Tetrahedron. Vol. 31, pp. 2621 to 2624. Pergamon Press 1975. Printed in Great Britain

CONFORMATIONAL EFFECTS IN COMPOUNDS WITH 6-MEMBERED RINGS—IX

CONFORMATIONAL EQUILIBRIA IN N-CHLOROPIPERIDINES

K. W. BALDRY and M. J. T. ROBINSON*
The Dyson Perrins Laboratory, South Parks Road, Oxford

(*Received in UK 7 March 1975; Accepted for publication 6 May 1975*)

Abstract—Nitrogen inversion equilibria in the anancomeric piperidines **3–6**, **8** and **9** have been studied by variable temperature ^{1}H NMR in order to determine free energy differences $\Delta G^0_{e\rightarrow a}$ for one class of N-substituted piperidines by an unequivocal method, i.e. direct integration of separate NMR signals for conformers whose interconversion is slow on the NMR timescale at an easily accessible temperature. Using **6** as a model $\Delta G^0_{e\rightarrow a}$ (N-chloropiperidine) has been found to be $5{\cdot}3 \pm 0{\cdot}1$ kJ mol^{-1} at 193 K; similarly a study of **10** leads to $\Delta G^0_{e\rightarrow a}$ (N-chloromorpholine) = $4{\cdot}2 \pm 0{\cdot}1$ kJ mol^{-1} at 203 K.

Conformational equilibria in piperidine derivatives have been studied extensively at a qualitative or semi-quantitative level. Quantitative studies, however, have been much more limited in scope and often discordant.[1] Because piperidine is so important, both as the closest heterocyclic analogue of cyclohexane and as the parent of many biologically active compounds, it is desirable to have reliable data for conformational equilibria in simple derivatives.

Conformational equilibria are more complex in piperidine than in cyclohexane derivatives because there can be inversion at nitrogen as well as inversion of the ring. A C-monosubstituted piperidine has *four* chair conformers; it is usual for ring inversion to be much slower than nitrogen inversion or intermolecular proton exchange for N-H and a full analysis of such a system presents considerable difficulties. An N-substituted piperidine (**1**) has two chair conformers† like the cyclohexane **2** but the relative rates of ring and of nitrogen inversion are extremely sensitive to the electronic character of the substituent.

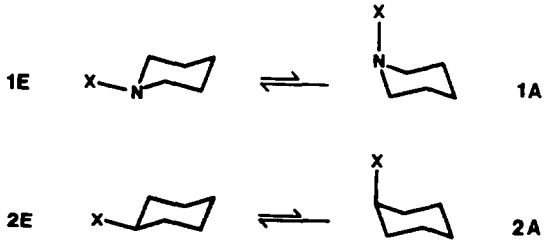


Fig. 1. Equilibria between chair conformers of an *N*-substituted piperidine (**1**) and a monosubstituted cyclohexane (**2**).

In general, however, we must expect inversion at nitrogen to be too fast to allow the use of stereoisomeric model compounds such as are required for many methods used to study derivatives of cyclohexane.[2]

The degree of similarity between the equilibria $1E \rightleftharpoons 1A$ and $2E \rightleftharpoons 2A$ will depend very much upon whether X is unsaturated and therefore able to interact with the unshared pair on the nitrogen in **1** or not. Even when X is a "saturated" substituent such as Me, Cl, OAc or NH_2 the equilibrium may be expected to differ from equilibrium (**2**) as a result of one or more of the following factors, among others:

(a) Bond lengths[3] are shorter for C–N than for C–C bonds;

(b) Bond angles[3] tned to be smaller at nitrogen than at carbon;

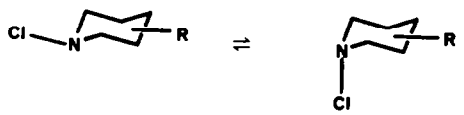
(c) The bending vibration that leads tc inversion at nitrogen, commonly the most effective means of relieving syn-1,3-diaxial repulsions, must be less stiff for *large* displacements than the analogous bending vibration centered at carbon, for which no inversion of this type is possible,[4] but for *small* distortions the force constants are not well determined for nitrogen.

Factors (a) and (b), by bringing the group X closer to the syn-axial-3- and -5-hydrogen atoms in **1A**, will usually increase the strain energy in **1A** compared with **2A**. There is no obvious reason why the third factor should be dominant as was implied when it was originally proposed[4a] as an explanation for a very low value of $\Delta G^0_{e\rightarrow a}$ (**1**; X = Me) = 2·72 kJ mol^{-1} (derived from electric dipole moment studies),[4b] that is *not* supported by a more recent result.[1] The latter (11·3 kJ mol^{-1}) indicates that $\Delta G^0_{e\rightarrow a}$ for **1**(X = Me) is not less than for **2**(X = Me) (7·1 kJ mol^{-1})[5], a conclusion confirmed qualitatively by studies of H[6] and ^{13}C[6,7] NMR chemical shifts. In this paper we consider a class of compounds, N-chloropiperidines, that can be studied by an unambiguous quantitative method, NMR integration on "frozen" equilibria. In later papers based on work in progress we will cover more common substituents for which there has been (a) conflicting results in the past (N–H,[6] N–Me,[6] N-Alkyl[8]), (b) little data (e.g. 3- and 4-OH[9]), and (c) no quantitative results at all (N-OH[8], C-alkyl[8]).

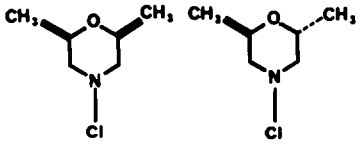
The only reported example of the use of NMR integration at low temperatures on piperidines appears to be for *cis*- and *trans*-2,6-dimethyl-N-fluoropiperidine,[10] in which vicinal fluorine-methyl interactions complicate the interpretation; unhindered N-fluoropiperidines have not been prepared. Both ring and nitrogen inversion in **1** must be slow at a temperature at which $|\log K| < 2$ and preferably < 1 to allow signals to be integrated with reasonable accuracy; chlorine seemed a suitable N-substituent. The nitrogen and ring inversion barriers in **1**(X = Cl) are 42·1 kJ mol^{-1} (empirical calculation)[11] and

†We will assume that twist conformers can be neglected, by analogy with cyclohexane, for small substituents.

56·5 kJ mol^{-1} (measured)[12] respectively. The NMR spectrum of 3,3,5,5-d_4-1(X = Cl) at low temperatures, however, showed no bands attributable to a minor conformer,[12] and the major conformer was not identified with certainty. In contrast the IR spectrum of 1(X = Cl) has been reported to show bands at 512 and 566 cm^{-1} assigned to N-Cl stretching vibrations in 1E and 1A (X = Cl).[13] We accordingly decided to study a set of C-Me derivatives of N-chloropiperidine **3–9** and a pair of N-chloromorpholines **10** and **11**. In **3–5** it was expected that



3: R = 2-Me
4: R = *cis*-2,6-Me_2
5: R = 4-2, c-4, c-6-Me_3
6: R = *cis*-3-5-Me_2
7: R = 3,3-Me_2
8: R = 4-Me
9: R = *trans*-2-Me, 5-Et



10 **11**

the chemical shifts of the 2- and 6-Me groups would be sensitive to the axial or equatorial orientation of the N-chlorine and the relatively intense sharp signals of these groups would therefore be a convenient way of detecting and estimating the minor conformer. Vicinal Me–Cl interactions, however, would be expected to change the equilibrium relative to 1(X = Cl). The anancomeric compound **6** is a better model than **3–5** for 1(X = Cl) and the methyl groups help to narrow the bands for the C-2(6)-methylene groups by eliminating many small couplings and virtual couplings. The *syn*-1,3-diaxial Me–Cl interactions in **7A** will greatly destabilise this conformer and the low temperature spectrum should serve to characterise 2- and 6-H chemical shifts in conformers with chlorine equatorial in **6**, **8** and **9**. The morpholine **10** provides a morpholine analogue of **6** with a relatively simple spectrum in which all the chemical shifts can be determined, while **11** at low temperature provides chemical shifts needed for a correlation between N-chloro- and N-methylpiperidines and -morpholines, used to determine the configurations of the major and minor conformers of **6** and **10**.

