79. NMR Conformational Study of Aminoalkylbenzamides, Aminoalkyl-*o*-anisamides, and Metoclopramide, a Dopamine Receptor Antagonist

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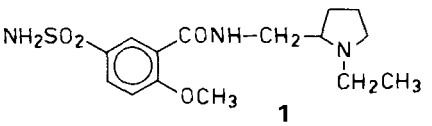
Summary

The conformational behaviour of metoclopramide, a neuroleptic benzamide, and model compounds was investigated by ^{1}H-NMR spectroscopy. An intramolecular amide-methoxy H-bond is shown to exist in $CDCl_3$-solution, but not in D_2O-solution, independently of the length and protonation state of the basic side-chain. This H-bond creates a virtual cycle which may be a key feature for the binding of neuroleptic benzamides to the dopamine receptor. The conformational behaviour of the aminoethyl side-chain is shown to be markedly condition-dependent. For metoclopramide and its analogues in their protonated form, the *gauche*- and *trans*-rotamers have identical energies in D_2O- as well as in $CDCl_3$-solutions. For the non-protonated molecules, the *trans*-rotamer is favoured in D_2O-solution, while the *gauche*-rotamer is favoured in $CDCl_3$-solution ($\Delta G^0 \simeq |0.5|$kcal/mol in both cases). The side-chain conformation of neuroleptic benzamides is discussed in terms of receptor affinity.

1. Introduction. – Substituted benzamide drugs (substituted *o*-anisamides, orthopramides) are a group of dopamine antagonists clinically used as neuroleptics (*e.g.*, sulpiride (**1**)), antiemetics (*e.g.*, metoclopramide (**2**)), or against various forms of dyskinesia (*e.g.*, tiapride (**3**)). These compounds are now receiving considerable attention in connection with their therapeutic potential and their mechanism(s) of action at the receptor and molecular level.



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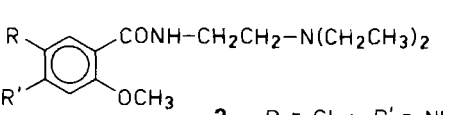
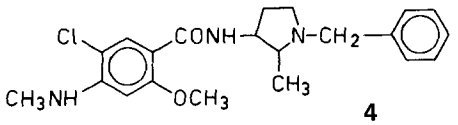


2 R = Cl ; R' = NH_2

3 R = SO_2CH_3 ; R' = H

The current evidence indicates that orthopramides act primarily as antagonists of a population of dopamine receptors not linked to adenylate cyclase (D-2 receptors) [1–4]. To help unravel topographical elements of the D-2 receptor and the pharmacophore of

orthopramides, we have calculated their conformational behaviour using a semi-empirical quantum mechanical method [5–7]. The results indicate that aminoethyl derivatives such as metoclopramide (**2**) and tiapride (**3**) exist, without solvent interactions, in a folded *(gauche)* conformation 10–15 kcal/mol more stable than the extended *(trans)* conformation [5]. In 2-pyrrolidyl derivatives such as sulpiride (**1**) and 3-pyrrolidyl derivatives such as YM-09151-1 (**4**), the energy difference is decreased to 3–4 kcal/mol and 5–6 kcal/mol, respectively [6] [7]. In contrast, 4-piperidyl derivatives such as clebopride (**5**) display the basic side-chain in an extended conformation, the folded forms (boat conformations) being less stable by *ca.* 30 kcal/mol [7].



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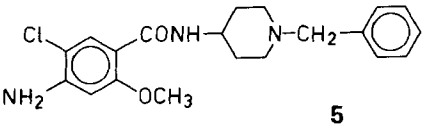

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These results, to be meaningful, must be compared with experimental data. In the present work, the conformational behaviour of metoclopramide (**2**) and aminoalkylbenzamides is examined in solution by ^{1}H-NMR spectroscopy at 60 and 360 MHz. Two aspects are studied, namely, the conformation of the aminoethyl side-chain *(Sect. 3)*, and the coplanarity of the phenyl ring and the amide moiety *(Sect. 4)*. The latter is also investigated using a quantum mechanical method.

2. Methods. – 2.1. *^{1}H-NMR Spectra.* ^{1}H-NMR spectra were recorded at 60 MHz on a *Varian EM-360* spectrometer operating in the CW mode and at 360 MHz on a *Bruker WH-360* spectrometer operating in the FT mode. The chemical shifts are in ppm relative to TMS (org. solutions) or to sodium 3-(trimethylsilyl)-(2,2,3,3-$^2H_4$)propionate (TSP) (aq. solutions). If necessary the FID's at 360 MHz were multiplied by a *Gaussian*-exponential function [8] before FT to yield resolution-enhanced spectra. The concentration of the solutions ranged from 0.2 to 0.002M. If not mentioned otherwise, the temperature was maintained at 24 ± 1°.

