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^{13}C-NMR AND THEORETICAL STUDIES OF INTERNAL ROTATION IN METHYLATED ANILINES

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SUMMARY

The conformational properties of ten ring-methylated N-methyl- and N,N-dimethylanilines have been studied using ^{13}C-NMR chemical shifts and spin-lattice relaxation times in $CDCl_3$, and semi-empirical (AM1) quantum-chemical calculations. The experimental results indicate that, like aryl methyl ethers, N-methylanilines prefer conformations in which the N-methyl carbon lies near the ring plane. Ortho-substitution in these compounds, while forcing the N-methyl group to adopt an *anti* orientation with regard to the *ortho* substituent, does not induce any important changes from the vantage point of the electron donor ability of the amine function and therefore does not affect the N-methyl ^{13}C chemical shifts or spin-lattice relaxation times to any appreciable extent. The preferred conformations of *ortho*-unsubstituted N,N-dimethylanilines leave the N-methyl carbon atoms oscillating on either side of the ring plane, but the conformational space of these compounds is strongly limited by *ortho*-methylation, so that in these cases one of the N-methyl carbon nuclei is forced to remain close to the aromatic ring plane, resulting in much shortened relaxation times and deshielding of that nucleus. The quantum mechanical calculations reproduce these results, allowing the relative stability of the methylated aniline conformers to be discussed in terms of competition between the nuclear repulsion energy and electron delocalization. *Ortho*-methylation of N,N-dimethylanilines leads to an increase of electron density around the nitrogen atom and a change from almost sp^2 to almost sp^3 nitrogen hybridization, in agreement with the experimental results, including the increased basicity of these compounds.

Key words: ^{13}C-NMR spin-lattice relaxation AM1 conformation methylated anilines.

RESUMEN

Las propiedades conformacionales de diez N-metil- y N,N-dimetilanilinas metiladas en el anillo han sido estudiadas utilizando desplazamientos químicos y tiempos de relajación espín-red de ^{13}C-RMN en $CDCl_3$ y cálculos mecano-cuánticos semi-empíricos (AM1). Los resultados experimentales indican que, al igual que los aril metil éteres, las N-metilanilinas prefieren conformaciones en las cuales el carbono del N-metilo yace cerca del plano del anillo. La sustitución de estos compuestos en *orto*, aunque fuerza el grupo N-metilo a adoptar una orientación *anti* con respecto al sustituyente en *orto*, no induce cambios importantes desde el punto de vista de la capacidad dadora de electrones de la función amina y por lo tanto no afecta apreciablemente ni los desplazamientos químicos ni los tiempos de relajación espín-red de ^{13}C del N-metilo. Las conformaciones preferidas de las N,N-dimetilanilinas no sustituidas en *orto* dejan los carbonos del N-metilo oscilando a cada lado del plano del anillo, pero el espacio conformacional de estos compuestos está fuertemente limitado por la metilación en orto, de modo que en estos

casos uno de los núcleos de carbono de N-metilo se ve forzado a permanecer cerca del plano del anillo aromático, dando por resultado tiempos de relajación mucho más cortos y un desapantallamiento de dicho núcleo. Los cálculos mecano-cuánticos reproducen estos resultados, permitiendo discutir la estabilidad relativa de las conformaciones de las anilinas metiladas en términos de competencia entre la energía de repulsión nuclear y la deslocalización electrónica. La metilación en orto de las N,N-dimetilanilinas conduce a un aumento de la densidad electrónica en torno al átomo de nitrógeno y a un cambio desde una hibridación casi sp2 de éste a una casi sp3, lo que está de acuerdo con los datos experimentales, incluyendo la mayor basicidad de estos compuestos.
Palabras claves: RMN-^{13}C relajacion espin-red AM1 conformacion anilinas metiladas.

INTRODUCTION

The number of commercial drugs incorporating simple aromatic amine functionalities in their structures amounts to only about six percent of the total, and structure-activity analyses of compounds bearing amino, methylamino or dimethylamino groups directly bonded to a benzene ring are scarce. Nevertheless, approximate bioisosteric relationships may be expected between amino and methylamino groups on one hand and the very common hydroxy and methoxy functions on the other. Methylamino and hydroxy, and dimethylamino (or ethylamino) and methoxy groups may be regarded as coarsely matched pairs with regard to their volume, lipophilicity and hydrogen bond donor/acceptor character and, in principle, isosteric replacement of aryl oxygen substituents by nitrogen functions should allow increased flexibility in drug design[1]. More detailed knowledge is necessary, however, if both electronic and steric properties are to be considered in the interpretation of drug-receptor interactions. During the last fifteen years, many 4-aminophenethylamine derivatives have been prepared and tested as selective monoamine oxidase (MAO) inhibitors leading up to amiflamine, (S)-(+)-4-dimethylamino-2.α-dimethylphenethlamine, which appeared promising as a clinically useful antidepressant[2,3]. In this series of compounds, *ortho*-substitution with regard to a 4-dimethylamino group seems to be associated with an unexplained loss of biological activity. We therefore considered it interesting to carry out an experimental study of the conformational preferences of a number of model N- and ring-methylated anilines and to examine their consequences at the electronic level.

Methoxyl carbon atoms bonded to aromatic systems are known to lie near the median plane of the ring unless they are flanked by two bulky substituents, in which case they are pushed away from this plane forming a dihedral angle of at least 70°[4-8]. In the latter conformations, the methyl ^{1}H and ^{13}C chemical shifts are smaller than in analogs with only one or with no *ortho* groups, the corresponding spin-lattice relaxation times are longer, and electron donation to the ring π system is reduced. Chemical intuition suggests that the behavior of (mono)-methylamino groups should be rather similar, with the expected lack of sensitivity to mono-*ortho*-substitution and analogous consequences of di-*ortho*-substitution on their NMR chemical shifts and relaxation times and on their electron donating ability. Microwave and dynamic ^{13}C-NMR spectra of ring-unsubstituted N-methylaniline have been analyzed in terms of torsional barriers of the methylamino group around the aryl-N bond[11-14], estimated by the latter method to be about 7.4 kcal/mol. We are unaware of any systematic study of the effect of *ortho*-substitution upon this behavior, aside from a paper reporting the exclusive existence of 2, N-dimethylaniline (**3**) as the more stable (coplanar) *trans* conformer[15].