N-Chloropiperidines and analogues compounds have been prepared from the appropriate secondary amine and a neutral halogenating agent such as sodium hypochlorite[14] or N-chlorosuccinimide.[12] Earlier workers have differed about the need to purify the products but in our experience the purest samples, as judged by the absence of unassignable and irreproducible minor NMR absorption bands, are obtained directly as solutions in methylene chloride with all the operations carried out rapidly at 0°. A dilute (0·1–0·2M) solution of the amine in a phosphate buffer was treated with sodium hypochlorite solution in the presence of methylene chloride to extract the N-chloroamine as soon as it was formed. Such solutions were dried rapidly and immediately used for NMR studies.

EXPERIMENTAL

Preparation of N-*chloropiperidines.* 2- and 4-Methyl-, *cis*-2,6- and 3,3-dimethyl-piperidine were commercial samples purified by distillation. *cis*-3,5-Dimethylpiperidine, prepared by a modification[6] of the published procedure, was purified by repeated crystallisation of the hydrochloride from methanol-ether (*trans* isomer <0·5%). r-2, c-4, c-6-Trimethylpiperidine[16] was purified by crystallisation of the hydrochloride from 5M HCl. *cis*- and *trans*-2,6-Dimethylmorpholine and *trans*-2-methyl-5-ethylpiperidine were isolated from commercial *cis*-*trans* mixtures by fractional crystallisation of picrates (**10** and **11**) and hydrochlorides (**9**).

In a typical preparation commercial sodium hypochlorite solution (10–14% available chlorine, 2 ml) was added to a rapidly stirred mixture of an amine (2 mmole) in 0·5M K_2HOP_4 (10 ml) and CH_2Cl_2 (containing 2% TMS, 2 ml) at 0°. After stirring for one minute the methylene chloride layer was pipetted onto $MgSO_4$ (*ca.* 0·2 g), with which it was shaken (0·5 min) before being filtered through fresh $MgSO_4$ into an NMR sample tube, all operations being carried out at 0°. The samples were stored at −20° before spectra were measured, usually within a few hours although decomposition products were commonly not detectable within a day or two.

Measurement of NMR spectra. All spectra were run on a Perkin Elmer R32 spectrometer using TMS as an internal standard and lock. Accurate chemical shifts for the 2(6)-axial protons in **6** were obtained on expanded spectra (9 mm Hz^{-1}) calibrated with a frequency counter. Integration of selected bands was carried out by cutting and weighing or by numerical integration (Simpson's Rule).

RESULTS AND DISCUSSION

All the compounds studied showed NMR spectral changes consistent with coalescence phenomena within the temperature range 0° to −60° and new absorption bands attributable to minor conformers were fully developed below about −50 to −70°, 2- and 6-Me groups tending to raise the barriers to inversion at nitrogen. The bands attributed to the minor isomers diminished in relative intensity as the temperature was lowered still further, as would be expected. No attempt was made to determine barriers to inversion at nitrogen accurately. Band areas were estimated by cutting and weighing or by numerical integration because the bands due to minor conformers were always overlapping the edges of absorption bands of the major conformers. Because these methods involve estimating a sloping baseline we also determined the equilibrium in the most important compound, **6**, from the chemical shifts of the C-2(6)-axial protons in **6A** and **6E**, derived by a rather long and therefore uncertain extrapolation from measurements at −70 to −100°, and the observed weighted average chemical shift at −20, 0 and 20° (Table 1 and Fig. 2). The free energy differences estimated by the two methods, bearing in mind that the entropy difference should be small, are in good agreement.