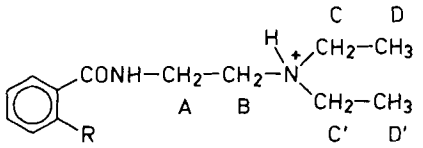
2.2. *Spectrum Calculation.* The chemical shifts and coupling constants of the ethane fragments were analyzed as *AA'XX'* spin systems. After peak assignment the parameters N and L [9] were calculated and the time-averaged vicinal coupling constants J and J' determined. In all cases the parameter K, and therefore, the geminal coupling constants J_A and J_X, could not be evaluated. The spectra were sensitive only to the difference M of these couplings. Finally the spectrum parameters were refined by a least-squares iteration procedure using the program PANIC [10] of the *Aspect-2000* computer. The accuracy of the actual fits was determined by the digital resolution in the experimental spectra (0.2 Hz/point).

2.3. *Quantum Mechanical Calculations.* Conformational calculations were performed using a semi-empirical all-valence-electron procedure, the PCILO method [11]. The molecules under study were constructed by standard geometry [12].

3. Side-Chain Conformation in *N*-(Aminoethyl)benzamides and -*o*-Anisamides. – 3.1. *Analysis of Coupling Constants.* Vicinal ^{1}H,^{1}H coupling constants were measured to study the conformation of the X–CH_2CH_2–Y moiety in metoclopramide (**2**) and in the model molecules *N*[(diethylamino)ethyl]benzamide and -*o*-anisamide (**6** and **7**, respectively, see *Table 1*; for the description of model compounds, see also [13]).

Abraham & Gatti [14] established an empirical relationship between vicinal coupling constants and populations of rotamers in 1,2-disubstituted ethanes. The latter display three remarkable rotamers as shown in *Fig. 1*. Due to the usually fast interconversion between *gauche*- and *trans*-rotamers, it is only seldom possible to observe the individ-

Table 1. *Chemical Shifts* (ppm) *and Coupling Constants* (Hz) *of the Side-Chain Protons of* N-*[(Diethylamino)-ethyl]benzamides*[a])



Compound	R	Solvent	δ_A	δ_B	J_{AB}	$\delta_{C/C'}$	$\delta_{D/D'}$	J_{CD}
6	H	D_2O[b])	3.808	3.435	6.1	3.325	1.327	7.1
		$CDCl_3$	3.900	3.294	5.9	3.185	1.404	7.2
7	OCH_3	D_2O[b])	3.822	3.443	6.1	3.335	1.337	7.3
		$CDCl_3$	4.004	3.283	6.2	3.167/3.178[d])	1.420	7.3
		CD_2Cl_2[c])	3.886	3.198	6.2	3.111/3.115[d])	1.341	7.1
Metoclopramide (**2**)		D_2O[b])	3.776	3.401	6.0	3.312	1.320	7.3
		$CDCl_3$	3.948	3.248	6.1	3.147/3.153[d])	1.442	7.3

[a]) From 360-MHz ^{1}H-NMR spectra of 0.002 M solutions at 24 °C.
[b]) Amide and ammonium protons are exchanged by deuterium.
[c]) At −68 °C.
[d]) Determined by decoupling of the ammonium protons.

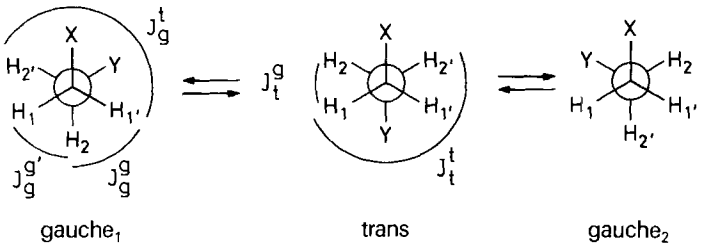


Fig. 1. *Staggered rotamers and vicinal coupling constants in 1,2-disubstituted ethanes* [14]

ual coupling constants. Instead two time-averaged coupling constants are obtained which are defined according to *Eqn. 1–3*:

$$J = n_t \cdot J_t^g + n_g \cdot (J_g^t + J_g^{g'})/2 \quad (1)$$

$$J' = n_t \cdot J_t^t + n_g \cdot J_g^g \quad (2)$$

$$n_t + n_g = 1 \quad (3)$$

where n_t and n_g are the populations of the *trans*- and *gauche*-rotamers, respectively [14]. Using 1,2-disubstituted ethanes of known conformational behaviour, *Abraham & Gatti* showed that the individual coupling constants can be expressed as a function of E_x and E_y, the electronegativity of the X and Y substituents, respectively [15]. This treatment has been refined by *Phillips & Wray* [16]. The results obtained using the two methods are remarkably similar, but the second one involves longer calculations.

In the case of the N–C–C–O fragments of interest, $E_X = E_Y = 3.05$, hence [15]: $J_t^g = 5.19$ Hz, $J_t^t = 12.70$ Hz, $J_g^g = 3.21$ Hz, $J_g^t + J_g^{g'} = 14.54$ Hz.

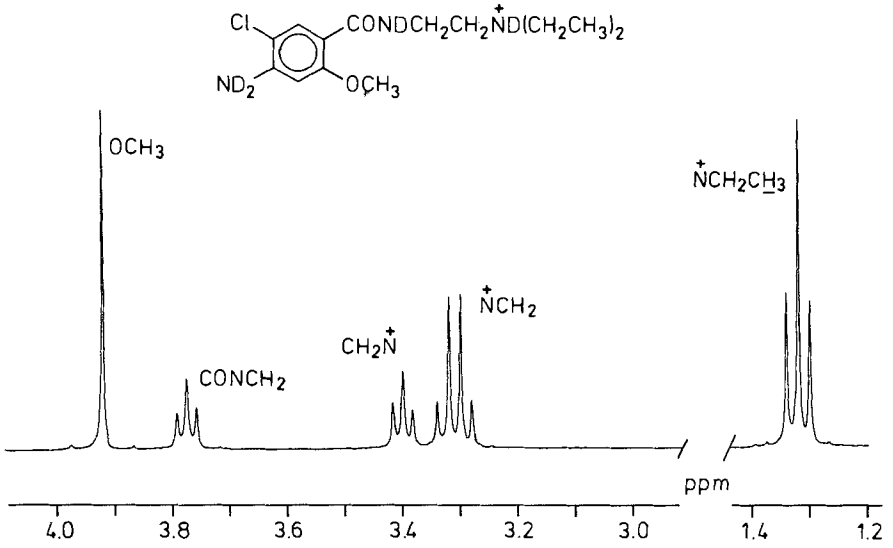


Fig. 2. *Low-frequency part of the 360-MHz ^{1}H-NMR spectrum of* **2** · *HCl in D_2O.* Assignments of the side-chain resonances are indicated.

3.2. *Side-Chain Conformation in the Protonated State.* ^{1}H-NMR spectra were recorded at 360 MHz for **6**·HCl, **7**·HCl, and **2**·HCl in D_2O- and $CDCl_3$-solutions *(Table 1)*. In each case an apparently perfect A_2X_2-system was observed for the $-CH_2-CH_2-$ moiety, as exemplified by the 1:2:1 intensity distribution of the CH_2-multiplets, *e.g.*, see the spectrum of **2**·HCl in D_2O *(Fig. 2)*. This implies that the two *A*-protons are magnetically equivalent, as are the two X-protons. No difference exists in the free energy of the *gauche*- and *trans*-conformations, hence the population of each conformer must be identical, $n_t = n_g/2 = 0.33$. This conclusion is supported by the fact that the spectrum of **7**·HCl in CD_2Cl_2 did not change upon decreasing the temperature to −68°C *(Table 1)*.

These results contrast with those reported by *Makriyannis et al.* [17] who for **6**·HCl in D_2O observed an *AA'BB'*-system with $J = 6.60$ Hz, $J' = 5.70$ Hz and $n_g = 0.74$, $n_t = 0.26$. Their data, however, were calculated from spectra recorded at 60 and 100 MHz and we believe that the A_2B_2-type spectrum was erroneously interpreted as an *AA'BB'*-system.

3.3. *Side-Chain Conformation of the Neutral Molecules.* The 360-MHz ^{1}H-NMR spectra for **6** and **7** as bases in D_2O show the ethane proton resonances very close to an *AA'XX'*-system. The partial spectrum of **6** is shown in *Fig. 3A*. Spectral analysis (*Fig. 3B*, see *Methods*) gave the couple of *J*, *J'* values equal to 8.1 and 6.1 Hz, fully identical for the two compounds. Since *J* and *J'* cannot be assigned from the spectral analysis, energetic considerations were required [14]. To satisfy *Eqn. 1–3* simultaneously, it was necessary to assign $J = 8.1$ Hz and $J' = 6.1$ Hz, with $n_t = 0.53$ and $n_g = 0.47$ *(Table 2)* corresponding to an energy difference $\Delta G^\circ \simeq |0.5|$kcal/mol. This result agrees well with that obtained at 100 MHz by *Makriyannis et al.* [17] for non-protonated **6** in CD_3OD.

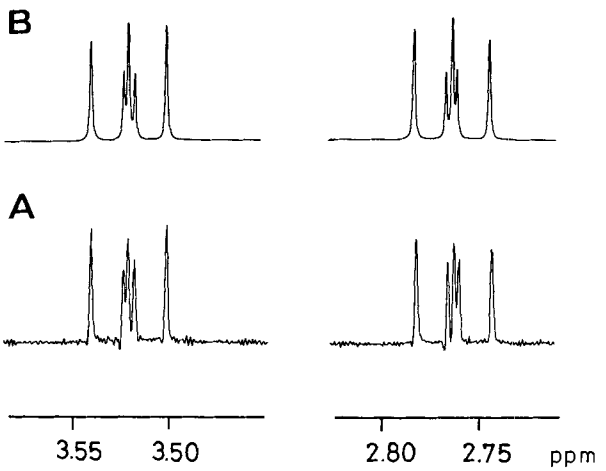


Fig. 3. *The $-CH_2-CH_2-$ part of the 360-MHz ^1H-NMR spectrum of* **6** *base in D_2O.* (A) Experimental spectrum (resolution-enhanced). (B) Simulated spectrum (linewidth 0.3 Hz; for details of the calculation see *Methods*).

