Stereochemistry of Aldehyde Dimethylhydrazone Anions

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Summary The structures of the anions formed by deprotonation of acetaldehyde dimethylhydrazone (DMH), propionaldehyde DMH, phenylacetaldehyde DMH, and trimethylsilylacetaldehyde DMH have been determined by ^1H nuclear magnetic resonance spectroscopy, and limits for rotational barriers in these aza-allyl anions have been calculated.

STABILIZED carbanions formed by deprotonation of carbonyl derivatives have found widespread use in organic synthesis. Recently anions of dimethylhydrazones (DMH) prepared from aldehydes and ketones have been shown to be useful intermediates in the synthesis of various carbonyl compounds with both regio- and stereo-selectivity.[1] Related chiral anions have also been used for asymmetric syntheses of chiral aldehydes.[2] We report that anions of aldehyde DMH's are formed with substantial stereoselectivity and that the resulting diastereomeric anions do not equilibrate under conditions typical for alkylation or acylation of enolate anions. Our results show that in at least one case the stereoselectivity of the deprotonation step can be controlled. These results may be related to the observed stereoselectivity in reactions of DMH anions and disclose a previously unreported feature of asymmetric alkylation reactions in related systems.

The aldehyde DMH's (**1a**—**d**) were deprotonated to form the anions (**2a**—**d**) (equation 1) by two methods. In method (A), the DMH was treated with 1·2 equiv. of lithium

$$\underset{(\mathbf{1})}{RCH_2CH{=}N{-}NMe_2} \longrightarrow \underset{(\mathbf{2})}{RCH{=}CH{-}\bar{N}{-}NMe_2\ Li^+} \qquad (1)$$

a; R = H **c**; R = Ph

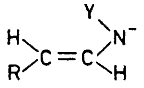
b; R = Me **d**; R = Me_3Si

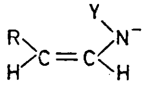
di-isopropylamide (LDA) in tetrahydrofuran (THF)–hexane in a procedure similar to that previously described[1a] to give a suspension of the anions (**2a**—**d**) (**2d** appeared to be colloidal). