Experimental Test of Structural Predictions of Semiempirical Methods: Bis(1,2-dioxa-4,6-diazacycloheptano)[4′,5′,6′:1,6,5][4″,5″,6″:2,3,4]-1,2,4,5-tetraazacyclohexane, A 7:6:7-Tricyclic System Correctly Calculated by AM1 as More Stable than Its 6:6:6-Tricyclic Isomer

Alan R. Katritzky*[a], Hudson H. Luce[a], Ernst Anders[b], and John M. Sullivan[c]

Department of Chemistry, University of Florida[a],
Gainesville, Florida 32611 (USA)

Institut für Organische Chemie, Universität Erlangen-Nürnberg[b],
D-8520 Erlangen (FRG)

Department of Chemistry, Eastern Michigan University[c],
Ypsilanti, Michigan 48197 (USA)

Received April 18, 1989

Key Words: AM1 / Conformational analysis / Hexahydrotetrazine / Tetrahydrodioxadiazine

The condensation product **3a** of hydrazine sulfate, formaldehyde, and hydrogen peroxide, for which the tricyclic 7:6:7-ring structure **3a** was previously established for the solid state by X-ray analysis, exists as a mixture of conformations **3a** and **3b** in solution. AM1 calculations show the two 7:6:7-tricyclic conformers **3a** and **3b** to be of approximately equal energy, and substantially *lower* in energy than the three isomeric 6:6:6-perhydroheteroanthracene conformers **2a**, **2b**, and **2c**. By contrast, analogous MNDO calculations predicted that the perhydroanthracene analog conformers **2** should be *more* stable than **3** [$\Delta H_f(2) < \Delta H_f(3)$]. AM1 calculations of model compounds, containing various subunits of the tricyclic systems, demonstrate that three significant factors are responsible for the relative energies: a) The 1,3-lone pair repulsions in the 6:6:6 system. b) The ring strain of the central tetra-aza unit in the 7:6:7 system. c) The advantageous energetic consequences of the anomeric effect in the stable conformation of the 7:6:7 system.

Experimenteller Test der Strukturvorhersagen semiempirischer Methoden: Bis(1,2-dioxa-4,6-diazacycloheptano)[4′,5′,6′:1,6,5]-[4″,5″,6″:2,3,4]-1,2,4,5-tetraazacyclohexan: Ein 7:6:7-tricyclisches System, das von der AM1-Methode korrekt als stabiler als sein 6:6:6-tricyclisches Isomer beschrieben wird

Das aus Hydrazinsulfat, Formaldehyd und Wassserstoffperoxid entstehende tricyclische Kondensationsprodukt **3a**, dessen 7:6:7-Struktur bereits früher durch Röntgenstrukturanalyse bestimmt wurde, liegt laut NMR-spektroskopischen Untersuchungen in Lösung als Konformerengemisch aus **3a** und **3b** vor. Aus AM1-Rechnungen ergibt sich, daß die beiden 7:6:7-Strukturen **3a** und **3b** nahezu energiegleich und stabiler sind als die 6:6:6-Isomeren **2a**, **2b** und **2c**. MNDO sagt die umgekehrte Stabilität voraus [$\Delta H_f(2) < \Delta H_f(3)$]. Durch AM1-Berechnungen von Modellverbindungen, die in den tricyclischen Systemen als Untereinheiten enthalten sind, wird gezeigt, daß für die relativen Energieunterschiede drei wesentliche Einflüsse verantwortlich sind: a) Die 1,3-Wechselwirkung nichtbindender Elektronenpaare in den 6:6:6-Systemen,b) die Ringspannung der zentralen Tetraazacyclohexan-Einheit der 7:6:7-Systeme und c) die günstigen sterischen Voraussetzungen zur konformativen Stabilisierung des 7:6:7-Systems durch den anomeren Effekt.

