Amidines. Part 41.[1] Effects of substitution at the amidino carbon atom and at the imino nitrogen atom on the preferred configuration at the C=N bond in the ^{13}C NMR spectra of N^1,N^1-dimethyl-N^2-alkylamidines

Jolanta Jaroszewska-Manaj, Janusz Oszczapowicz and Włodzimierz Makulski

Chemistry Department, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland

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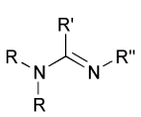
A new approach, based on the correlation between the chemical shifts of carbon atoms directly bonded to the two nitrogen atoms, enabled the determination of the preferred configuration of the C=N bond in N^1,N^1-dimethylamidines containing a CH_2 group at the imino nitrogen atom. The ^{13}C NMR chemical shifts of 40 N^1,N^1-dimethyl-N^2-alkylamidines and 35 N^1,N^1-dimethyl-N^2-benzylamidines of general formula $Me_2N–CR^1=NR^2$, each divided into seven series depending on the substituent R^1, have been determined in $CDCl_3$ solutions. The V-shaped relationship between the chemical shifts of carbon atoms bonded directly to the amino and the imino nitrogen atoms reveals that, in the case of N^2-alkyl and N^2-benzylamidines, the volume of the substituent (R^1) at the amidino carbon atom determines the preferred isomer. For amidines where R^1 is isopropyl, isobutyl, *tert*-butyl or cyclohexyl the *Z* configuration is the preferred one.

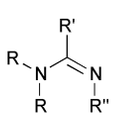
Introduction

The two nitrogen atoms of the amidine group are formally differently bonded to the functional carbon atom—the amino nitrogen (N^1) by a single bond and the imino nitrogen (N^2) by a double bond—and in the earlier literature these were referred to as sp^3 and sp^2 nitrogens[2–4] respectively. However, later investigations have shown that, due to strong conjugation between the C=N double bond and the electron pair on the amino nitrogen, both nitrogen atoms are in the sp^2 hybridization state[5] and all four atoms of the substituents bonded to the amidino group are in the plane of the amidine group.[6–9] As a result of the conjugation, rotation around the "single" C–N bond is hindered[10,11a,12d,13] and two definite conformations can be discerned.

Acyclic amidines may exist as the two configurational isomers *E* and *Z* with respect to the formal C=N double bond[10] often referred to as *cis* and *trans* isomers (substituent R″ at the imino nitrogen atom with respect to the amino nitrogen).



E *(trans)*



Z *(cis)*

Although the structures of amidines have been the subject of numerous studies and have been summarized in several reviews and monographs,[4,10,11,12b,14–17] the question of the configuration of individual compounds is still uncertain.

It is generally assumed that for trisubstituted amidines the most favorable isomer has the *E* configuration because only in a few cases was an appreciable amount of the unstable *Z* isomer noticed.[18,19] Molecular orbital calculations on some formamidines also show that usually the *E* form of the amidine is more stable.[20–24] In the ^{1}H and ^{13}C NMR spectra of free base amidines the presence of the second isomer usually is not detected. The ^{13}C NMR chemical shifts for 65 different *N*-arylamidines and guanidines indicated that all of them possess the same configuration.[25] Separate signals for the two isomers were found only in the cases of some amidinium salts[26] and of crotonamidines[27] where the two forms *E* and *Z* were observed in addition to the *cis* and *trans* isomers with respect to the C=C double bond.

In a survey[28] of the Cambridge Crystallographic Database in 1988 only nine N^1,N^1,N^2-trisubstituted amidines were found to be of the *E* configuration; our recent survey[29] of this database did not reveal any more. Only *N*,*N*′-disubstituted amidines are found as the *Z* isomer,[30] because it is stabilized through dimer formation with hydrogen bonds between the hydrogens of the amino nitrogen and the imino nitrogen atoms.

On the other hand, the results of 3-21 G optimizations for several model fluorine-substituted formamidines have shown that the predominance of the *E* or *Z* isomer depends also on the polar effects of a substituent at the imino nitrogen atom;[24] *e.g.* for N^1-fluoroformamidine and N^2-fluoroformamidine the *Z* isomers are more stable. The results of the structure–basicity relationship for symmetrically *N*,*N*′-disubstituted acetamidines and propionamidines[31] indicated that in solution propionamidines may exist to a considerable extent as the *Z* isomers due to the formation of the hydrogen-bonded dimers. Recently, IR investigations of collision complexes of amidines with chloroform have shown that for N^2-alkylamidines the *Z* form may be the preferred one.[1]

However, it has to be mentioned that in solution the *E*–*Z* isomerisation in trisubstituted amidines may occur by two mechanisms:[12c,32] one, occurring in the case of all compounds containing the C=N double bond, referred to as the "*lateral shift*" which involves a linear transition state, and the other, termed the "*internal rotation*" mechanism, which involves rotation about an axis that passes through the C and N atoms of the double bond, and which is most probably subject to acid catalysis. As a result, amidines exist in solution as an equilibrium mixture of the *E* and *Z* isomers, and the observed chemical shift for each nucleus $\delta_{obs}(Z_i)$, *i.e.* for ^{1}H, ^{13}C or ^{15}N, in the amidine molecule depends on the chemical shifts of this nucleus $\delta_E(Z_i)$ and $\delta_Z(Z_i)$ in the individual isomers *E* and *Z* and on their molar fractions x_E and x_Z as expressed by eqn. (1).

$$\delta_{obs}(Z_i) = x_E\delta_E(Z_i) + x_Z\delta_Z(Z_i) \quad (1)$$

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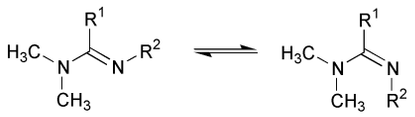
Table 1 Studied amidines[a]



1

			Compound no.	
R^1	Series	Code	Alkyl	Benzyl
H	N^1,N^1-Dimethylformamidines	**FDM**	**1–6**	**41–45**
Me	N^1,N^1-Dimethylacetamidines	**ADM**	**7–12**	**46–50**
Et	N^1,N^1-Dimethylpropionamidines	**PrpDM**	**13–18**	**51–55**
i-Pr	N^1,N^1-Dimethylisobutyramidines	**iBtrDM**	**19–24**	**56–60**
t-Bu	N^1,N^1-Dimethylpivalamidines	**PivDM**	**25–30**	**61–65**
i-Bu	N^1,N^1-Dimethylisovaleramidines	**iValDM**	**31–35**	**66–70**
c-Hex	N^1,N^1-Dimethylcyclohexanecarboxamidines	**cHexDM**	**36–40**	**71–75**

[a] R^2 is *n*-hexyl, *n*-butyl, *n*-propyl, isopropyl, isobutyl, cyclohexyl, and substituted benzyl groups $–CH_2–C_6H_4X$, where X = H, *p*-Me, *p*-OMe, *m*-OMe and *p*-Cl.

If the chemical shifts of any of these nuclei were known for individual isomers, it would be possible to determine the ratio of the isomers in the equilibrium state just on the basis of the observed chemical shift.

While the *E* isomer is mostly energetically more favored than the *Z* form, it seems obvious that steric repulsion between substituents at the amidino carbon atom and imino nitrogen may cause the higher stability of the *Z* isomer. Thus, in the case of amidines containing an alkyl or aralkyl group at the imino nitrogen atom, a bulky substituent at the amidine carbon atom should cause a noticeable shift of the equilibrium state towards the *Z* isomer.

The results of X-ray structure determinations concern compounds in the solid state. In the case of compounds that may exist in the two forms (*E* and *Z* isomers in this case) it might happen that, due to the differences in their solubility, the form isolated in the crystalline state and subjected to X-ray analysis is not the one that predominates in solution.

Thus, the question of the configuration of the C=N bond in amidines should be put another way: "*Which of the two isomers predominates?*" instead of "*Which configuration does the amidine have*?" ^{13}C NMR spectroscopy seems to be the most suitable tool to provide an answer to this question. Unfortunately, papers on the ^{13}C NMR spectra of amidines are not numerous.[12c,13,27,32–34] Most of the papers did not concern compounds containing bulky substituents at the amidino carbon atom and *E–Z* isomerism was not the subject under investigation. Moreover, in the ^{13}C NMR spectra of amidines the signals of individual isomers are usually not observed, most probably because of the fast inversion of configuration and averaging of their signals.

In the search for evidence of the presence of the two isomers in solution in this work the ^{13}C NMR chemical shifts of 76 N^1,N^1-dimethylamidines of general formula **1** (containing various alkyl groups at the functional carbon atom and at the imino nitrogen atom, Table 1) were determined in $CDCl_3$ solution. The chemical shifts are summarized in Tables 2–4.

Results and discussion

For this study N^2-substituted N^1,N^1-dimethylamidines were chosen since trisubstituted amidines do not display tautomerism, which could cause ambiguities in the spectral interpretation, and, moreover, they do not form hydrogen-bonded dimers, which might cause considerable changes in the preference for one of the two isomers. The identity of the two substituents at the amino nitrogen makes it possible to avoid the conformational problem of which of them is in the synperiplanar and which is in the antiperiplanar position with respect to the second nitrogen.

The studied amidines contained at the amidino carbon atom substituents of volume gradually increasing in the following order: H, Me, Et, *i*-Pr, *c*-Hex, and *t*-Bu, which were supposed to increase the preference for the *Z* isomer. At the imino nitrogen atom they contained the following alkyl groups: *n*-hexyl, *n*-butyl, *n*-propyl, isopropyl, isobutyl and cyclohexyl.