The pairs of conformers in **3–6** and **8–10** were distinguished by differences in chemical shifts and coupling constants. In all instances the differences show that the major conformers have equatorial chlorine. The *minor* conformers have the C-2 and C-6 axial protons at *lower* field (Table 1) and have smaller values of δ_{ae} for the C-2 or C-6 methylene groups; these are the expected changes for moving an N-substituent from equatorial to axial.[17] In the morpholine **10** the axial C-3 and C-5 are at lower field (by 0·36 ppm) in the minor conformer and a qualitatively similar effect can be inferred for **6A** from the relative intensities of the signals of the C-2(6)-protons, although the absorpition of the C-3(5)- protons in **6A** cannot be directly observed. Such deshielding of axial protons by a syn-axial electronegative atom is well known.[18] The values of δ_{ae} for the C-2 and C-6 geminal protons in **7** and in **11**, which presumably must have equatorial N-chlorine, at −80° and in the major, but *not*

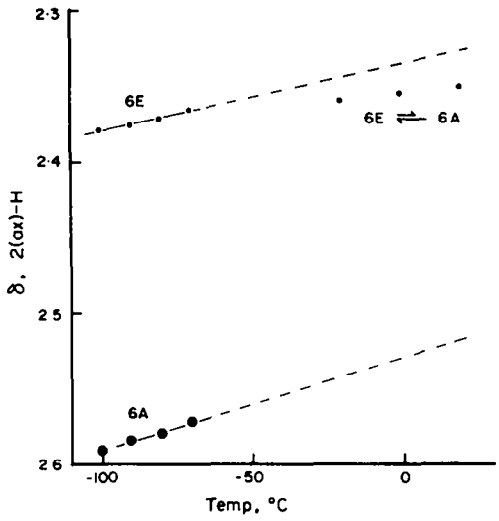


Fig. 2. Temperature dependence of the chemical shift, relative to internal TMS, of the 2(ax)-H protons in **6** (1M in CH_2Cl_2).

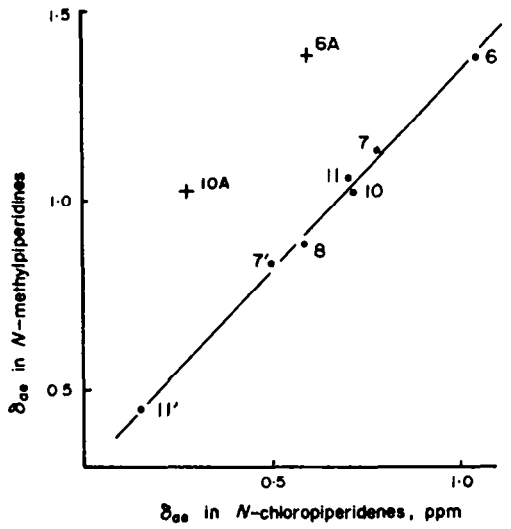


Fig. 3. Correlation between differences in chemical shifts, δ_{aa}, for geminal protons in N-CH_2 groups in N-chloro-piperidines (**6–8**) and -morpholines (**10, 11**) and the analogous N-methyl compounds[14,23]: ●, equatorial N–Cl; +, axial N–Cl (excluded from the correlation). Slope 1·06, intercept 0·28, r = 0·997. (7: 2-CH_2; 7′: 6-CH_2; 11: CH_2 adjacent to eq-C-Me; 11′: CH_2 adjacent to ax-C-Me). *N.B.* The temperatures at which chemical shifts for related pairs of N–Cl and N–Me compounds were measured were not always the same but it is known that ^{1}H chemical shifts for N-methylpiperidines are relatively insensitive to temperature.[14]

the minor, conformers of **6**, **8** and **10** correlate well with values of δ_{ae} for the N-methyl analogues (see Fig. 3) in which equatorial N-methyl is strongly preferred,[1] and it must be concluded that the chemical shifts are consistent only with the major conformers all having equatorial N-chlorine.