Background

The easily synthesized crystalline reaction product of hydrazine, formaldehyde, and hydrogen peroxide proved elusive as to its correct structural assignment for sixty years. The original structure **1**, assigned in 1921[1], was modified first to **2** in 1960[2] on the basis of infra-red and molecular weight data, and finally conclusively proven to be **3** in 1981 by the X-ray studies of Dunitz and co-workers[3].

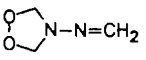
The conclusion that the compound possesses the 7:6:7 tricyclic form rather than the – intuitively more to be expected – 6:6:6 structure is of considerable theoretical interest. We have therefore made further NMR measurements to clarify the situation in solution and have examined the alternative ring systems theoretically.

Complex molecules such as the title compound are not yet accessible by ab initio methods. For the synthetically oriented chemist there remains, and will remain for the foreseeable future, the need for a reliable semiempirical method, for which the error limits are estimable. After many initial successes, certain deficiencies in the MNDO method[4] became apparent, and this finally led Dewar to develop the AM1 method. The advantages of AM1, particularly with respect to H-bonding, to nonbonding interactions, and for the complete description of cycloaddition reactions, have been convincingly documented[5]. MNDO is still highly suitable for the description of certain types of problems, e.g. of several complex lithium organics with surprising agreement with the crystallographic parameters[6a].

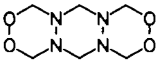
In 1979, we had collected low-temperature 300-MHz ^{1}H- and 75-MHz ^{13}C-NMR data of the title compound, and we speculated[7] on its conformational equilibria assuming that

Chem. Ber. **122** (1989) 1989–1993 © VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1989 0009–2940/89/1010–1989 $ 02.50/0

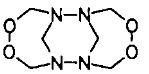
2 was the correct structure. We have now obtained 500-MHz ^1H- and 125-MHz ^{13}C-NMR data which, particularly in the case of the ^{13}C-NMR data, have shed further light on the situation by separating signals which had coincided in the spectra obtained earlier.



1



2



3

Dunitz's X-ray studies showed the geometry of **3** in the crystalline state to be centrosymmetric, with the N–C bonds labeled "a" and "a′" having different lengths, and the C–O bonds labeled "b" and "b′" also having different lengths (Figure 1). Structure **3** can also exist as another conformer of very similar geometry, having the C_2 symmetry of Figure 2 instead of the centrosymmetric (S_2) symmetry of Figure 1. These two conformations should have little enthalpy difference, since they differ only in the remote relationship of one seven-membered ring to the other. The C_2 conformation is chiral and thus possesses an entropy of mixing of $R\ln2$; however, it also possesses a 2-fold rotational axis and thus a symmetry number of 2. Hence, a symmetry-entropy contribution of $-R\ln2$ arises for the C_2 conformation[8], which cancels out that from the entropy of mixing, to leave the overall entropy difference between the two conformations (C_2 and S_2) as zero (the symmetry number of the S_2 conformation is 1). We have now shown that **3** does indeed exist in solution both in the S_2 conformation (Figure 1) and in the C_2 conformation (Figure 2).

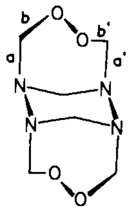


Figure 1. Compound **3**: centrosymmetric S_2 conformation **3a**

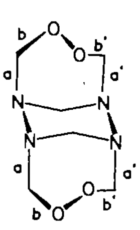


Figure 2. Compound **3**: chiral C_2 conformation **3b**

NMR Spectroscopy

Our new NMR data[9] are consistent with both of the above conformations being significantly populated in solution. In the carbon-13 NMR, each conformation should give one signal for $N-CH_2-N$ and two signals for $N-CH_2-O$ for a total of six signals. This is in agreement with the actual spectrum (Figure 3). The closely spaced $N-CH_2-N$ signals coincided in our earlier[7] lower resolution spectra.