To see whether, and, if so, to what extent, polar effects may influence the preference for a certain isomer we have also studied amidines containing at the imino nitrogen atom a benzyl group that is substituted on the phenyl ring by various substituents X ($–CH_2–C_6H_4X$) of differing polarity (*p*-Me, *p*-OMe, H, *m*-OMe and *p*-Cl). Substituent X on the phenyl ring was far enough from the C=N bond for the steric effect to be identical for all of the benzyl derivatives studied. A phenyl ring itself, even directly bonded to the imino nitrogen, does not cause steric hindrance sufficient for a change of configuration. X-Ray analysis of N^2-phenylbenzamidines has shown that they exist as the *E* isomers.[8,35,36]

As can be seen from the data in Tables 2–4 the largest changes in chemical shift caused by substituent R^1 at the functional carbon atom occur for carbon atoms of methyl groups at the amino nitrogen atom (36.8 to 40.34 ppm), of the CH_2 group bonded to the imino nitrogen (47.37 to 57.86 ppm in the case of N^2-alkyl derivatives and 51.15 to 59.59 ppm in the case of N^2-benzyl derivatives), and of the amidino carbon atom (154.74 to 170.82 ppm in the case of N^2-alkyl derivatives and 155.65 to 172.05 ppm in the case of N^2-benzyl derivatives).

It is known that the influence of a substituent on one side of the C=C double bond on the chemical shift of the α carbon atom of a substituent on the other side depends to a considerable degree on the mutual position (*E* or *Z*) of both these substituents. Due to the steric compression shift (γ-effect), the chemical shift for the *Z* isomer is lower, usually by 2 to 4 ppm, but in the case of substituents of larger volume the upfield shift is higher, *e.g.* for 1-chlorobut-2-ene in the *Z* isomer the chemical shift of the methyl group is lower by 5.6 ppm, whereas for CH_2Cl it is lower by 6.1 ppm. It seemed reasonable to assume that the same relation will also hold in the case of substituents at the C=N double bond.

The amidines studied can be divided either into 7 series in which the alkyl group (R^1) at the functional carbon atom is unchanged and only the substituent at the imino nitrogen atom (R^2) is varied, or into 6 series in which the substituent at the imino nitrogen atom (R^2) is constant but the substituent at the amidino carbon atom (R^1) is varied.

Table 2 ^{13}C NMR chemical shifts (δ, ppm) of the carbon atoms in N^1,N^1-dimethyl-N^2-alkylamidines ($Me_2N–CR^1=NCH_2R^2$)