Table 1. Chemical shifts (δ)[a], relative to internal $SiMe_4$ (2%) for protons attached to ring positions 2–6 and side chains R in *N*-chloro-piperidines (**3–9**) and -morpholines[b] (**10, 11**) (1M in CH_2Cl_2)

Compound (Temp. K)[c]	2 ax	2 eq	6 ax	6 eq	3 ax	3 eq	5 ax	5 eq	4 ax	4 eq	R
3E (223)	~2·9	—	~2·7	3·52	1·15					1·85[d]	1·22 (2-Me)
3A (223)											1·13 (2-Me)
4E (223)	2·82	—	2·82	—	1·2					1·85[d]	1·26 (2,6-Me_2)
4A (223)	3·07[e]	—	3·07[e]	—							1·17 (2,6-Me_2)
5E (223)	2·86	—	2·86	—		1·73		1·73		—	0·86 (4-Me)
											1·26 (2,6-Me_2)
5A (223)	3·08[e]	—	3·08[e]	—						—	1·18 (2,6-Me_2)
6E (173)	2·38	3·39	2·38	3·39	~1·8	—	~1·8	—	~0·6	~1·65	0·88 (3,5-Me_2)
6A (173)	2·58	3·20	2·58	3·20		—		—			0·95 (3,5-Me_2)
7 (213)	2·57	3·08	2·66	3·45	—	—	~1·9	~1·6	~1·1	~1·3	0·90 (3-eq-Me)
											1·03 (3-ax-Me)
8E (213)	2·83	3·43	2·83	3·43	~1·2				~1·8	—	0·88 (4-Me)
8E (223)	3·05		3·25[d,e]							—	
9E (203)	~2·6[f]	—	2·59	3·54				—			1·22 (2-Me)
											0·92[f] (CH_2-Me)
											1·22 (CH_2-Me)
9A (203)		—	2·9[e]	3·4[e]				—			
10E (193)	3·74	—	3·74	—	2·62	3·34	2·62	3·34	—	—	1·17 (2,6-Me_2)
10A (193)	4·18	—	4·18	—	2·89	3·14	2·89	3·14	—	—	
11 (213)[g]	4·20[f]	—	—	4·06[f]	2·64	3·36	3·09	3·24	—	—	1·38 (2-eq-Me)
											1·11 (6-ax-Me)

[a] Where signals for particular protons in minor conformers were not observed spaces are left blank. Dashes indicate no proton at the position specified.

[b] Note that numbering begins at oxygen in morpholine.

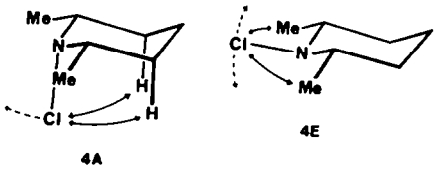
[c] Spectra were recorded at up to 8 temperatures for each compound. Data are reported for temperatures most favourable for measurement of minor conformers, or for the best resolution.

[d] Broad unresolved absorption.

[e] Absorption of minor conformer overlapped by absorption of major conformer; assignment and value of chemical shift tentative.

[f] Broad multiplet overlapping absorption in the same conformer; chemical shift not determinable with accuracy.

[g] Assignment of signals for 3- and 5-protons based on spectra at 273 K (rapid ring inversion) as well as spectra at low temperatures (slow ring inversion).