Figure 3. ^{13}C-NMR spectrum taken at −60°C in $CDCl_3$ at 125 MHz for compound **3** (N–C–O and N–C–N region)

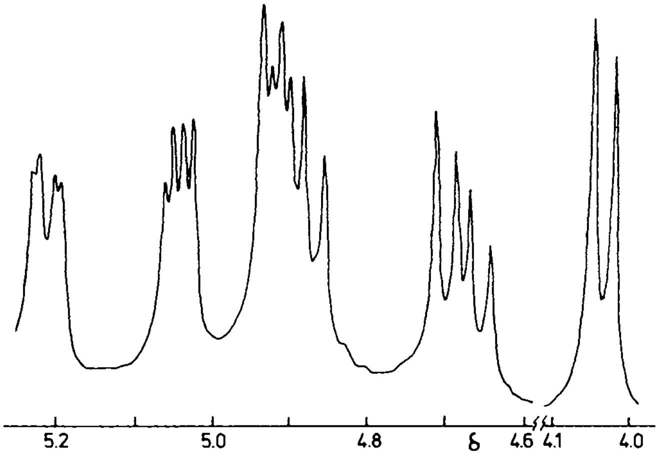


Figure 4. ^1H-NMR spectrum taken at −85°C in CD_2Cl_2 at 500 MHz for compound **3**

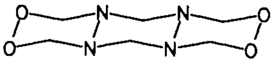
In the ^1H-NMR spectrum each conformation should give one AB quadruplet for $N-CH_2-N$ and two AB quadruplets for $N-CH_2-O$ for a total of six AB quadruplets or twenty-four signals. The spectrum obtained (Figure 4) at 500 MHz, while considerably clearer than that obtained earlier at 300 MHz, is still too complex for complete interpretation: it has at least twenty signals and is in our opinion consistent with six AB quadruplets exhibiting some overlap.

The fact that the reaction of hydrazine with H_2O_2 and formaldehyde forms structure **3** rather than **2** is interesting, since six-membered rings are generally formed preferentially to seven-membered rings. In addition, the seven-membered ring structure imposes two *syn*-1,3-diaxial ring fusions on the central hexahydrotetrazine ring. The *syn*-1,3-diaxial methyl-to-methyl interaction in cyclohexane rings was reported by Allinger[10] to be 3.7 kcal/mol, and the two CH_2-O groups of each seven-membered ring should have about the same unfavorable interaction.

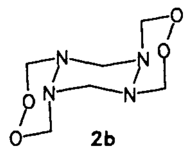
On the other hand, as Dunitz points out[3], the X-ray studies show the O–O torsional angle in **3** to be 100°, a more favorable angle than the 60° angle which the six-membered chair of structure **2** would impose. Molecular orbital calculations on hydrogen peroxide[11] predict that the 100° O–O torsional angle is about 3 kcal/mol more favorable than the 60°C angle. We have now attempted to resolve this question by calculations of optimized geometries and energies using an appropriate semiempirical technique.

Calculations

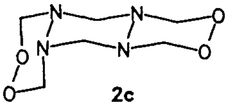
The geometries of conformers **2a**, **2b**, **2c**, **3a**, and **3b** were optimized using the MNDO parameters and formalism[4] in the MOPAC standard program package[12]. Since each of these molecules has significant symmetry, it was possible in each case to do a symmetry-constrained optimization.



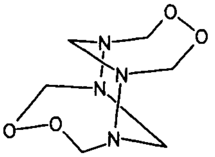
2a



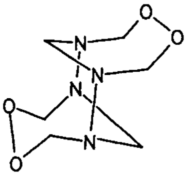
2b



2c



3a



3b

The results of the optimizations are given in Table 1. The MNDO calculations predict that of the three 6:6:6 tricyclic conformers **2a** is the most thermodynamically stable structure by 1.3 kcal over **2c** or 4.2 kcal/mol over **2b**, and that the energies of the S_2 and C_2 structures **3a** and **3b** are nearly equal and about 12 kcal less stable than **2a**. The MNDO calculations thus do not correctly predict the product obtained. However, the optimizations were repeated using the newer AM1 parameterization[5a] in MOPAC, with results (Table 1) that correctly predict that the S_2 (Figure 5) conformer **3a** and the C_2 conformer **3b**, have almost equal energy and that **2a–c** (e.g. Figure 6) are between 14 and 28 kcal *more* energetic than these. That is in excellent accord with the experimental data: not only is **3** the product formed but also in solution, it exists as equal amounts of conformers **3a** and **3b** (the ΔH_f difference of 0.06 kcal/mol calculated compares to K_{eq} of 1.02 at 298 K, assuming that the change in entropy, S, is equal to zero).