Table 2. *^1H-NMR Parameters and Conformational Populations of the Ethane Fragment of* **6** *and* **7** *Bases*[a])

Compound	R	Solvent	δ_A	δ_B	^3J	$^3J'$	$(^2J_A-^2J_B)$	n_g	n_t
6 base	H	$CDCl_3$	3.491	2.655	7.0	4.9	0.7	0.84	0.16
		D_2O	3.525	2.758	8.1	6.1	~0	0.47	0.53
7 base	OCH_3	$CDCl_3$	3.531	2.646	7.0	5.4	0.9	0.80	0.20
		D_2O	3.525	2.758	8.1	6.1	~0	0.47	0.53

[a]) Measured at 360 MHz; T = 24°C. Chemical shifts in ppm (estimated error ±0.002 ppm), spin-spin couplings in Hz (error determined by the digital resolution, ±0.2 Hz).

When the **6** and **7** bases were dissolved in $CDCl_3$ the resonances of the NCH_2-protons were additionally split due to their coupling with the amide proton, $^3J_{(NH,CH_2)} = 4.8$ Hz *(Fig. 4A)*. Simulation of the spectra was again possible *(Fig. 4B)*, and the coupling constants J, J' and their assignments are collected in *Table 2*. Surprisingly the *gauche*-conformers were strongly favoured in $CDCl_3$-solution ($n_g = 0.84$ for **6** and $n_g = 0.80$ for **7**) corresponding to energy differences of $\Delta G^\circ \simeq |0.6|$kcal/mol and $\Delta G^\circ \simeq |0.4|$kcal/mol, respectively.

3.4. *Discussion.* The above results indicate that the side-chain conformation in the investigated molecules is influenced by the protonation state of the basic nitrogen atom. In the protonated state, the *gauche*- and *trans*-forms have apparently identical free energy levels in water like in chloroform. This appears to rule out any major conformational influence of solvation factors. Also, these results do not confirm the existence in solution of an intramolecular H-bond between N^+-H and O=C as postulated in vacuum from PCILO calculations [5]. This semi-empirical method, however, is known to exaggerate attractive non-bonded interactions. Also noteworthy is the fact that the side-chain conformation is not influenced by the *o*-methoxy moiety (compare **6** and **7**) no more than by other ring substituents (compare metoclopramide (**2**) with **6** and **7**).

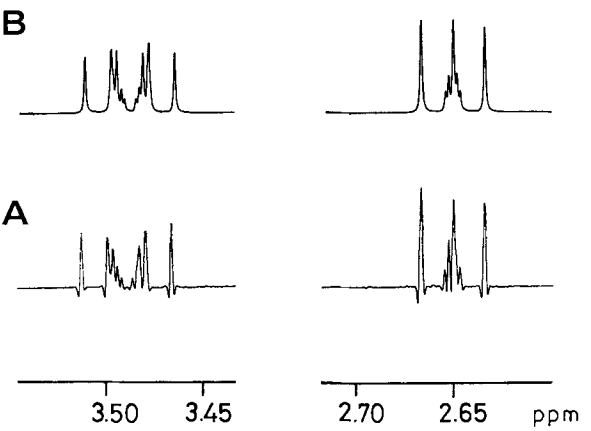
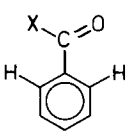


Fig. 4. *The $-CH_2-CH_2-$ part of the 360-MHz ^{1}H-NMR spectrum of* **6** *base in $CDCl_3$.* The multiplet structure at high frequency is determined by an additional coupling (^3J = 4.8 Hz) with the amide proton (δ = 7.21 ppm). (A) Experimental spectrum (resolution-enhanced). (B) Simulated spectrum (linewidth 0.4 Hz).

For the non-protonated molecules in D_2O the *trans*-conformer is favoured by *ca.* 0.5 kcal/mol over the *gauche*-conformers while in $CDCl_3$ the reverse is found true. Therefore the conformational behaviour in $CDCl_3$ resembles that found in the crystal [18]. Solvation interactions thus play a critical conformational role for the neutral as opposed to the protonated molecules. These results also stress the need for caution when deriving structure-activity relationships and topographical models solely from conformations found in the crystal.

4. Intramolecular H-Bond between the Methoxy-O-Atom and the Amide-H-Atom. – 4.1. *^{1}H-NMR Investigations.* In aromatic carbonyl derivatives of general structure **8** the chemical shift of the *ortho*-H-atoms is under the influence of the magnetic anisotropic effect of the carbonyl group and may undergo a conformation-dependent high-frequency shift which is largest when the system is coplanar.