Pioneering research on *ortho*-substituted N,N-dimethylanilines showed long ago that in these compounds conjugation between the nitrogen lone pair and the aromatic ring is decreased, as evidenced by a variety of physical, spectroscopic and chemical properties including the ^{13}C-NMR chemical shifts of the ring atoms[9]. In these compounds, a single *ortho*-methyl substituent shifts the N-methyl ^{13}C resonance downfield by about 4 ppm, with simultaneous deshielding of the *para* carbon nucleus. Two methyl groups flanking the dimethylamino function lead to somewhat smaller downfield shifts of the N-methyl carbon resonances, an apparent anomaly which has been related to the decreased basicity of *ortho-ortho*-dimethylated N,N-dimethylanilines vs. their *ortho*-monomethylated counterparts[4]. These results may be interpreted qualitatively if it is assumed that the functional group is forced to adopt such a position with regard to the ring plane that the overlap of the

nitrogen lone pair and the ring carbon p orbitals is sacrificed. A pyramidal aryldimethylamino group, forced away from the median plane of the aromatic ring by an *ortho* substituent, was observed some years ago in a crystallographic study[10]. Nevertheless, detailed theoretical interpretations of the NMR data in terms of conformational preferences in solution are still lacking.

The unsubstituted arylamino group is usually pyramidal, as shown by spectroscopic, crystallographic and quantum-chemical studies[11,16,17], but it is flattened when the lone pair on the amine nitrogen is conjugated with an electron deficient centre[18,19]. Although a number of structures obtained by X-ray diffraction would seem to suggest that when the amino group is mono- or dimethylated and not protonated or hydrogen bonded it becomes practically co-planar with the aromatic ring[20-22], closer examination of the published data shows that a common feature of these structures is the presence of an electron-attracting substituent *para* to the nitrogen function which could well be responsible for the observed conformations as well as the increased C-N rotational barrier in *para*-substituted methylanilines[15]. It would therefore seem reasonable to assume that, in the absence of groups which might favor a planar conformation by conjugative mechanisms, the arylmethylamino and aryldimethylamino moieties are generally more or less pyramidal and thus donate little electron density to the aromatic ring, as is seen for aniline[18,19].

Considering the paucity of relevant studies, and in order to obtain some experimental indication of whether the undisturbed methyl carbon atom in N-methylanilines, as in aryl methyl ethers, tends to lie close to the benzene ring plane, to ascertain the preferred conformations of N,N-dimethylanilines, and to evaluate the effect of electron-donating ring substituents on the conformations of the amino groups in these compounds, we have carried out a preliminary study of the ^{13}C-NMR spectra of several ring-methylated N-methyl- and N,N-dimethylanilines, henceforth designated as MA's, and interpreted the results using Self Consistent Field (SCF) Molecular Orbital (MO) calculations at the semi-empirical AM1 level[23]. The 3,4- and 2,4-dimethylated derivatives were included in both the N-methyl and the N,N-dimethyl series in order to mimic the electronic effect of the aliphatic side chain, *para*- with regard to the arylamino group, in bioactive compounds such as the monoamine oxidase inhibitors 4-dimethylamino-α-methylphenethylamine and amiflamine.

EXPERIMENTAL

Ten commercially unavailable compounds: 4,N-dimethylaniline (**1**), 3,N-dimethylaniline (**2**), 2,N-dimethylaniline (**3**), 3,4,N-trimethylaniline (**4**), 2,4,N-trimethylaniline (**5**), 4,N,N-trimethylaniline (**6**), 3,N,N-trimethylaniline (**7**), 2,N,N-trimethylaniline (**8**), 3,4,N,N-tetramethylaniline (**9**), and 2,4,N,N-tetramethylaniline (**10**), were selected for the NMR studies and synthesized by straightforward transformations of toluidines and xylidines. All products and intermediates were characterized by ^{1}H-NMR.

^{13}C-NMR (Tables I, II) were carried out at 50 MHz using a Bruker WS-200 spectrometer with a 180°, τ, 90° pulse sequence for the determination of T_1 values. The samples, dissolved in $CDCl_3$, were deoxygenated by bubbling He in the sample tube.

The AM1 calculations were carried out on an Apollo 10000 computer, using the AM1 version in the MOPAC 6.0 program package[24]. The AM1 geometry optimization process was carried out by the gradient method of Broyden, Fletcher, Goldfarb and Shanno[25-28], implemented in MOPAC 6.0.

RESULTS AND DISCUSSION

^{13}C-NMR studies

The observed chemical shifts (δ) and spin-lattice relaxation times (T_1 values) of the MA's examined by us in $CDCl_3$ solution are presented in Tables I and II, respectively. The results of the ^{13}C-NMR studies of the five mono-N-methylanilines: 4,N-, 3,N-, and 2,N-dimethylaniline (**1-3**) and 3,4,N- and 2,4,N-trimethylaniline (**4,5**), show that *ortho*-substitution does not greatly affect the

^{13}C chemical shifts and T1 values of the N-methyl carbon nuclei in these compounds. Table I shows that the chemical shifts are all very similar (d 30.7-31.3 ppm), regardless of the presence or absence of an ortho methyl substituent. Table II shows that the T_1 values of these substances cover a rather narrow range (3.5-4.8 s), with no obvious trend related to ortho-substitution.

TABLE I. 13C-NMR chemical shifts (d) of methylanilines (50 MHz, CDCl3)a.