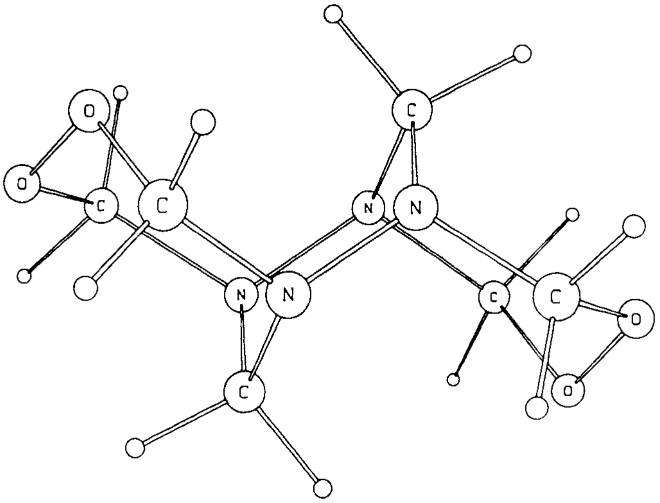


Figure 5. AM1 structure of **3a**

The calculations were repeated for molecules **2a–c** and **3a–b** using the VAMP package[13], a vectorized version of AMPAC[14], with similar results. The MNDO results do not correctly model the anomeric effect. Decreasing 1,3-lone pair interactions should give rise to increased stability[15], i.e., the order of stability is expected to be **2b** < **2c** < **2a**; MNDO predicts just the opposite. The AM1 parameterization cor-

Table 1. Calculated geometric parameters and energies ΔH_f [kcal/mol] for compounds **2a–c**, **3a**, and **3b**, and comparison with experimental data for **3a**

Parameter	Compound										
	3a			3b		2a		2b		2c	
Bond Length [Å]	X-ray[a]	AM1	MNDO	AM1	MNDO	AM1	MNDO	AM1	MNDO	AM1	MNDO
N - N	1.444	1.403	1.390	1.403	1.389	1.414	1.398	1.406	1.389	1.401	1.384
O - O	1.472	1.287	1.288	1.287	1.288	1.293	1.289	1.293	1.290	1.294	1.290
N - C(2)	1.468	1.492	1.494	1.493	1.494	1.488	1.488	1.494	1.485	1.482	1.480
N - C(1)	1.459	1.472	1.494	1.471	1.496	1.477	1.501	1.482	1.499	1.477	1.491
	1.434	1.472	1.494	1.472	1.497	1.477	1.501	1.474	1.495	1.491	1.496
C(1) - O	1.428	1.457	1.432	1.459	1.432	1.455	1.419	1.458	1.423	1.455	1.425
	1.445	1.459	1.433	1.460	1.432	1.455	1.419	1.458	1.423	1.456	1.425
Bond Angle [°]											
N-C(2)-N	113.8	115.6	109.4	115.8	109.6	110.8	109.0	112.3	111.1	115.8	109.5
N-N-C(2)	112.6	113.2	114.4	113.9	114.5	111.8	112.1	112.6	114.3	112.9	112.3
N-N-C(1)	111.6	112.7	112.7	112.7	112.6	110.7	111.2	111.8	110.0	114.3	115.6
N-C(1)-O	111.5	113.8	112.4	115.6	112.9	109.5	107.9	110.1	108.1	111.3	106.8
C(1)-O-O	109.2	112.0	116.3	114.2	117.3	112.8	114.1	112.0	113.6	112.3	114.8
Energy											
ΔH_f [kcal/mol]		69.41	49.48	69.33	49.42	97.07	37.90	92.77	42.14	83.61	39.21

[a] X-ray diffraction data: S. N. Whittleton, P. Seiler, J. D. Dunitz, *Helv. Chim. Acta* **64** (1981) 2614.