This argument was applied by *Kondo* [19] to investigate the conformational behaviour of *o*-substituted benzoic-acid derivatives, in particular in the *o*-methoxylated compounds. For *o*-anisic acid **9a** and *N*-methyl-*o*-anisamide **9c** in $CDCl_3$-solution, he found that the H(6)-signal is deshielded between 0.3 and 0.4 ppm relative to that in methyl *o*-anisate (**9b**). This was taken as evidence for the existence of an intramolecular H-bond (*cf.* **10**) acting as conformational lock and allowing maximal deshielding of



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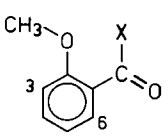

9a X = OH
b X = OCH_3
c X = $NHCH_3$
d X = NH_2

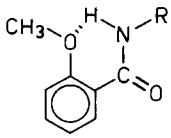

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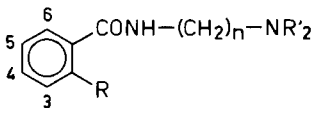
Table 3. *^{1}H-NMR Chemical Shifts of the Aromatic Protons of Various Benzamides and o-Anisamides*[a])



Compound	R	n	R'	Base/ salt	Solvent	H–C(2–6)	H–C(3–6)	H–C(3–5)	H–C(6)	H–C(2,6)	OCH_3
Benzamide	H	–	–	–	$CDCl_3$	–	–	7.3–7.7	–	7.86	–
9d	OCH_3	–	–	–	$CDCl_3$	–	–	6.9–7.7	8.32	–	3.97
9c[b])	OCH_3	–	–	–	$CDCl_3$	–	–	6.97–7.43	8.22	–	?
9c[b])				–	(D_6)DMSO	–	–	7.04–7.46	7.80	–	?
11	H	1	CH_3	base	$CDCl_3$	–	–	7.3–7.7	–	~7.8	–
11				base	D_2O	7.4–7.9	–	–	–	–	–
11				HCl	D_2O	7.5–8.1	–	–	–	–	–
12	H	1	Et	base	$CDCl_3$	–	–	7.2–7.7	–	~7.8	–
12				base	D_2O	7.4–8.0	–	–	–	–	–
12				HCl	D_2O	7.3–7.9	–	–	–	–	–
13	OCH_3	1	CH_3	base	$CDCl_3$	–	–	6.9–7.6	8.20	–	3.97
14	OCH_3	1	Et	base	$CDCl_3$	–	–	6.9–7.7	8.25	–	3.97
14				HCl	$CDCl_3$	–	–	7.0–7.8	8.23	–	4.13
14				HCl	D_2O	–	–	7.0–8.0	7.88	–	3.93
15	H	2	H	base	$CDCl_3$	–	–	7.3–7.5	–	7.80	–
15				HCl	D_2O	–	–	7.5–7.8	–	7.92	–
16	OCH_3	2	H	base	$CDCl_3$	–	–	6.9–7.5	8.20	–	3.93
16				HCl	D_2O	–	–	7.0–7.7	7.90	–	3.98
6[c])	H	2	Et	base	$CDCl_3$	–	–	7.3–7.5	–	7.81	–
6				base	D_2O	–	–	7.5–7.6	–	7.76	–
6				HCl	$CDCl_3$	–	–	7.3–7.5	–	8.08	–
6				HCl	D_2O	–	–	7.5–7.7	–	7.81	–
7[c])	OCH_3	2	Et	base	$CDCl_3$	–	–	7.0–7.4	8.23	–	3.91
7				base	D_2O	–	–	7.1–7.6	7.76	–	3.95
7				HCl	$CDCl_3$	–	–	7.0–7.5	8.14	–	4.06
7				HCl	D_2O	–	–	7.1–7.6	7.83	–	3.97
2	OCH_3	2	Et[d])	HCl	$CDCl_3$	–	–	6.31	8.04	–	4.00
2				HCl	D_2O	–	–	6.62	7.82	–	3.92
17	H	3	CH_3	base	$CDCl_3$	–	–	7.4–8.0	–	7.93	–
18	OCH_3	3	CH_3	base	$CDCl_3$	–	–	6.8–7.5	8.18	–	3.90
18				HCl	$CDCl_3$	–	–	6.9–7.5	8.11	–	3.95
18				HCl	D_2O	–	–	7.0–7.8	~7.8	–	3.96
19	H	3	Et	base	$CDCl_3$	–	–	7.4–7.7	–	7.95	–
20	OCH_3	3	Et	base	$CDCl_3$	–	–	6.9–7.7	8.31	–	4.00
20				base	D_2O	–	7.0–7.9	–	–	–	3.92
20				HCl	D_2O	–	6.9–7.8	–	–	–	3.85
21	H	4	H	HCl	D_2O	7.3–7.8	–	–	–	–	–
22	OCH_3	4	H	base	$CDCl_3$	–	–	6.8–7.6	8.18	–	3.90
22				HCl	D_2O	–	6.9–7.8	–	–	–	3.93

[a]) The spectra were recorded at 60 MHz unless otherwise specified. The chemical shifts are in ppm relative to internal TMS (in $CDCl_3$) or TSP (in D_2O). The aromatic ring proton signals have been assigned on the basis of the distinct *ortho* (7–9 Hz), *meta* (1–2 Hz), and *para* (0.2–0.5 Hz) coupling constants.