Comp.	N-CH3	o-CH3	m-CH3	p-CH3	C-1	C-2	C-3	C-4	C-5	C-6
1	31.32	—	—	20.83	n.d.	113.0	130.1	n.d.	130.1	113.0
2	30.71	—	21.64	—	149.5	113.2	137.0	118.2	129.1	109.6
3	30.74	17.37	—	—	147.3	121.9	129.9	116.6	127.2	109.1
4	31.11	—	20.00	18.00	n.d.	114.4	n.d.	n.d.	130.2	109.9
5	31.05	17.31	—	20.37	n.d.	n.d.	127.4	n.d.	130.9	109.4
DMAb	**(39.9)**	**—**	**—**	**—**	**(150.3)**	**(111.9)**	**(129.3)**	**(115.5)**	**(129.3)**	**(111.9)**
6	40.99	—	—	20.26	n.d.	113.2	129.6	n.d.	129.6	113.2
	(40.1)	—	—	(21.5)	(148.4)	(112.6)	(129.9)	(124.6)	(129.9)	(112.6)
7	40.66	—	21.92	—	n.d.	113.5	n.d.	117.7	128.9	110.0
	(39.5)	—	(n.d.)	—	(150.8)	(111.8)	(137.8)	(117.2)	(128.7)	(110.1)
8	44.16	18.31	—	—	152.6	132.6	131.1	118.3	126.4	118.3
	(43.9)	(18.2)	—	—	(152.6)	(131.1)	(130.8)	(122.8)	(125.9)	(118.6)
9	41.08	—	20.33	18.81	149.4	114.9	137.0	125.0	130.2	110.8
10	44.51	18.17	—	20.06	n.d.	n.d.	131.9	n.d.	126.9	118.3
	(44.2)	(17.9)	—	(20.8)	(149.9)	(131.6)	(131.3)	(131.6)	(126.9)	(118.6)

[a]Values in parentheses recalculated from ref 4, measured in and referenced to CS_2.
[b]N,N-dimethylaniline.

TABLE II. ^{13}C-NMR spin-lattice relaxation times (T_1, s) of protonated carbons of methylanilines (50 MHz, $CDCl_3$).

Comp.	N-CH_3	*o*-CH_3	*m*-CH_3	*p*-CH_3	C-2	C-3	C-4	C-5	C-6
1	4.4	—	—	7.2	4.4	4.3	—	4.3	4.4
2	4.9	—	8.4	—	5.8	—	4.9	5.4	4.9
3	4.2	4.3	—	—	—	5.5	5.3	5.8	5.5
4	4.3	—	7.7	7.0	4.8	—	—	4.6	4.2
5	3.5	4.7	—	7.6	—	4.6	—	4.6	4.6
6	8.3	—	—	8.2	6.0	5.9	—	5.9	6.0
7	8.6	—	9.0	—	6.1	—	4.8	5.7	5.2
8	4.1	9.5	—	—	—	6.6	5.7	6.5	6.4
9	8.0	—	8.2	7.3	5.4	—	—	5.2	4.7
10	3.2	8.4	—	7.6	—	5.0	—	4.7	4.8

It is generally acknowledged that the rotation of methyl groups around the CH_3-X axis is usually faster than overall molecular motion, leading to such shorter correlation times (τ_C) for methyl carbon atoms than for the rest of the molecule. The T_1 values for CH_3 groups are consequently larger than for CH_2 and CH groups and quaternary carbon atoms, and the spin-lattice relaxation times of methyl carbon nuclei are largely determined by their rates of rotation. Thus, more rapidly rotating methyl groups exhibit larger T_1 values. Our results, then, suggest that in all these mono-N-methylated compounds the N-methyl groups are able to rotate around the CH_3-N bonds at similar rates, i.e., that *ortho*-substitution does not modify the rotational freedom of the N-methyl groups to any significant extent, although the T_1 values in the 3,5-4.8 second range suggest that an *ortho* hydrogen atom interferes appreciably with this mode of rotation. It is worth pointing out that the microwave spectrum of N-methylaniline indicates that the torsional barrier of the methylamino group around the aryl-N bond is similar to that found for the methoxy group around the aryl-O bond, and that rotation around the N-CH_3 axis is likewise hindered[11,12]. Dynamic ^{13}C-NMR experiments on N-methylaniline show torsional barriers of 7.2 kcal/mole in the hydrogen bond-accepting dimethyl ether[13], and 6.6 kcal/mole in the low-polarity, weakly hydrogen bond-

donating $CHFCl_2$ and CHF_2Cl [14]. It is interesting to note that Lunazzi *et al.*[15] were unable to detect rotational isomers for 2,N-dimethylaniline (3) in dimethyl ether even at -150°C which, in this context, indicates that the anti conformer is strongly preferred. A similar conclusion was reached in the case of the structurally analogous N-methyl-1-naphthylamine[15]).

In our series, the meta and para methyl carbon nuclei exhibit relaxation times in the 7-8 second range, indicating that they are able to rotate quite freely, even in the 3,4-methylated derivative **4**, where a cogwheel-type interaction might be expected. The ortho methyl carbon nuclei in compounds **3** and **5**, however, they have much lower T_1 values, suggesting that an ortho methylamino group is a considerable hindrance to rotation around the CH_3-C bond.

In the cases of 4,N,N- and 3,N,N-trimethylanilines and 3,4,N,N-tetramethylanilines (**6,7,9**), i.e., N,N-dimethylanilines without any *ortho* substituents, the chemical shifts of the N-methyl carbon nuclei are in the 40.7-41.2 ppm range (see Table I), 9-10 ppm downfield from the corresponding mono-N-methyl carbon resonances, in agreement with previous results[9]). Although these values suggest lower average electron densities and/or stronger deshielding by the ring current at the N-methyl carbons of N,N-dimethylanilines in comparison with the N-methylanilines, the relative magnitudes and even signs of these complementary or competing effects cannot be determined directly.

In Lauterbur's early work on the ^{13}C-NMR spectra of MA's [9], it was shown that N,N-dimethylation of an amino group on the benzene ring leaves the *meta* carbon resonances practically unchanged, while the *ortho* and *para* carbon signals are shifted slightly upfield (by 1-3 ppm) or more strongly downfield (by 4-9 ppm) depending on the absence or presence, respectively, of an *ortho* methyl group. The downfield shift in *ortho*-methylated compounds, implying reduced electron density in the benzene ring of these derivatives, was interpreted in terms of steric inhibition of conjugation[9]). Our results allow a similar analysis of the mono-N-methylation of a methylamino group. Upon going from the *meta*-substituted N-methylaniline **2** to its N,N-dimethylated counterpart **7**, the *para* carbon nucleus resonance is shifted upfield by less than 1 ppm, while in the *ortho*-substituted pair **3** and **8** a slight downfield shift of 1.7 ppm is observed, suggesting that conjugation effects are not very important in these cases. On the other hand, *ortho* carbon nuclear δ values are much more sensitive to the introduction of the second N-methyl group in *ortho*-methylated MA's. While the variation of the *ortho* carbon chemical shift is less than 1 ppm in the *ortho*-unsubstituted compounds, in the *ortho*-methylated pairs **3/8** and **5/10** the corresponding unsubstituted *ortho*-carbon resonances are shifted downfield by 9-10 ppm, pointing to a considerable loss of electron density at these positions. This, however, could be at least in part a direct response to the change in the preferred orientation of the amino group rather than an effect of conformational change on electron donation to the aromatic ring.