						R^1		R^2					
	R^1	R^2	Formula	N–C=N	NMe_2	C-α	C-β	C-1	C-2	C-3	C-4	C-5	C-6
1	H	*n*-Hex	$C_9H_{20}N_2$	154.74	37.10	—	—	56.43	32.68	26.96	31.81	22.71	14.09
2	H	*n*-Bu	$C_7H_{16}N_2$	154.74	37.10	—	—	56.04	35.02	20.37	14.04		
3	H	*n*-Pr	$C_6H_{14}N_2$	154.91	37.10	—	—	58.12	25.75	11.66			
4	H	*i*-Bu	$C_7H_{16}N_2$	154.78	37.10	—	—	64.58	30.56	20.46			
5	H	*i*-Pr	$C_6H_{14}N_2$	154.09	37.10	—	—	55.07	25.70				
6	H	*c*-Hex	$C_9H_{18}N_2$	152.92	36.80	—	—	64.48	35.89	25.18	25.40		
7	Me	*n*-Hex	$C_{10}H_{22}N_2$	158.68	38.01	12.40	—	50.24	32.42	27.35	31.99	22.76	14.13
8	Me	*n*-Bu	$C_8H_{18}N_2$	158.73	38.01	12.40	—	49.89	34.63	20.72	14.17		
9	Me	*n*-Pr	$C_7H_{16}N_2$	159.03	38.10	12.53	—	51.97	25.40	12.01			
10	Me	*i*-Bu	$C_8H_{18}N_2$	158.30	37.97	12.57	—	58.17	30.86	20.72			
11	Me	*i*-Pr	$C_7H_{16}N_2$	156.91	38.01	12.40	—	49.07	25.10				
12	Me	*c*-Hex	$C_{10}H_{20}N_2$	156.64	37.93	12.44	—	57.86	35.50	25.40	25.96		
13	Et	*n*-Hex	$C_{11}H_{24}N_2$	162.89	37.84	18.94	11.27	49.41	32.81	27.35	31.94	22.76	14.13
14	Et	*n*-Bu	$C_9H_{20}N_2$	160.20	39.05	18.94	11.79	49.28	33.25	20.50	14.00		
15	Et	*n*-Pr	$C_8H_{18}N_2$	160.11	37.84	18.98	11.83	51.19	24.23	12.05			
16	Et	*i*-Bu	$C_9H_{20}N_2$	162.47	37.88	19.00	11.62	57.20	30.95	20.72			
17	Et	*i*-Pr	$C_8H_{18}N_2$	161.06	37.93	18.98	12.01	48.46	25.57				
18	Et	*c*-Hex	$C_{11}H_{22}N_2$	160.98	37.88	18.98	12.18	57.34	35.93	25.4	25.92		
19	*i*-Pr	*n*-Hex	$C_{12}H_{26}N_2$	165.66	39.40	27.13	19.46	48.94	32.73	27.26	31.90	22.71	14.09
20	*i*-Pr	*n*-Bu	$C_{10}H_{22}N_2$	165.75	39.44	27.18	19.46	48.55	34.94	20.68	14.17		
21	*i*-Pr	*n*-Pr	$C_9H_{20}N_2$	165.79	39.44	27.18	19.46	50.63	25.75	11.96			
22	*i*-Pr	*i*-Bu	$C_{10}H_{20}N_2$	165.31	39.40	27.31	19.33	56.61	30.99	20.63			
23	*i*-Pr	*i*-Pr	$C_9H_{20}N_2$	163.71	39.49	27.31	19.25	47.59	25.49				
24	*i*-Pr	*c*-Hex	$C_{12}H_{24}N_2$	163.84	39.53	27.26	20.57	56.43	35.63	25.23	25.92		
25	*t*-Bu	*n*-Hex	$C_{13}H_{28}N_2$	170.73	42.17	40.74	29.39	50.54	31.73	27.22	31.60	22.71	14.09
26	*t*-Bu	*n*-Bu	$C_{11}H_{24}N_2$	170.73	42.17	40.76	29.39	50.24	33.85	20.63	14.00		
27	*t*-Bu	*n*-Pr	$C_{10}H_{22}N_2$	170.82	42.19	40.79	29.36	52.32	24.79	12.01			
28	*t*-Bu	*i*-Bu	$C_{11}H_{24}N_2$	170.51	42.17	40.79	29.43	58.43	30.71	20.68			
29	*t*-Bu	*i*-Pr	$C_{10}H_{22}N_2$	169.12	42.78	40.77	29.00	48.81	24.10				
30	*t*-Bu	*c*-Hex	$C_{13}H_{26}N_2$	169.48	42.87	40.76	29.00	57.69	35.07	25.01	25.88		
31	*i*-Bu	*n*-Hex	$C_{13}H_{28}N_2$	164.56	39.26	35.91	23.53	48.61	32.72	27.29	31.93	22.71	14.09
32	*i*-Bu	*n*-Bu	$C_{11}H_{24}N_2$	164.50	39.26	35.95	23.55	48.31	35.55	20.69	14.20		
33	*i*-Bu	*n*-Pr	$C_{10}H_{22}N_2$	164.19	39.24	35.92	23.55	50.36	25.96	11.95			
34	*i*-Bu	*i*-Bu	$C_{11}H_{24}N_2$	164.04	39.29	35.92	23.53	56.18	31.08	20.62			
35	*i*-Bu	*i*-Pr	$C_{10}H_{22}N_2$	163.27	39.38	35.95	23.52	47.37	25.55				
36	*c*-Hex	*n*-Hex	$C_{15}H_{30}N_2$	166.92	39.97	36.45	24.17	49.30	32.37	27.27	31.80	22.71	14.09
37	*c*-Hex	*n*-Bu	$C_{13}H_{26}N_2$	166.90	39.99	36.48	24.33	48.99	34.31	20.67	14.13		
38	*c*-Hex	*n*-Pr	$C_{12}H_{24}N_2$	166.83	40.00	36.61	24.34	51.05	25.49	11.98			
39	*c*-Hex	*i*-Bu	$C_{13}H_{26}N_2$	166.48	40.09	36.55	24.15	57.01	30.92	20.65			
40	*c*-Hex	*i*-Pr	$C_{12}H_{24}N_2$	165.51	40.34	36.62	24.16	48.02	25.06				

All of the studied amidines contained the same two substituents at the amino nitrogen atom, and therefore comparison of the values of the additivity parameters (SCS, substituent-induced chemical shifts) for the dimethylaminomethyleneamino group ($Me_2N–CR^1=N–$) should show the influence of an alkyl substituent R^1 at the amidino carbon atoms on the *α* carbon atom of the substituent R^2 at the imino nitrogen. On the other hand, comparison of the additivity parameters for the N^1,N^1-dimethylamidino group [$R^2N=C(NMe_2)–$] should show the influence of the substituent R^2 at the imino nitrogen on the chemical shifts of the *α* carbon atom of an alkyl group R^1 at the amidino carbon atom. Therefore, we have calculated the SCS values of the $Me_2N–CR^1=N–$ and $R^2N=C(NMe_2)–$ groups (Tables 5 and 6).