4A 4E

Fig. 4. Relatively favourable (4A) and unfavourable (4E) relief of non-bonded H–Cl and Me–Cl interactions (⇌) in the two conformers of N-chloro-*cis*-2,6-dimethylpiperidine (4). The outward bending of chlorine in 4A, which directly relieves H–Cl interactions, flattens the nitrogen atom thereby easing the M–Cl interactions (↔ omitted for clarity). In 4E bending of the chlorine is not directly effective in reducing Me–Cl interactions. Analogous effects have been observed for N-Me[1] and C-Me.[14]

Relatively few coupling constants can be determined with any precision but in all cases it is found that ^2J and ^3J values involving C-2(6) axial protons are *smaller* in the *major* conformers. This is consistent with the unshared pair on the nitrogen being in a *trans*-diaxial relationship with these protons,[17,19] i.e. the N-chlorine is equatorial. The examples (major conformer first) are: $^2J(2(6)\text{-}CH_2)$ = 10·2 and 11·8 Hz in **6**, and 10·3 and 11·0 Hz in **10**; $^3J(2a,3a)$ = 10·5 and 15 Hz in **6**, and 10·3 and 13·6 Hz in **10**; $^3J(2a,2\text{-}CH_3)$ = 6·07 and 6·51 Hz in **4**.

Using **6** as a model, $\Delta G^0_{e\to a}$ (1; X = Cl) = 5·3 kJ mol^{-1}, i.e. about 2·6 times the value for chlorocyclohexane (2; X = Cl) determined by the same method.[20] This ratio is even larger than for 1(X = Me)[1] and 2(X = Me)[6] (ratio of free energy differences ~1·65) and confirms that conformational equilibria at nitrogen in piperidines can be more strongly biased than the analogous cyclohexane systems when the substituents do not conjugate with the unshared pair. The greater ratio for chlorine than for Me can probably be ascribed largely to the greater barrier to inversion in a chloramine than in ananalogous methylamine (ratio of barriers to inversion 1·28[10]) diminishing the flexibility of the N–X bond, although differences in "normal" bond angles, also related to differences in electronegativity, may also play a part.

The free energy differences for **6**(5·3 kJ mol^{-1}) and **10** (4·15 kJ mol^{-1}) are similar. The relatively small difference may be caused by the electrostatic effect of the oxygen dipole in **10** or by differences in the puckering of the ring, resulting from the difference between C–C and C–O bond lengths, altering non-bonded interactions. Since the N–Cl group has a low electric dipole moment[21] and the nitrogen inversion equilibria in piperidine and in morpholine are very similar [22] it seems probable that the second effect is the more important.

The effect of two equatorial Me groups at C-2 and C-6 is substantial and reduces $\Delta G^0_{e\to a}$ from 5·3 kJ mol^{-1} in **6** to 2·7 kJ mol^{-1} in **4**, although a single Me group as in **3** has a small, barely significant effect. The large effect of the second Me group is presumably because the chlorine, when equatorial, cannot bend away in the plane of the ring from one methyl without bumping into the other, while bending out of the plane (roughly orthogonal to the methyl-chlorine vectors) is ineffective in reducing Me chlorine interactions (Fig. 4). Conversely the two equatorial Me groups do not strongly hinder the outward bending of axial chlorine in 4A and can move away from it by an out of plane bending that is easier than the in plane bending in 4E. A qualitatively similar difference has been found for the N–Me analogues of **4** and **6**.[1]

The results for **5**, **8** and **9** are of low accuracy because spectra of the two conformers of each compound overlap badly but within the large experimental errors agree with the results for the related compounds **4**, **6** and **3** respectively.

