroïde*, Expansion scientifique française, Paris, 1992.
4 C. Delage, F. Fauré, J. M. Léger, C. Raby and M. Goursolle, *C.R. Acad. Sci. Hebd. Seances*, 1990, **311**, 781.
5 SPARTAN, Wavefunction, Inc. 18401 Von Karman Avenue, Irvine, California 92715 USA.
6 O. Exner, *Dipole moments in Organic Chemistry*, G. Thieme Verlag, Stuttgart, 1975.
7 B. Plesničar and O. Exner, *Collect. Czech. Chem. Commun.*, 1981, **46**, 490.
8 O. Exner and Z. Paspoušková, *Collect. Czech. Chem. Commun.*, 1980, **45**, 2410.
9 C. W. N. Cumper and G. D. Pickering, *J. Chem. Soc.*, 1972, 2045.
10 T. L. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 3513.
11 T. L. Brown, *Spectrochim. Acta*, 1960, **18**, 1615.
12 G. Guihéneuf, C. Bénard, A. Lachkar and M. Luçon, *Can. J. Chem.*, 1984, **64**, 2343.
13 L. J. Bellamy, *The IR spectra of complex molecules*, Chapman and Hall, London, 2nd edn., 1980, vol. 2.
14 C. Laurence, M. Berthelot and D. G. Morris, *Spectrochim. Acta, Part A*, 1983, **39**, 699.
15 W. L. Jorgensen, *J. Phys. Chem.*, 1983, **87**, 5304.
16 C. Reichardt, *Solvents and solvent effects in organic chemistry*, VCH Weinheim, 1988.



*Paper* 8/00621K
*Received* 22*nd January* 1998
*Accepted* 23*rd February* 1998