The data for the series containing identical substituents at the amidino carbon atom (Table 5) indicate that the kind of alkyl or aralkyl substituent at the imino nitrogen (R^2) has only a small influence on the chemical shifts of the carbon atoms of substituent R^1 at the amidino carbon atom. Very small differences between the SCS values for the $Me_2N–CR^1=N–$ group, falling in the range of 0.17 ppm, indicate that all of the amidines studied that possess the same substituent at the amidino carbon atom have an identical configuration of the C=N double bond. However on this basis, it cannot be concluded which configuration is correct.

The data for the series containing an identical substituent at the imino nitrogen atom (Table 6) show that the substituent at the amidino carbon atom (R^1) exerts considerable influence on the chemical shifts of the methyl groups in the dimethylamino moiety and on the carbon atom bonded directly to the imino nitrogen; the differences in the SCS values are in the range of about 8 ppm. The influence on the β-carbon atoms of the N^2-alkyl group or on the phenyl carbon atom bonded to the benzyl CH_2 group is smaller but still discernible.

The SCS values obtained for the N^1,N^1-dimethylamidino group depend to a considerable degree on whether R^2 is an *n*-alkyl or an isoalkyl group, and therefore do not allow one to draw unequivocal conclusions concerning the configuration of the C=N double bond.

For this reason and in order to determine the preferred configuration of the amidines studied we have applied a new approach based on the comparison of the influence of a substituent R^1 at the amidino carbon atom on the chemical shifts of the carbon atoms directly bonded to the two nitrogen atoms. These carbon atoms are at the same distance in terms of bonds from the substituent R^1 and the only difference is that one of the CN bonds is single and the second is a double bond. In a series of amidines where only substituent R^1 is varied as a result of its polar effects, the chemical shifts of these atoms should change in a similar way, *i.e.* should be proportionally either shielded or deshielded.

Thus, for a given substituent R^2 at the imino nitrogen atom and a given configuration of the C=N bond, the changes in the chemical shift of the C-1 carbon atom caused by a substituent at the amidino carbon atom should be proportional to those of the *N*-methyl groups and a linear correlation between their chemical shifts should occur.

Table 3 ^{13}C NMR chemical shifts (δ, ppm) of the carbon atoms in N^1,N^1-dimethyl-N^2-benzylamidines ($Me_2N–CR^1=NCH_2C_6H_4X$)[a]