Table 2. Free energy differences for inversion equilibria at nitrogen in *N*-chloro-piperidines (3–6, 8) and -*cis*-2,6-dimethylmorpholine (10) (1M in CH_2Cl_2)

Compound	Temp. (K)	Signal used	Equilibrium constant (e–n)	ΔG° (kJ mol^{-1})
3	223	2-Me	0·075 ± 0·005	4·80 ± 0·15
4	223	2,6-Me_2	0·217 ± 0·005	2·74 ± 0·08
5	228	2,6-Me_2	0·224 ± 0·010	2·74 ± 0·15
6	193	3(5)-ax-H	0·037 ± 0·002	5·30 ± 0·1
	253[a]	2-ax-H	0·071 ± 0·025	5·5 ± 0·7[a]
	273[a]	2-ax-H	0·085 ± 0·030	5·5 ± 0·7[a]
	293[a]	2-ax-H	0·116 ± 0·030	5·3 ± 0·7[a]
8	223	2(6)-CH_2	0·035 ± 0·15	6 ± 1
10	203	2(6)-ax-H	0·085 ± 0·005	4·15 ± 0·10

[a] Based on chemical shifts (rapid inversion conditions) rather than peak areas (slow inversion); see text.

Acknowledgement—We thank the Science Research Council for a Research Studentship (to K.W.B.).

REFERENCES

[1] P. J. Crowley, M. J. T. Robinson and M. G. Ward, *J. Chem. Soc. Chem. Comm.* 825 (1974); and refs therein.

[2] See, e.g. E. I. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformaitional Analysis*, Chap. 2. Interscience, New York (1965).

[3] *Tables of Interatomic Distances and Configuration in Molecules and Ions* (1958) and *Supplement* (1965) Edited by L. E. Sutton, The Chemical Society, London.

[4a] R. J. Bishop, D. Dineen, R. A. Y. Jones, A. R. Katritzky, L. E. Sutton and R. J. Wyatt, *J. Chem. Soc.* (B), 493 (1967); [b] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky and K. A. F. Record, *J. Chem. Soc.* Perkin II 332 (1973).

[5] J. A. Hirsch, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 1, p. 199. Interscience, New York (1967).

[6] P. J. Crowley, M. J. T. Robinson and M. C. Ward, unpublished results.

[7] E. L. Eliel and F. W. Vierhapper, *J. Am. Chem. Soc.* **96**, 2257 (1974).

[8] M. J. T. Robinson, unpublished results.

[9] D. J. Loomes and M. J. T. Robinson, unpublished results.

[10] J. Cantecuzene and J. Leroy, *J. Am. Chem. Soc.* **93**, 5263 (1971).

[11] K. Horst and D. Leibfriz, *Tetrahedron Letters* 4297 (1970).

[12] J. B. Lambert, W. L. Oliver and B. S. Packard, *J. Am. Chem. Soc.* **93**, 933 (1971).

[13] O. S. Anisimova, Y. A. Pentin and L. G. Yudin, *Zh. Prikl. Spectrosk.* **8**, 1027 (1968), *Chem. Abstr.* **68**, 91476y (1969).

[14] G. H. Coleman, *J. Am. Chem. Soc.* **55**, 3001 (1933).

[15] H. Little and J. H. Booth, *J. Chem. Soc.* Perkin II, 1846 (1972).

[16] H. Booth, J. H. Little and J. Feeney, *Tetrahedron* **24**, 279 (1968).

[17] F. G. Riddell and J. M. Lehn, *J. Chem. Soc.* (B) 1224 (1968); and references therein.

[18] H. Booth, *Tetrahedron* **22**, 615 (1966).

[19] See, e.g. W. B. Jennings, D. R. Boyd, C. G. Watson, E. D. Becker, R. B. Bradley and D. M. Jerina, *J. Am. Chem. Soc.* **94**, 8501 (1972), and the many references to earlier work therein.

[20] F. R. Jensen, C. H. Bushweller and B. H. Beck, *Ibid.* **91**, 344 (1969).

[21] A. L. McClennan, *Tables of Experimental Dipole Moments*. Freeman, San Francisco, (1963).

[22] R. W. Baldock and A. R. Katritzky, *J. Chem. Soc.* (B) 1470 (1968).

[23] D. Wendisch, H. Reiff and R. Schubart, *Org. Mag. Res.* **4**, 431 (1972).