The T_1 values of the N-methyl carbon nuclei of the *ortho*-unsubstituted N,N-dimethylanilines lie between 8.0 and 8.6 s (see Table II), indicating much greater rotational freedom than in their N-monosubstituted congeners. This suggests that, on the average, the N-methyl groups of these N,N-dimethylanilines lie further from the ring plane than those of N-methylanilines, where rotation of the N-methyl group is somewhat hindered by an *ortho* hydrogen atom.

The ^{13}C resonances of the N-methyl groups in 2,N,N-trimethyl- and 2,4,N,N-tetramethylanilines (**8,10**) - N,N-dimethylanilines with a methyl substituent *ortho* to the amine group - are shifted further downfield by about 4 ppm (δ 44.5 and 44.1 ppm), in accordance with previous observations[9]), while the corresponding T_1 values are only 3.4-4.1 s (see Table II). These results may be taken as evidence that the N-methyl groups of *ortho*-substituted N,N-dimethylanilines lie, on the average, closer to the ring plane than in their *ortho*-unsubstituted counterparts, in the region deshielded by the ring current, and that the rotation of any N-methyl group which may come very close to this plane is hindered by the *ortho* hydrogen atom on the aromatic ring. The relatively large T_1 values of the *ortho* methyl groups in compounds **8** and **10** (9.5 and 7.6 s, respectively) lend further support to this interpretation, as they suggest that these substituents may rotate very freely when the two N-methyl groups are directed away from them.

In summary, the ^{13}C-NMR data for N-methylanilines indicate that the N-methyl group tends to lie sufficiently close to the ring plane for its rotation around the N-CH_3 axis to be significantly slowed. Furthermore, they strongly suggest that methylation of an ortho-ring carbon has little if any effect upon the time-averaged twist angle around the ring carbon-amine nitrogen bond, judging by the unchanged N-methyl chemical shifts and relaxation times. In this respect, then, N-methyl and O-methyl groups exhibit similar behavior towards ortho-substitution.

N,N-Dimethylanilines behave quite differently with regard to their N-mono-methylated counterparts. The long N-methyl ^{13}C relaxation times in the absence of an ortho-substituent suggest that ortho-unsubstituted N,N-dimethylanilines prefer conformations in which both N-methyl carbon atoms remain far from the benzene ring plane. Or*tho*-methylation of these compounds, however, introduces a strong conformational restriction resulting in one of the N-methyl carbons being forced to remain close to the ring plane, as indicated by the time-averaged deshielding of the N-methyl carbon nuclei and their considerably lower T_1 values.

Theoretical calculations

The purpose of the quantum chemical calculations on all the MA's, i.e., N-methylanilines and N,N-dimethylanilines, was to look for a molecular explanation of the relative stabilities of the MA conformers already suggested by the ^{13}C-NMR experimental results. Since these experiments were carried out in dilute solutions in a low-polarity solvent ($CDCl_3$), the conformational energy as well as the electronic structure of each rotamer can be modelled reasonably well using calculations for isolated MA molecules. In addition, intramolecular hydrogen bonding interactions are not expected in these systems, so therefore the most stable rotamer should exhibit the lowest nuclear repulsion energy and/ or the lowest electronic repulsion energy.

The conformational and electronic structures of the MA's were studied using the AM1 methodology[23]. The various terms in the Fock matrix are obtained from parametric functions built up with atomic parameters only, i.e., no bond parameters are included. This parametrization procedure is developed to reproduce four gas-phase properties of molecules containing these atoms, namely: heat of formation, dipole moment, ionization potential and molecular geometry. The AM1 results obtained for geometry optimized molecules have been shown to be in good agreement with the experimental data for chemical properties associated with the molecular parameters listed above[29]. They have also been successfully compared with those obtained from *ab initio* calculations involving large basis sets[30]. Regarding this work, it is important to remember that the AM1 parameters for the C-H-N-O set have been obtained from a much larger number of compounds than for any other element, thus making them even more reliable.

Accurate results are expected for the conformational and electronic structures of the MA's using the AM1 model because: (i) these compounds consist only of carbon, nitrogen and hydrogen atoms and should thus reflect the parametrization better than molecules containing other elements; (ii) the molecular geometries obtained from AM1 calculations are known to be in good agreement with the experimental data for a large number of compounds[29], and the accuracy of the results should increase in the case of the MA's because of their atomic composition; (iii) we will be mainly concerned with the relationship between the energy distribution and the electronic structure of the MA conformers, for which AM1 calculations should give accurate results if complete geometry optimization is carried out.

Although Anet *et al.*[14] have reported that the barrier to aryl-nitrogen internal rotation in N-methylaniline is dependent upon the solvent's hydrogen bond acceptor or donor properties, our ^{13}C-NMR studies were all performed in the same solvent, i.e., the weakly hydrogen-bond donating $CDCl_3$. Since our AM1 results for energies are given as relative parameters, differences between solutes should not reflect solvent effects which we expect to be minimal in the experimental work. AM1 model calculations have led to erroneous predictions of the conformational structures of some saturated amines due to overestimation of the conformational energy of the nitrogen lone pair[31]. Nevertheless, in our case the AM1 conformational energies of arylamines compare well with experimental data obtained in solution which are directly related to the conformational free energies. As our AM1 results correlate well with the experimental values, the reliability of this methodology in the description of the methylated anilines analyzed in this paper is substantiated.