						R¹		R²							
	R^1	X	Formula	N–C=N	NMe_2	C-α	C-β	CH_2	C-1	C-2	C-3	C-4	C-5	C-6	Me
41	H	H	$C_{13}H_{20}N_2$	155.78	37.15			59.56	142.30	127.34	128.17	126.26	128.17	127.34	
42	H	*p*-Me	$C_{14}H_{22}N_2$	155.65	37.15			59.30	139.27	127.34	128.86	135.67	128.86	127.34	21.07
43	H	*p*-OMe	$C_{14}H_{22}N_2O$	155.65	37.15			59.59	135.34	128.43	113.65	157.60	113.65	128.43	55.07
44	H	*m*-OMe	$C_{14}H_{22}N_2O$	155.78	37.15			59.42	144.03	113.00	159.59	111.66	129.08	119.72	55.09
45	H	*p*-Cl	$C_{13}H_{19}N_2Cl$	155.87	37.15			58.78	140.87	128.69	128.21	131.85	128.21	128.69	
46	Me	H	$C_{14}H_{22}N_2$	159.94	38.10	12.92		53.27	142.64	127.04	128.04	125.87	128.04	127.04	
47	Me	*p*-Me	$C_{15}H_{24}N_2$	160.15	38.19	13.00		52.97	139.52	127.00	128.82	135.28	128.82	127.00	21.07
48	Me	*p*-OMe	$C_{15}H_{24}N_2O$	160.12	38.18	12.99		53.06	135.69	128.13	113.61	157.30	113.61	128.13	55.07
49	Me	*m*-OMe	$C_{15}H_{24}N_2O$	160.07	38.14	12.95		53.10	144.38	112.74	159.59	111.26	128.95	119.46	55.09
50	Me	*p*-Cl	$C_{14}H_{21}N_2Cl$	160.03	38.10	12.96		52.58	141.30	128.38	128.13	131.37	128.13	128.38	
51	Et	H	$C_{15}H_{24}N_2$	164.02	37.93	19.38	11.10	52.45	142.99	127.04	128.04	125.87	128.04	127.04	
52	Et	*p*-Me	$C_{16}H_{26}N_2$	163.93	37.93	19.33	11.14	52.19	139.92	126.96	128.73	135.28	128.73	126.96	21.07
53	Et	*p*-OMe	$C_{16}H_{26}N_2O$	164.00	37.97	19.40	11.14	52.22	136.04	128.13	113.52	157.27	113.52	128.13	55.07
54	Et	*m*-OMe	$C_{16}H_{26}N_2O$	164.06	37.98	19.38	11.09	52.32	144.77	112.70	159.55	111.60	129.08	119.72	55.09
55	Et	*p*-Cl	$C_{15}H_{23}N_2Cl$	164.19	37.97	19.46	11.01	51.67	141.43	128.38	128.13	131.46	128.13	128.38	
56	*i*-Pr	H	$C_{16}H_{26}N_2$	166.70	39.44	27.57	19.29	51.88	142.77	126.96	128.04	125.87	128.04	126.96	
57	*i*-Pr	*p*-Me	$C_{17}H_{28}N_2$	166.74	39.57	27.57	19.29	51.54	139.52	126.87	128.73	135.31	128.73	126.87	21.07
58	*i*-Pr	*p*-OMe	$C_{17}H_{28}N_2O$	167.65	40.05	27.55	19.30	51.60	135.59	128.08	113.52	157.27	113.52	128.08	55.07
59	*i*-Pr	*m*-OMe	$C_{17}H_{28}N_2O$	168.24	40.00	26.98	18.94	52.08	144.28	112.78	159.52	111.34	129.00	119.58	55.09
60	*i*-Pr	*p*-Cl	$C_{16}H_{25}N_2Cl$	166.79	39.44	27.70	19.20	51.15	141.30	128.30	128.13	131.46	128.13	128.30	
61	*t*-Bu	H	$C_{17}H_{28}N_2$	172.05	42.13	41.09	29.60	53.66	142.25	127.09	128.04	125.96	128.04	127.09	
62	*t*-Bu	*p*-Me	$C_{18}H_{30}N_2$	171.56	42.17	41.09	29.56	53.44	139.18	127.04	128.73	135.32	128.73	127.04	21.07
63	*t*-Bu	*p*-OMe	$C_{18}H_{30}N_2O$	172.47	42.28	41.10	29.55	53.54	135.29	128.13	113.52	157.27	113.52	128.13	55.07
64	*t*-Bu	*m*-OMe	$C_{18}H_{30}N_2O$	172.01	42.28	41.05	29.65	53.49	144.03	112.57	159.55	111.42	128.95	119.46	55.09
65	*t*-Bu	*p*-Cl	$C_{17}H_{27}N_2Cl$	171.94	42.13	41.05	29.65	53.01	140.87	128.43	128.13	131.51	131.51	128.43	
66	*i*-Bu	H	$C_{17}H_{28}N_2$	166.66	39.22	34.44	20.02	51.64	142.85	127.00	128.04	125.87	128.04	127.00	
67	*i*-Bu	*p*-Me	$C_{18}H_{30}N_2$	166.68	39.38	34.48	20.00	51.35	139.72	126.97	128.74	135.31	128.74	126.97	21.07
68	*i*-Bu	*p*-OMe	$C_{18}H_{30}N_2O$	166.60	39.47	34.42	20.03	51.37	135.84	128.10	113.53	157.29	113.53	128.10	55.07
69	*i*-Bu	*m*-OMe	$C_{18}H_{30}N_2O$	167.00	39.40	34.40	20.00	51.60	144.55	112.72	159.50	111.40	128.99	119.60	55.09
70	*i*-Bu	*p*-Cl	$C_{17}H_{27}N_2Cl$	166.68	39.29	34.39	20.00	51.30	141.31	128.39	128.11	131.52	128.11	128.39	
71	*c*-Hex	H	$C_{19}H_{29}N_2$	167.56	39.71	35.08	22.06	51.93	142.64	127.02	128.04	125.87	128.04	127.02	
72	*c*-Hex	*p*-Me	$C_{20}H_{31}N_2$	167.13	39.77	35.11	22.04	51.46	139.74	127.00	128.73	135.32	128.73	127.00	21.07
73	*c*-Hex	*p*-OMe	$C_{20}H_{31}N_2O$	167.81	39.82	35.06	22.02	51.50	135.75	128.06	113.53	157.29	113.53	128.06	55.07
74	*c*-Hex	*m*-OMe	$C_{20}H_{31}N_2O$	168.09	39.80	35.04	22.03	51.71	144.40	112.60	159.50	111.34	128.96	119.48	55.09
75	*c*-Hex	*p*-Cl	$C_{19}H_{28}N_2Cl$	167.60	39.69	35.04	22.00	51.37	141.33	128.41	128.11	131.50	128.11	128.41	

[a] For the sake of clarity, the phenyl carbon atoms are numbered uniformly, beginning from the amidino group, regardless of the priority of the substituents in the nomenclature.