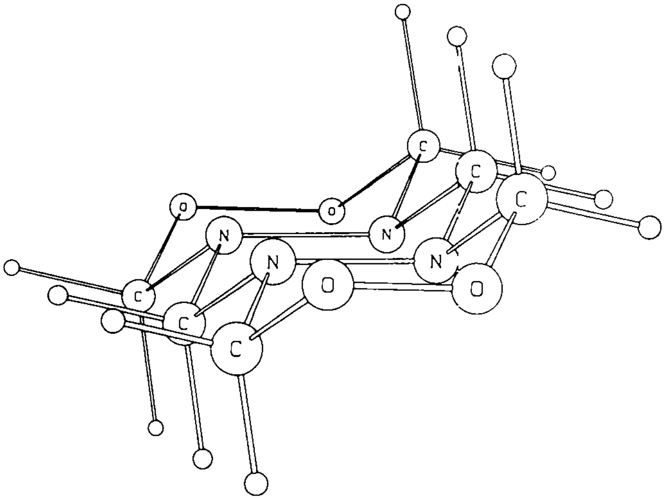


Figure 6. AM1 structure of **2a**

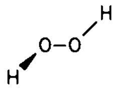
Table 2. Calculated and experimental energies[a] for analogs **4**–**7**

Compound	ΔH_f [kcal/mol] AM1	MNDO	Obsd.
4	−35.3	−38.2	−32.5
5	−27.0	−28.1	−30.0
6	13.0	14.2	22.8
7	21.6	14.1	22

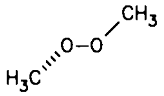
[a] Data from ref.[14].

rectly predicts **2a** to have the highest energy. This result can be interpreted as follows: the O/N lone pair repulsion is avoided, the O/C/N moieties are stabilized due to the influence of "negative hyperconjugation"[16].

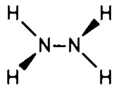
Since the predictions from AM1 and MNDO were so different, in both VAMP and MOPAC, with AM1 predicting the correct ordering of relative stabilities of conformers **2a**–**c**, but MNDO not doing so, an analysis of the energies calculated was performed. This was done by examining the energies and optimized geometries of smaller molecules. Results for four of these, hydrogen peroxide (**4**), dimethyl peroxide (**5**), hydrazine (**6**), and 1,2-dimethylhydrazine (**7**), were published by Dewar et al.[5a] and are summarized in Table 2. 1,2-Diaza-4,5-dioxacyclohexane (**8**), 1,3-diaza-5,6-dioxacycloheptane (**9**), and 1,2,4,5-tetraazacyclohexane (**10**) were calculated by us, and the resulting energies and selected geometrical parameters are given in Table 3.



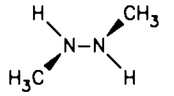
4



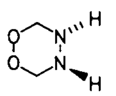
5



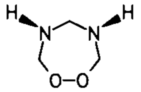
6



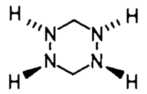
7



8



9



10

Structures **4**–**7** are simplified subunits of **2** and **3** reflecting the influence of 1,2-lone pair interactions, which influence the conformational situation present in the larger molecules. Analysis of these results reveals that AM1 is a better model for **4** and **7** than MNDO, whereas **5** and **6** are described with similar results[17]. However, the effects of 1,2-lone pair interactions are seen to be too small to explain the differences between AM1 and MNDO for the heat of formation of **3a**, even though the (correct) tendency for AM1 to give a higher energy for **3** relative to MNDO is observed.