[b]) Data from [19].

[c]) From the 360-MHz spectra.

[d]) Additional ring substituents: NH_2–C(4), Cl–C(5).

H–C(6). In (D_6)DMSO solution on the other hand, the chemical shifts of H–C(6) in the three compounds were nearly identical indicating that the intramolecular H-bond in **9a** and **9c** is destabilized by solute-solvent H-bonds (see *Table 3* for the results of **9c**).

These results [19] compare well with the behaviour of various anilides in which the presence of an *ortho*-substituent capable of H-bonding with the amide-H-atom induced a strong deshielding of the H–C(6) signal [20–22].

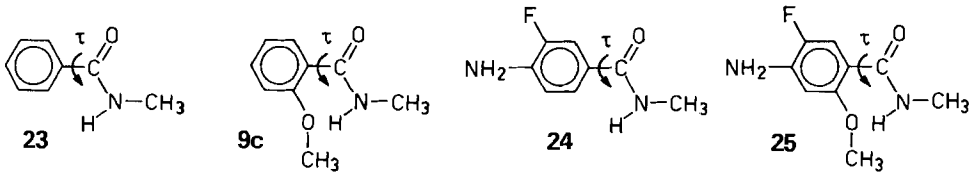
Our results with benzamide and *o*-anisamide (**9d**) in $CDCl_3$ confirm the finding of *Kondo* [19]. In the case of benzamide, the magnetic anisotropy of the carbonyl group is distributed to the two *ortho*-H-atoms and averaged by the process of rotation, resulting in a relatively moderate deshielding. This contrasts with a significantly larger deshielding of H–C(6) in **9d** *(Table 3)*. The method had thus been used to investigate the existence of an intramolecular H-bond (*cf.* **10**) in a series of aminoalkylbenzamides and aminoalkyl-*o*-anisamides synthesized as model compounds for dopamine antagonists [13]. Whenever feasible, the spectra were recorded for the compounds as bases and as hydrochlorides, in $CDCl_3$ and in D_2O *(Table 3)*. The spectra were independent on solute concentration excluding the possibility of an intermolecular association.

In the compounds lacking an *o*-methoxy group (compounds **6**, **11**, **12**, **15**, **17**, **19** and **21**), the signals of the *ortho*-H-atoms are not always distinguishable at 60 MHz from those of the other aromatic H-atoms; this is the case for **11**, **12** and **21** in D_2O. In all other cases, however, the signal of the *ortho*-H-atoms appears somewhat deshielded from those of the other aromatic H-atoms. The recorded values range from 7.80 to 7.95 ppm for the bases in $CDCl_3$; the signal is found at 7.76 ppm for the **6** base in D_2O, at 8.08 ppm for its hydrochloride in $CDCl_3$, and at 7.81 and 7.92 ppm for **6**·HCl and **15**·HCl, respectively, in D_2O. This signal thus appears relatively unaffected by solvent and protonation conditions.

In contrast, the *o*-methoxy derivatives (**7**, **13**, **14**, **16**, **18**, **20** and **22**) display a solvent-dependent signal for H–C(6). In $CDCl_3$, the signal is observed between 8.2 and 8.3 ppm for the bases and between 8.0 and 8.2 ppm for the salts. In D_2O, on the other hand, the same signal is seen between 7.8 and 7.9 ppm *(Table 3)*. These data support the existence of an amide-methoxy intramolecular H-bond (*cf.* **10**) in $CDCl_3$-solution as opposed to solutions in D_2O.

4.2. *Quantum Mechanical Calculations.* Quantum mechanical calculations were performed to confirm the interpretation of the NMR spectra given in *Sect. 4.1.* Using the PCILO method [11], we investigated the conformational behaviour of the phenyl-carbonyl single bond in the model molecules *N*-methylbenzamide (**23**), **9c**, *N*-methyl-4-amino-3-fluorobenzamide (**24**) and *N*-methyl-4-amino-5-fluoro-*o*-anisamide (**25**). The dihedral angle τ (shown equal to 0° in **23** and **24**, and to 180° in **9c** and **25**) was rotated by 30° increments. Because in the PCILO program the two *Kékulé* structures of benzene are not equivalent, distorsions appear in the curves of conformational energy. This problem has been extensively investigated by *Gerhards et al.* [23], who showed that it can be solved by taking the arithmetic mean of the energy of the two *Kékulé* structures.