Table 4 ^{13}C NMR chemical shifts (δ, ppm) of the γ and δ carbon atoms of the alkyl group R^1 at the amidino carbon atom in N^1,N^1-dimethylisovaleramidines (**iValDM**) and N^1,N^1-dimethylcyclohexanecarboxamidines (**cHexDM**)

	R^1	R^2	C-γ	C-δ
31	*i*-Bu	*n*-Hex	20.35	—
32	*i*-Bu	*n*-Bu	20.65	—
33	*i*-Bu	*n*-Pr	20.67	—
34	*i*-Bu	*i*-Bu	20.61	—
35	*i*-Bu	*i*-Pr	20.68	—
36	*c*-Hex	*n*-Hex	30.07	23.29
37	*c*-Hex	*n*-Bu	30.09	23.28
38	*c*-Hex	*n*-Pr	30.14	23.28
39	*c*-Hex	*i*-Bu	30.19	23.27
40	*c*-Hex	*i*-Pr	30.13	23.27
	R^1	X	C-γ	C-δ
66	*i*-Bu	H	15.95	—
67	*i*-Bu	*p*-Me	15.98	—
68	*i*-Bu	*p*-OMe	15.99	—
69	*i*-Bu	*m*-OMe	15.95	—
70	*i*-Bu	*p*-Cl	15.94	—
71	*c*-Hex	H	28.11	22.17
72	*c*-Hex	*p*-Me	28.09	22.17
73	*c*-Hex	*p*-OMe	28.09	22.17
74	*c*-Hex	*m*-OMe	28.06	22.17
75	*c*-Hex	*p*-Cl	28.07	22.17

The results of these correlations are presented in Fig. 1. At first glance it is seen that for both N^2-alkyl as well as for N^2-benzyl derivatives two separate linear correlations exist:

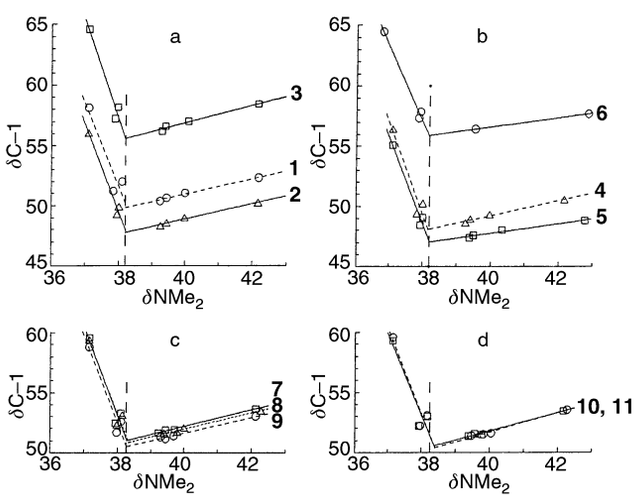


Fig. 1 Correlation of the ^{13}C NMR chemical shifts of the carbon atoms of substituent R^2, bonded to the imino nitrogen, with those of the methyl groups at the amino nitrogen in (a), (b) N^1,N^1-dimethyl-N^2-alkylamidines and in (c), (d) N^1,N^1-dimethyl-N^2-benzylamidines. **1**: N^2-propyl, **2**: N^2-butyl, **3**: N^2-isobutyl, **4**: N^2-*n*-hexyl, **5**: N^2-isopropyl, **6**: N^2-cyclohexyl, **7**: N^2-benzyl, **8**: N^2-*m*-methoxybenzyl, **9**: N^2-*p*-chlorobenzyl, **10**: N^2-*p*-methylbenzyl, **11**: N^2-*p*-methoxybenzyl derivatives.

one for formamidines, acetamidines and propionamidines and the second for the rest of the series. Moreover, in the case of N^2-alkyl derivatives the correlation lines for the two groups cross each other at the same value of the *x*-axis; in the case of N^2-benzyl derivatives they cross near the same value.

Table 5 Influence of the substituent R^2 at the imino nitrogen atom on the chemical shifts of the α carbon atom of the substituent R^1 at the functional carbon atom in N^1,N^1-dimethylamidines [increments for the $R^2N{=}C(NMe_2)–$ group]

	R^2 (Alkyl derivatives)						R^2 (Benzyl derivatives)				
R^1	*n*-Hex	*n*-Bu	*n*-Pr	*i*-Bu	*i*-Pr	*c*-Hex	H	*p*-MeC_6H_4	*p*-$OMeC_6H_4$	*m*-$OMeC_6H_4$	*p*-ClC_6H_4
Me	14.70	14.70	14.83	14.87	14.70	14.74	6.42	6.50	6.49	6.45	6.46
Et	12.44	12.44	12.48	12.50	12.48	12.48	3.08	3.03	3.10	3.08	3.16
i-Pr	10.83	10.88	10.88	11.01	11.01	10.96	4.27	4.27	4.25	3.68	4.40
t-Bu	17.44	17.46	17.49	17.49	17.47	17.46	9.69	9.69	9.70	9.65	9.65
i-Bu	11.31	11.35	11.32	11.32	11.35	–	4.54	4.58	4.52	4.50	4.49
c-Hex	9.45	9.48	9.61	9.55	9.62	–	1.98	2.01	1.96	1.94	1.94