The ring systems **8**, **9**, and **10** have been optimized (selected geometrical parameters and energies are given in Table 3) and are found to be quite similar to the analogous

Table 3. Calculated energies and selected geometric parameters for analogs **8**–**10**

Parameter Bond Length [Å]	AM1	MNDO	Bond Angle [°]	AM1	MNDO	Total ΔH_f	[kcal/mol]
Compound **8**							
N–N	1.378	1.397	N–N–C	116.3	113.1	AM1:	17.61
O–O	1.289	1.291	N–C–O	114.5	108.4	MNDO:	4.22
N–C	1.474	1.490	C–O–O	112.7	114.1		
C–O	1.463	1.423					
C–O	1.463	1.421					
Compound **9**							
N–C(2)	1.438	1.462	N–C(1)–N	118.9	115.0	AM1:	−11.55
N–C(1)	1.459	1.468	C(2)–N–C(1)	116.5	122.3	MNDO:	−13.05
C(2)–O	1.463	1.429		115.1	120.1		
	1.466	1.431	N–C(2)–O	117.3	114.5		
O–O	1.238	1.287		113.6	111.6		
			C(2)–O–O	114.6	116.3		
				111.4	114.5		
Compound **10**							
N–N	1.378	1.380	N–C(2)–N	118.4	115.9	AM1:	56.82
N–C(2)	1.483	1.483	N–N–C(2)	116.0	117.6	MNDO:	48.14

subunits in **2** and **3**. The energies from AM1 are always more positive in these cases. The largest energy difference between AM1 and MNDO is found in the case of 1,2-diaza-4,5-dioxacyclohexane (**8**) (AM1: 17.61 kcal/mol, MNDO: 4.22 kcal/mol, for a difference of 13.39 kcal/mol). The structures obtained from both MNDO and AM1 show that the AM1 structure is considerably more distorted to reduce the 1,3-lone pair interactions. In the case of the 6:6:6 systems, the differences in energies seen between AM1 and MNDO arise from the contribution of this 1,2-diaza-4,5-dioxa subunit, and to a lesser extent, from the 1,2,4,5-tetraazacyclohexane subunit. AM1 and MNDO give similar energies for the seven-membered ring system **9**, so the major contribution to the energy difference between systems **2** and **3** is ascribed to the 1,3-lone pair interactions in the central ring, modeled by 1,2,4,5-tetraazacyclohexane (**10**). Steric effects in the 7:6:7 systems are thought to cause further energy differences, since certain bond angles in **3** [N – C(2) – N: 115.8°, C(1) – N – C(2): 110.6°] are seen to vary significantly from those in the analogous subunit **9** [N – C(1) – N: 118.9°, C(1) – N – C(2): 116.5°] and could give rise to enhanced ring strain and lone pair interactions in **3a**. This effect is underestimated by MNDO.

Conclusions

Our NMR investigations agree with the 7:6:7-ring structure obtained by X-ray diffraction studies, and signals which previously coincided are now resolved. The NMR results show that the two conformers, of S_2 (**3a**) and of C_2 symmetry (**3b**) are present in solution in equal amounts. The semiempirical MO calculations, performed with both MNDO and AM1 parameters using both VAMP and MOPAC program packages, show that these conformers (**3a** and **3b**) are of nearly equal energy. Only AM1 results in **3** being more stable than **2** and agrees with **3** and not **2** being formed in the synthesis. Energy trends amongst analogous molecules which represent smaller subunits of **2** and **3** are also examined. This analysis shows that the AM1 parameterization gives a better description of ring systems with significant 1,3-lone pair interactions, such as **2a – c**, **8**, and **10**. This 1,3-lone pair interaction is greatest in **2a** in the 6:6:6 systems, and is largely not seen in the 7:6:7 systems; it gives an explanation for the order of stabilities observed in the AM1 calculations. The interaction is not seen in the MNDO results. The 1,2-lone pair interaction studied in molecules **4 – 7** is seen to be of minor importance. However, ring strain contributions are thought to play a limited role in determining the order of stabilities observed, with the parameterization in AM1 being more accurate in this regard than that for MNDO.