For the molecules under study, the difference in conformational energy between two corresponding *Kékulé* structures is always smaller than 1.7 kcal/mol, a situation where use of the arithmetic mean is recommended [23]. The results *(Fig. 5)* show some



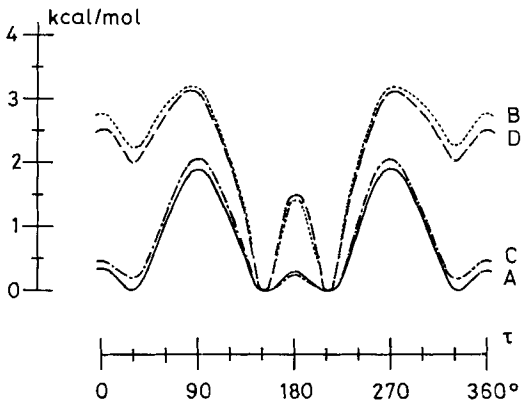


Fig. 5. *The conformational behaviour of* N-*methylbenzamide* (A), N-*methyl*-o-*anisamide* (B), N-*methyl-4-amino-3-fluorobenzamide* (C) *and* N-*methyl-4-amino-5-fluoro*-o-*anisamide* (D), *as calculated by the PCILO method.* For a definition of τ, see **9c**, **23**–**25** and text.

differences between the benzamides and the *o*-anisamides. In the four molecules (**9c**, **23**–**25**), two identical global minima exist at 150° and 210°, *i.e.* close to the coplanarity of the phenyl and amide moieties. At $\tau = 180°$, a difference appears in that the energy level is *ca.* 0.3 kcal/mol above the minimum for the benzamides, while for the *o*-anisamides the difference is *ca.* 1.4 kcal/mol. Such an effect may not be physically genuine and could reflect the manner in which the lone pairs of electrons of the methoxy-O-atom are defined by the PCILO program.

In all four molecules (**9c**, **23**–**25**), two symmetrical barriers of rotation are apparent when the phenyl and amide moieties are perpendicular. In the benzamides, these barriers have a value of *ca.* 2 kcal/mol above the global minimum, while in the *o*-anisamides the energy difference is larger, 3.1–3.2 kcal/mol. The energy barrier is thus 1.0–1.3 kcal/mol higher in the *o*-anisamides, and this difference can be taken as evidence for the existence of an intramolecular H-bond between the amide H-atom and the methoxy-O-atom. These theoretical results are compatible with the interpretation of the ^{1}H-NMR spectra given in *Sect. 4.1.*

Another conformational difference between benzamides and *o*-anisamides is seen for τ-values in the region of 0°. Here, repulsive effects between the two O-atoms exist in the *o*-anisamides.

Finally, *Fig. 5* shows that the presence of NH_2- and F-substituents in the aromatic ring does only moderately influences the conformational behaviour of the investigated model molecules, the largest effect being 0.26 kcal/mol.

4.3. *Discussion.* These investigations indicate that for *o-methoxybenzamides in $CDCl_3$ (Table 3)* or in vacuum *(Fig. 5)*, an intramolecular H-bond exists (*cf.* **10**) which is stable enough to markedly increase the population of coplanar or nearly coplanar conformers as compared to non-methoxylated analogs. This intramolecular H-bond does not appear to be influenced by the length of the aminoalkyl side-chain, by the protonation state of the amino group, or by the presence of some aromatic substituents other than the methoxy group.

In D_2O, the methoxy-amide H-bond is destabilized, certainly due to competition with intermolecular H-bonds. This observation is consistent with the finding of *Kondo* [19] who reported a similar solvent effect for *N*-methyl-*o*-anisamide (**9c**) in DMSO *(Table 3)*.

5. General Discussion. – The conformational behaviour of compound *N*-[(diethylamino)ethyl]-*o*-anisamide (**7**) under all conditions investigated is summarized in *Table 4*. Metoclopramide, its medicinal derivative, showed an identical conformational behaviour under all testable conditions. The solvent dependence of the intramolecular methoxy-amide H-bond is particularly interesting. We have recently postulated [7] that the pseudo-cycle resulting from this H-bond is a key feature for the receptor recognition of neuroleptic benzamides. The present work suggests that while such a H-bond does not occur in an aqueous medium, it must indeed exist in a lipophilic environment which is that of membranes and receptors.

Table 4. *Conformational Behaviour of* N-*[(Diethylamino)ethyl]*-o-*anisamide* (**7**), *a Model of Metoclopramide*

	Intramolecular H-bond between amide-H- and methoxy-O-atom	Rotamer populations $N-CH_2-CH_2-N$ moiety
Protonated state		
D_2O	Not present[a])	$n_t = 0.33$; $n_g = 0.67$
$CDCl_3$	Present	$n_t = 0.33$; $n_g = 0.67$
Non-protonated state		
D_2O	Not present[a])	$n_t = 0.53$; $n_g = 0.47$
$CDCl_3$	Present	$n_t = 0.20$; $n_g = 0.80$

[a]) If present, not in detectable proportion.

Theoretical conformational studies using the PCILO method [5] indicate for protonated aminoethyl-*o*-anisamides (*e.g.*, metoclopramide) an energy difference of 10–15 kcal/mol between the preferred *gauche*-conformation and the *trans*-forms. The present work brings experimental evidence that in D_2O- as well as in $CDCl_3$-solution, protonated metoclopramide exists in *gauche*- and *trans*-conformations of equal energy. Comparing these two results would suggest that for the compounds under consideration a correction factor of approximately 10 kcal/mol is indicated when deriving conformational energy differences in solution from PCILO data.