From a pharmacological point of view, the most relevant feature of this methodology is that Hartree-Fock SCF calculations can be performed on molecules in the size range of most drugs. Thus, if AM1 gives a reliable molecular description of rather small molecules like the MA's, it may also be applied to slightly larger systems containing the same functional groups, as is the case of amilflamine and related MAO inhibitors.

In order to estimate the nuclear repulsion energy, a suitable methodology had to be used, since the partition of the total energy in the semiempirical AM1 method does not account for this magnitude, *ab initio* STO-3G calculations were chosen to evaluate the nuclear repulsion energy in each MA rotamer[32]. Finally, the energetics of the conformational results were rationalized in terms of the relative contributions of both the nuclear repulsion energy and the electron repulsion energy, in order to obtain further information about the mechanisms which govern magnetic shielding in aromatic amines such as compounds **1-10**, in dilute solutions and in low polarity aprotic solvents such as $CDCl_3$, in which the ^{13}C-NMR experiments were performed.

Figure 1 shows the geometry scheme of the compounds under study. The N-C1 bond lies along the positive Cartesian X axis, with the N atom located at the origin of coordinates; while the aromatic ring lies on the XY plane, almost bisected by the X axis. The conformational analysis was carried out by rotation of the alkylamine moiety around the N-C1 bond. For this purpose, we defined the dihedral angle α as the angle formed by the N-C1-C2 plane and the C1-N-C7 plane.- Table III shows some relevant geometric parameters of the total optimized geometry of compounds **1-10**.

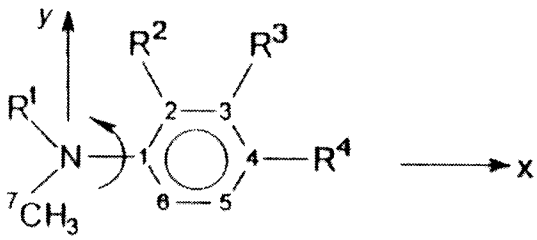

FIG. 1. Geometry scheme for compounds **1** to **10**, referred to the Cartesian coordinate system. The curved arrow represents the torsion angle α.

Internal relative rotational energies of N-methyl and N,N-dimethyl groups around the N-C1 bond were calculated using the AM1 method. This procedure was carried out with α increments of 10°; near the energy maxima and minima, these increments were narrowed until a good characterization of these extreme energy structures was attained. Since complete geometry optimization was performed for each α value, each curve obtained from the internal rotation energy as a function of the α value represents a minimum energy path across the potential energy hypersurface for each of the compounds under study. The results obtained are shown in Figures 2 to 5.

It can be seen in the Figures that the relative energies for the N-methylaniline rotamers (**1,2,4**) with no *ortho* substituents indicate that all possible conformations should be present, even at low temperatures (see Figures 2 and 3). *Ortho*-substituted compounds (**3,5**) evidence nuclear repulsion between neighboring substituents, producing internal rotational barriers of 6.5 and 8.6 kcal/mol, respectively, at an α value of 0°, with still very significant hindrance around $\alpha = 30°$. Regardless of the presence of an *ortho* substituent, the N-methyl groups of all the N-methylanilines are free to rotate through a wide angle, although residence in the ring plane is not favored. These results are consistent with the observed chemical shifts and T_1 values (see Tables I, II).

The most stable conformations for the *ortho-unsubstituted* N,N-dimethylanilines **6**, **7**, and **9** also have their N-methyl carbon nuclei out of the ring plane. For these compounds, however, although the amino group still appears to rotate fairly freely, the rotational barriers are slightly higher than for N-methylanilines. In the *ortho*-substituted N,N-dimethylanilines (**6,10**), conformations in which one of

the N-methyl carbons forms a dihedral angle of 30° or less with the X-Y plane are forbidden. In these compounds, therefore, the allowed conformations show the second N-methyl carbon nucleus lying less than 30° away from the ring plane.

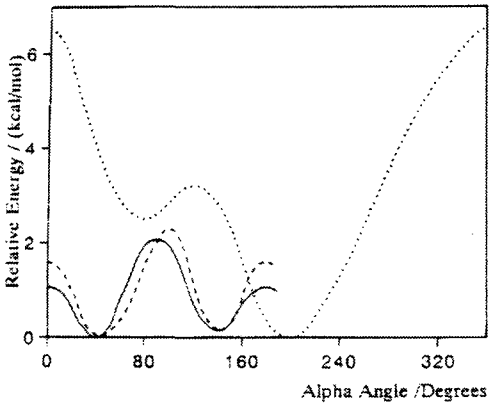

FIG. 2. AM1 internal rotational energy as a function of the α angle of compounds **1** (dashed line), **2** (solid line) and **3** (dotted line).

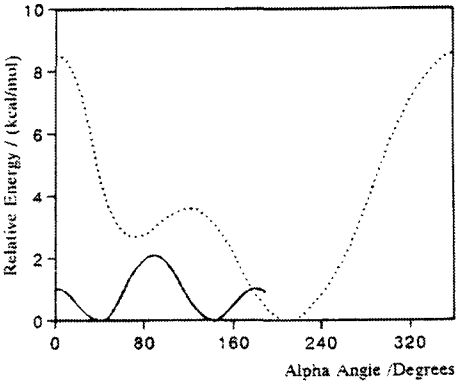

FIG. 3. AM1 internal rotation energy as a function of the a angle of compounds **4** (solid line) and **5** (dashed lines).

Taking the experimental spin-lattice relaxation time values as a measure of the microdynamics of these systems, the theoretical calculations described above are in agreement with these results, since the T_1 values for compounds **1-5** correspond to practically free rotation even in the presence of an *ortho* substituent. For compounds **6**, **7**, and **9**, the N-methyl carbons lying out of the ring plane show only moderately hindered rotation. Nevertheless, in compounds **8** and **10**, the N-methyl carbon nuclei exhibit smaller T_1 values, reflecting considerable hindrance to rotation as a consequence of their near-coplanarity with the ring and the resulting proximity of the N-methyl hydrogen atoms to the *ortho* ring hydrogen (see Table II). The same severe limitation of conformational space in N,N-dimethylanilines as compared to the N-methylated compounds may be taken as an explanation of why one of the N-methyl carbons, due to its position necessarily close to the aromatic ring plane, experiences less shielding.