Table 6 Influence of the substituent R^1 at the functional carbon atom on the chemical shifts of the C-1 carbon atom of the substituent R^2 at the imino nitrogen atom in N^1,N^1-dimethylamidines [increments for the $Me_2N–C(R^1){=}N–$ group]

	R^1						
R^2	H	Me	Et	*i*-Pr	*t*-Bu	*i*-Bu	*c*-Hex
n-Hexyl	42.73	36.54	35.71	35.24	36.84	34.91	35.60
n-Butyl	42.94	36.79	36.18	35.45	37.14	35.21	35.89
n-Propyl	42.72	36.57	35.79	35.23	36.92	34.96	35.65
Isobutyl	39.98	33.57	32.60	32.01	33.83	31.58	32.41
Isopropyl	38.77	32.77	32.16	31.29	32.51	31.07	31.72
Cyclohexyl	37.48	30.86	30.34	29.43	30.69	—	—
Benzyl	38.16	31.87	31.05	30.48	32.26	30.24	30.53
p-Methylbenzyl	38.40	32.07	31.29	30.64	32.54	30.45	30.56
p-Methoxybenzyl	39.19	32.66	31.82	31.20	33.14	30.97	31.10
m-Methoxybenzyl	37.96	31.64	30.86	30.62	32.03	30.14	30.25
p-Chlorobenzyl	38.08	31.88	30.97	30.45	32.31	30.60	30.67

The plots obtained indicate that, as assumed, the effects (both polar and steric) of a substituent at the amidino carbon atom on the chemical shifts of the CH_2 group at the imino nitrogen atom are proportional to those on the CH_3 groups at the amino nitrogen. However, the proportion factors for the two above-mentioned groups of amidines differ in value and— which is more significant—in sign. This shows that the preferred configuration is not the same for both groups.

In the first group (formamidines, acetamidines and propionamidines) the *E* configuration predominates and a gradual increase of the volume of the substituent R^1 causes an increase of the γ-effect and, as a result, in spite of the polar effects of R^1, causes an increase of the chemical shifts of the dimethylamino group and a decrease of the chemical shift of the CH_2 group bonded to the imino nitrogen.

In the second group, where the alkyl substituent at the amidino group is branched at the α carbon atom (isopropyl, cyclohexyl, *tert*-butyl, *i.e.* isobutyramidines, cyclohexanecarboxamidines and pivalamidines) or at the β carbon atom (isobutyl, *i.e.* isovaleramidines), the *Z* configuration is, in contrast, the preferred one; substituent R^1 is in a *trans* position with respect to the CH_2 group and the γ-effect does not take place. As a result the polar effects of R^1 cause a change in the chemical shifts of the CH_3 and CH_2 groups in the same direction.

Experimental

Materials

The amidines studied were synthesized and purified in our laboratory. Isovaleramidines (**iValDM**) and cyclohexanecarboxamidines (**cHexDM**) were synthesized from primary amines and chloroiminium chlorides obtained from corresponding dimethylamides in reaction with phosphorus pentachloride.[37] Other amidines were obtained according to previously described procedures: **FDM**,[38] **ADM**,[39] **PrpDM**,[39] **iBtrDM**,[39] and **PivDM**.[40]

The purity of the amidines studied was above 95%, as judged by gas chromatography. The details of the GC analysis have been given elsewhere: **FDM**,[41] **ADM**,[41] **PrpDM**,[42] **iBtrDM**,[42] and **PivDM**;[42] **iValDM** and **cHexDM** were analyzed under the conditions used for the **PivDM** series.

Spectra

The ^{13}C NMR spectra were recorded on a JEOL CoFX 90Q 22.50 MHz and on a Varian Unity-Plus 200 MHz spectrometer at room temperature. Samples were recorded as solutions in $CDCl_3$ to provide the deuterium lock, with internal TMS as a reference. A 20 mg amount of each compound was dissolved in 0.5 ml of $CDCl_3$.

For proton noise-decoupled ^{13}C spectra 1000 scans were accumulated. An 8 μs pulse, a repetition time of 1.2 s, a spectral width of 4000 Hz or 2000 Hz and 8 K data points were used for the accumulation of the interferograms, which were then Fourier transformed by computer. The ^{13}C chemical shifts are accurate to within 0.05 ppm.

Assignments

The assignments were based on the ^{13}C NMR chemical shifts of amidines presented in our previous paper[25] and on the relative intensities of the signals. The variety of substituents and the ^{13}C NMR spectra of the carbon atoms in the substrates used in the synthesis of the amidines (the corresponding amines and *N*,*N*-dimethylamides) facilitated unambiguous assignments.

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