Applying the above correction factor to neuroleptic benzamides of the 2-pyrrolidyl and 3-pyrrolidyl series [6] [7] indicates that these molecules, when in the protonated state and in aqueous solution, must exist in an extended conformation preferred by a few kcal/mol over the folded forms. Globally, neuroleptic benzamides can thus be classified into two groups according to their conformational behaviour in aqueous solution. The first group is that of aminoethyl derivatives (*e.g.*, metoclopramide and

tiapride) which display *gauche*- and *trans*-conformers of approximately equal energy. The second group comprises the pyrrolidyl and piperidyl derivatives, namely 2- and 3-pyrrolidyl derivatives for which the extended conformers are believed to be favoured by a few kcal/mol over the folded ones, and 4-piperidyl derivatives (*e.g.*, clebopride) for which the folded forms are of forbiddingly high energy [7].

We believe this conformational classification to be of pharmacological significance. Indeed, with an as yet limited series of compounds, binding data show that once lipophilicity has been accounted for, substituted benzamides of the pyrrolidine and piperidine series have a higher affinity for the dopamine D-2 receptor than analogues in the aminoethyl series [24] [25]. Such results, if confirmed for larger series of compounds, would be of significant interest in drug design.

Conformational investigations of neuroleptic benzamides by combined theoretical and experimental means may prove of interest in assessing the topography of the dopamine receptor(s) [7] and in designing novel and perhaps more selective dopamine antagonists.

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REFERENCES

[1] *J.W. Kebabian & D.B. Calne*, Nature (London) *277*, 93 (1979).
[2] *P. Jenner & C.D. Marsden*, Life Sci. *25*, 479 (1979).
[3] *P. Sokoloff, M.P. Martres & J.C. Schwartz*, N.S. Arch. Pharmacol. *315*, 89 (1980).
[4] *J.W. Kebabian & T.E. Cote*, Trends Pharmacol. Sci. *2*, 69 (1981).
[5] *A. Pannatier, L. Anker, B. Testa & P.A. Carrupt*, J. Pharm. Pharmacol. *33*, 145 (1981).
[6] *H. van de Waterbeemd & B. Testa*, Helv. Chim. Acta *64*, 2183 (1981).
[7] *H. van de Waterbeemd & B. Testa*, J. Med. Chem. *28*, 203 (1983).
[8] *A.G. Ferrige & J.C. Lindon*, J. Magn. Reson. *31*, 337 (1978).
[9] *H. Günther*, 'NMR Spectroscopy, an Introduction', Wiley, New York, 1980, chap. 5.3.
[10] PANIC Program: Copyright, *Bruker Spectrospin AG*, Switzerland.
[11] *S. Diner, J.P. Malrieu, F. Jordan & M. Gilbert*, Theor. Chim. Acta *15*, 100 (1969).
[12] *L.E. Sutton*, 'Tables of Interatomic Distances and Configuration in Molecules and Ions', The Chemical Society, London, 1965.
[13] *L. Anker, B. Testa, H. van de Waterbeemd, A. Bornand-Crausaz, A. Theodorou, P. Jenner & C.D. Marsden*, Helv. Chim. Acta *66*, 542 (1983).
[14] *R.J. Abraham & G. Gatti*, J. Chem. Soc. B *1969*, 961.
[15] *M.L. Huggins*, J. Am. Chem. Soc. *75*, 4123 (1953).
[16] *L. Phillips & V. Wray*, J. Chem. Soc., Perkin Trans. 2 *1972*, 536.
[17] *A. Makriyannis, R.F. Sullivan & H.G. Mautner*, Proc. Natl. Acad. Sci. U.S.A. *69*, 3416 (1972).
[18] *M. Cesario, C. Pascard, M. El Moukhtari & L. Jung*, Eur. J. Med. Chem. *16*, 13 (1981).
[19] *M. Kondo*, Bull. Chem. Soc. Jpn. *45*, 2790 (1972).
[20] *R.E. Carter*, Acta Chem. Scand. *21*, 75 (1967).
[21] *T.H. Siddall III & W.E. Stewart*, J. Mol. Spectrosc. *24*, 290 (1967).
[22] *W.E. Stewart & T.H. Siddall III*, Chem. Rev. *70*, 517 (1970).
[23] *J. Gerhards, T.-K. Ha & X. Perlia*, Helv. Chim. Acta *65*, 105 (1982).
[24] *H. van de Waterbeemd, B. Testa, P. Jenner & C.D. Marsden*, in 'Quantitative Approaches to Drug Design', ed. J.C. Dearden, Elsevier, Amsterdam, 1983, p. 284.
[25] *P. Jenner, B. Testa, H. van de Waterbeemd & C.D. Marsden*, in 'Special Aspects of Psychopharmacology', eds. M. Ackenheil and N. Matussek, Expansion Scientifique Française, Paris, 1983, p. 153.