A larger fraction of the molecules is expected to be in their lowest energy state, thus minimizing both nuclear and electron repulsion energy. While the former minimum is attained by pushing the arylmethylamino or aryldimethylamino group away from the aromatic ring plane, the latter can be reached by electron delocalization, which implies an orientation of the nitrogen lone pair as parallel as possible to the aromatic π system and/or distribution of electron density throughout the σ skeleton. As a consequence of these interactions, the ^{13}C chemical shift can be interpreted as indicating that in *ortho*-unsubstituted anilines, the N-methyl carbon tends to remain further from the ring plane than in their *ortho*-substituted counterparts. Since these experimental results reflect an average of various rotamers, however, in those cases in which their relative energies are close enough to allow them to exist in about the same abundance, quantum chemical studies may be more informative. In fact, the AM1 results shown in Figures 4 to 7 indicate that the *ortho*-unsubstituted compounds present free rotation of the methylamino or dimethylamino group around the C1-N bond, while for the *ortho*-substituted compounds the rotation is restricted when the nitrogen atom is bonded to two methyl groups.

The nuclear geometry adopted by the amino group of each MA represents a powerful tool to account for the change in orbital hybridization of the nitrogen atom, predicted from the analysis of the experimental ^{13}C-NMR results, by using a MO approach like the present AM1 method which gives reliable molecular geometries. Four geometrical parameters were chosen to accomplish this

analysis: i) the dihedral angle ϕ, which is defined as the angle C1-N-C7-R, i.e. the angle between the C1-N-C7 plane and the C1-N-R1 plane (where, according to Figure , R1 is H or C for N-methylanilines and N,N-dimethylanilines, respectively); ii) the N-C1 distance, iii) the Euclidean (plane) angle C7-N-R1; iv) the a angle, already defined as the dihedral angle C2-C1-N-C7, i.e. the angle between the N-C1-C2 plane and the C1-N-C7 plane. In this context a ϕ value of 180° represents sp^2 hybridization of the nitrogen orbitals, while 120° is indicative of sp^3 hybridization. Regarding the N-C1 distance, larger values indicate greater single bond character, also implying a tendency towards sp^3 hybridization of the nitrogen. In addition, C7-N-R1 angle values of 109.5 and 120°, respectively, correspond to sp^3 and sp^2 hybridization.

It is noteworthy that the dihedral angles ϕ between the planes including each of the N-methyl carbons and the C1-N bond, presented in Table III, indicate considerable deviation from sp^3 hybridization for the amine nitrogen orbitals. An interesting feature of these data is that the N,N-disubstituted anilines exhibit wider dihedral angles ϕ suggesting practically sp^2 hybridization (around 174-176°) when not *ortho*-substituted (**6**, **7**, and **9**), while in the *ortho*-substituted congeners **8** and **10** these angles are contracted to about 133°. The latter value is practically identical to those found for all five mono-N-methylated compounds (**1-5**), in which electron delocalization should play a more important role than nuclear repulsion in their conformational stabilization. The narrower ϕ angles in the *ortho*-substituted N,N-dimethylanilines imply that, as neither N-methyl group can lie close to the *ortho*-substituent, the orientation of the nitrogen lone electron pair must approach the plane of the π system, pointing towards the *ortho*-methyl group, in agreement with an X-ray study cited earlier[10]. Increase of the C1-N bond length in compounds **8** and **10**, compared with the value for compound **9**, suggests sp^3 hybridization of the N atom in *ortho*-substituted N,N-dimethylanilines in contrast to the exhibited by congeners lacking an *ortho*-substituent. Moreover, the dihedral angle α between the aromatic ring plane and the plane defined by the C1-N bond and one of the N-methyl carbons indicates conformations in which the latter substituent lies at least 30 to 60° away from the ring plane (see Figures 4 and 5). Both parameters suggest that, in *ortho*-substituted N,N-dimethylanilines, the hybridization of the nitrogen orbitals is closer to sp^3 than sp^2, since this relaxation of geometry is necessary to minimize both nuclear and electronic repulsion.

TABLE III. Relevant geometrical parameters[a] provided by the AM1 optimized geometry of compounds **1** to **10**.

Compound	ϕ[b]	D_{C1-N}[c]	$A_{C7-N-R1}$[d]	α[e]
1	136.15	1.406	113.11	36.6
2	137.89	1.403	114.07	38.8
3	136.52	1.409	113.20	195.0
4	133.98	1.408	112.80	40.0
5	132.27	1.411	112.03	218.0
6	175.69	1.397	116.50	36.5
7	174.05	1.413	116.46	35.2
8	134.18	1.428	113.43	76.0
9	174.94	1.410	116.06	38.0
10	132.25	1.436	113.30	90.1

[a]Bond angles and dihedral angles in degrees, bond distances in Å, atoms named according to Fig. 2.
[b]Dihedral angle between the C1-N-C7 plane and the C1-N-R_1 plane (C1-N-C7-R1).
[c]Distance between N and C1.
[d]Angle formed by C7, N and R_1, with R_1 = H (for N-methylanilines) or the C atom of a second methyl group (for N,N-dimethylanilines).
[e]Dihedral angle between the XY plane and the C1-N-C7 plane (C2-C1-N-C7).

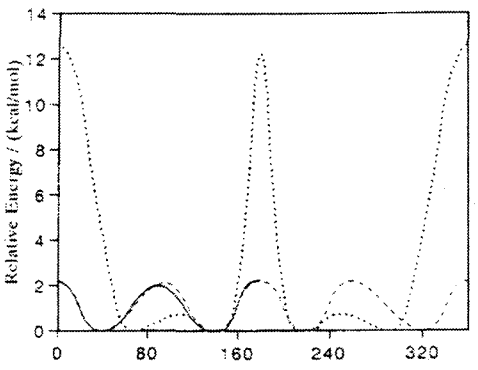

FIG. 4. AM1 internal rotation energy as a function of the α angle of compounds **6** (solid line), **7** (dashed line and **8** (dotted line).