We have reported here comparable investigations, using both the MNDO and AM1 methods, of molecules with N – N and O – O bonds in a condensed polycyclic heterocycle, and in analogous fragment molecules. Such studies have not to the best of our knowledge previously been carried out, although similar systems are of biological importance. In these new areas, we have based our assessment of the accuracy of the calculations on the experimental X-ray and NMR results.

This work clearly shows that for saturated O- and N-heterocycles, and particularly for rings containing several O and/or N-atoms, the AM1 is superior to the MNDO method which leads to false predictions. The extent of the 1,3-interactions of nonbonding electron pairs, and the influence of the anomeric effect, indicated by the AM1 method are surprisingly large, but reflect the experimental findings.

We thank *NATO* for a grant for partial support of this work.

CAS Registry Numbers

2: 262-38-4 / **3**: 81286-97-7 / **8**: 120926-89-8 / **9**: 120926-90-1 / **10**: 54226-33-4

---

[1] C. von Girsewald, H. Siegens, *Chem. Ber.* **54** (1921) 492.

[2] E. Schmitz, *Liebigs Ann. Chem.* **635** (1960) 73.

[3] S. N. Whittleton, P. Seiler, J. D. Dunitz, *Helv. Chim. Acta* **64** (1981) 2614.

[4] M. J. S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **99** (1977) 4899.

[5] [5a] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **107** (1985) 3902. – [5b] M. J. S. Dewar, S. Olivella, J. P. Stewart, *J. Am. Chem. Soc.* **108** (1986) 5771.

[6] [6a] R. Hacker, P. v. R. Schleyer, *J. Organomet. Chem.* **316** (1986) C4. – [6b] P. v. R. Schleyer, R. Hacker, H. Dietrich, W. Mahdi, *J. Chem. Soc., Chem. Commun.* **1985**, 622.

[7] A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, J. M. Sullivan, R. B. Finzel, *J. Chem. Soc., Perkin Trans. 2*, **1979**, 1133.

[8] E. L. Eliel, *Stereochemistry of Carbon Compounds*, p. 215, McGraw-Hill, New York, 1962.

[9] NMR spectra were obtained on a Bruker WM 500 instrument, courtesy of Sunney Chan and W. R. Croasum, Southern California Regional NMR Facility, supported by NSF Grant No. CHE 79-16324.

[10] N. L. Allinger, M. A. Miller, *J. Am. Chem. Soc.* **83** (1961) 2145.

[11] [11a] L. Radom, W. J. Hehre, J. A. Pople, *J. Am. Chem. Soc.* **94** (1972) 2371. – [11b] R. A. Bair, W. A. Goddard, *J. Am. Chem. Soc.* **104** (1982) 2719.

[12] MOPAC is available from the Quantum Chemistry Program Exchange at the University of Indiana, Bloomington, Indiana, 47014, USA.

[13] VAMP (T. Clark, unpublished program; Universität Erlangen-Nürnberg) is a vectorized version of AMPAC 1.0 updated to MOPAC 4.0 for the CONVEX C-Series computer.

[14] AMPAC: J. J. P. Stewart, *QCPE* **6** (1986) 506.

[15] [15a] A. J. Kirby, *Pure Appl. Chem.* **59** (1987) 1605. – [15b] E. Anders, F. Markus, H. Meske, J. Tropsch, G. Mass, *Chem. Ber.* **120** (1987) 735. – [15c] P. Deslongchamps in *Stereoelectronic Effects in Organic Chemistry* (J. E. Baldwin, Ed.), *Organic Chemistry Series*, vol. 1, Pergamon Press, Oxford, UK, 1983.

[16] P. v. R. Schleyer, A. Kos, *Tetrahedron* **39** (1983) 1141.

[17] Hydrazine is still a problem for both methods.

[115/89]