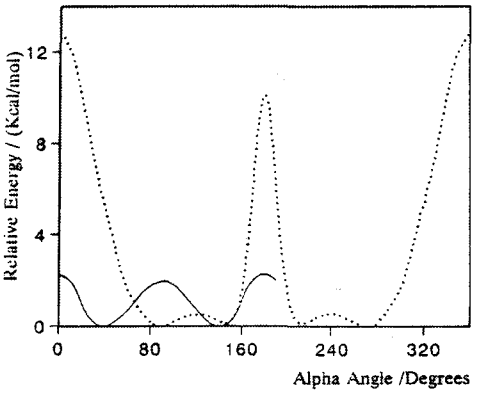

FIG. 5. AM1 internal rotation energy as a function of the a angle of compounds **9** (solid line) and **10** (dotted line).

The relative weight of the nuclear repulsion energy in the most stable conformation of each MA was also analyzed. As indicated above, this process was performed in the ab initio STO-3G framework. The STO-3G calculations were carried out with fully optimized geometry for each molecule using the Monstergauss program (version 21 May 1990)[33], performing the optimization process with a modified version of Davidson's gradient method[34]. The most stable rotamer of each MA proved to be the same as that obtained from AM1 calculations; in addition, both methodologies showed similar trends in the conformational energy distribution of these compounds.

The relative importance of the nuclear repulsion energy in the determination of the most stable rotamer was analyzed in order to further explain the NMR data and the steric hindrance to rotation around the N-C1 bond of compounds **8** and **10**. The AM1 core-core repulsion energy and the total electronic energy were also included in the analysis.

Table IV shows molecular parameters related to the nuclear repulsion energy for the N,N-dimethylanilines 8 and **10**, as a function of the α angle, which is shown in the first column of the table; the AM1 core-core repulsion energy, the STO-3G repulsion energy, the AM1 and the STO-3G total energies are shown in the second, third, fourth, and fifth column, respectively. Again, all the reported energy values are relative to the minimum energy of each compound. From the table, it can be observed that the nuclear repulsion energy does not follow the same trend as the core-core repulsion energy; for $\alpha = 0°$, the core-core repulsion energy is minimal, while the total energy indicates that this is the most unstable conformer. This difference may be produced by the fact that the core-core repulsion energy provided by the AM1 methodology completely ignores the presence of the valence electrons, and/or by the parametrization procedure. Regarding the *ab initio* calculations, the results indicate that the most stable conformation adopted by both of these compounds does not correspond to the lowest nuclear repulsion energy. These results suggest that electron delocalization should play a rather relevant role in the internal rotation of MA.

TABLE IV. AM1 and STO-3G nuclear repulsion parameters and relative energies of ortho-methylated N,N-dimethylanilines 8 and 10, as a function of dihedral angle α[a].

Compound	8				10			
α	CCb	NREc	TEd	TEe	CCb	NREc	TEd	TEe
0	0.00	186.20	12.72	14.36	0.00	196.7	12.85	15.12
30	278.57	215.06	6.96	9.22	305.5	220.9	7.03	10.08
60	555.83	553.54	0.36	2.89	562.1	547.0	0.44	3.04
90	313.17	158.16	0.54	0.00	368.7	167.3	0.36	0.00
120	258.54	0.00	0.60	0.16	301.6	0.00	0.53	0.44
150	571.44	545.34	0.81	0.09	610.6	523.0	0.82	0.99
180	514.01	641.47	8.00	5.26	576.2	623.5	10.08	12.32
210	573.76	580.14	1.08	14.52	621.6	725.9	8.82	15.22

[a] α in degrees and relative energies in kcal/mole.

b Relative AM1 core-core repulsion energy.

c Relative STO-3G nuclear repulsion energy.

d Relative AM1 total electronic energy.

e Relative STO-3G total electronic energy.

Electron delocalization was studied by analyzing some parameters based on Mulliken Population Analysis provided by the STO-3G calculations on all the MA. Table V shows the corresponding results. The second column reports the charge separation. It can be seen that this parameter shows rather irregular behavior. Nevertheless, for the *ortho*-substituted, *para*-unmethylated compounds (**3** and **8**), it decreases, indicating electron delocalization. The third column shows the total net charge of the amino fragment, i.e. the NCH_3R_1 group, where R_1 stands for H in the case of N-methyl-substituted MA, and for CH_3 in the case of the N,N-dimethyl-substituted MA. The most striking feature of these results is that only the *ortho*-N,N-trisubstituted anilines carry negative charge on the amino fragment. Column 4 shows the calculated charge on the aromatic ring assuming the absence of C-methyl groups to highlight the effect of the amine function. The results show that the aryl groups remain almost devoid of net charge, though slightly positive. This induced us to calculate the position of the negative center of charge, R-, in each molecule, and column 4 shows the x component R_x, of the position vector of this center. It clearly shows that R- lies closer to the nitrogen atom in the *ortho*-substituted anilines (compounds **3**, **5**, **8**, and **10**) than in the *ortho*-unsubstituted compounds (**1**, **2**, **4**, **6**, **7**, and **9**). This result could explain the increased basicity of the *ortho*-substituted anilines as due to the concentration of negative charge near the nitrogen atom. In the *ortho*, *para*-disubstituted compounds **5** and **10**, however, the negative charge center lies further away from the nitrogen

TABLE V. Charge distribution parameters of methylanilines based on Mulliken Population Analysis provided by STO-3G calculations.

Compound	CS[a]	C_{amino}[b]	C_{ring}[c]	$R_{x(cc)}$[d]	$D(R_+\text{-}R_-)$	eM.D.M.[f]
1	1.02	0.0203	0.038	2.00	0.17	0.83
2	1.03	0.0261	0.031	1.94	0.22	1.09
3	1.00	0.0274	0.040	1.50	0.23	1.11
4	1.26	0.0237	0.030	2.20	0.20	1.21
5	1.24	0.0220	0.044	1.73	0.14	0.83
6	1.02	0.0210	0.042	2.00	0.14	0.69
7	1.02	0.0112	0.047	2.00	0.12	0.59
8	0.92	-0.0125	0.063	1.40	0.08	0.35
9	1.13	0.0339	0.040	2.30	0.10	0.54
10	1.03	-0.0269	0.079	1.80	0.07	0.34

[a] Charge separation (Å).

[b] Charge on the amino (CH_3-N-R_1) fragment (a.u.).

[c] Charge on the phenyl fragment (a.u.).

[d] X component of the center of negative charge, R_- (Å).

[e] Distance between the centers of positive charge, R_+, and of negative charge, R_- (Å).

[f] Mulliken dipole moment = CS x $D(R_+\text{-}R_-)$ (D).

atom than in the para-unsubstituted substances (**3** and **8**). Column 5 shows the distance in Ångström between the center of positive charge, R+, and that of negative charge, R-; this result suggests that ortho-methylanilines show greater stabilization as a consequence of the decrease of this parameter. This effect is more marked in the N,N-dimethylated compounds. Finally, column 6 shows the corresponding Mulliken dipole moment. Again, greater stabilization is attained by the ortho-substituted MAs, and specially for the ortho-substituted N,N-dimethylanilines. The decrease in charge separation and dipole moment implies increasing electron delocalization.

Analysis of the Highest Occupied Molecular Orbital (HOMO) coefficients of all the compounds, as expected, showed that the π electron densities include contributions from the p_z orbitals of the aromatic carbon nuclei and from the nitrogen lone pair, regardless of the conformation: even in those conformations in which the lone pair lies in the ring plane, conjugation between the amino group and the aromatic ring is not completely lost. The p_z orbitals of the aromatic carbon nuclei tend to overlap with the lone pair orbital of the nitrogen atom, leading to delocalization of the non-bonding nitrogen electrons. This electron delocalization, however, is not limited to the π system; inspection of the HOMO coefficients calculated using either AM1 or STO-3G methodology shows that delocalization of the nitrogen lone pair occurs in both the π and the σ systems of the aromatic ring. The center of negative charge is shifted towards the nitrogen atom in all the *ortho*-substituted MAs, but the charge on the amino fragment only becomes negative in molecules **8** and **10**, explaining the greater basicity of the *ortho*-methylated N,N-dimethylanilines. Moreover, Table III shows that the N-C1 bond length increases slightly in these two compounds, in agreement with the calculated molecular coefficients. Figures 6 and 7 show contour diagrams of the HOMO of molecules **6** and **8** provided by AM1 methodology, which demonstrate the change in nitrogen hybridization on going from an *ortho*-unsubstituted N,N-dimethylaniline to an *ortho*-methylated derivative.

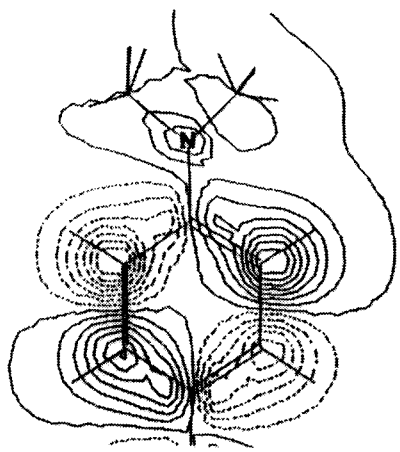

FIG. 6. HOMO contour plot of the most stable conformer of compound **6**.

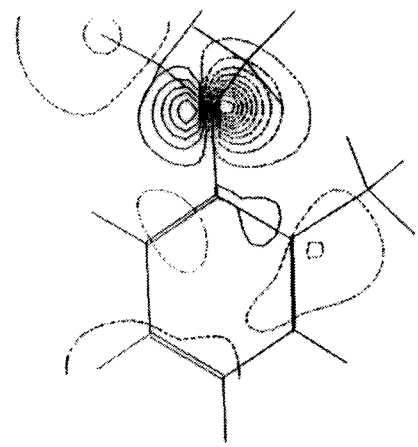

FIG. 7. HOMO contour plot of the most stable conformer of compound **8**.

For all possible conformations of the whole set of MA's (**1-10**), those N-methyl carbon nuclei which lie close to the ring plane are more deshielded, not only due to the anisotropic effect created by the ring current, but also to the positive local charge on the methyl carbons in these orientations. In the monomethylanilines (**1-5**), where the N-methyl group remains close to the ring plane most of the time, anisotropic deshielding plays a more important role than the development of a positive charge on the amino group.

Final remarks

The ^{13}C-NMR results reflect the time-averaged conformations of all the compounds in $CDCl_3$, a low polarity solvent which presumably mimics the environment of drug molecules at biomolecular receptor sites. The AM1 quantum chemical calculations give the relative energies of the different conformations for each compound and allow local minima to be identified which, it must be stressed, are not necessarily the same as the average conformations. The conclusion of the ^{13}C-NMR study of the ortho-substituted N-methylanilines (**3,5**) that the time-averaged conformations of these compounds should still correspond to those in which the N-methyl group lies close to the aromatic ring, is explained by the theoretical SCF MO calculations which point to virtually free rotation of methylamino group around the aryl-N bond, with exclusion of those conformations in which this group approaches the *ortho*-substituent. This implies that the N-methyl carbon nucleus lies in or near the ring plane most of the time. The behavior of the *ortho*-substituted N,N-dimethylanilines (**8,10**) indicted by the ^{13}C results is in agreement with and is explained by the SCF calculations in terms of competition between the nuclear repulsion energy and the electronic delocalization energy, which leads to strongly limited mobility of the N,N-dimethyl group with the nitrogen lone pair preferentially oriented towards the *ortho*-substituent. Unexpectedly, according to our Mulliken Population Analysis, only the *ortho*-N,N-trisubstituted anilines carry negative charge on the amino fragment, a conclusion which must be taken into consideration when analyzing the interactions of simple arylamine drugs with their receptors.

To the best of our knowledge, no attempt has been made to derive quantitative structure-activity relationships (QSAR) for drugs incorporating arylamine functions such as amiflamine. This circumstance may be due, in part, to specific difficulties inherent to the QSAR of substituted aromatic amines as a consequence of the specific conformational and electronic properties of the arylamine moiety which have not hitherto been analyzed systematically. The foregoing study should make such relationships more accessible, on the basis of reasonable conformational preferences and the associated electronic structures, thus leading to the improved rational design of arylamine-containing bioactive substances.

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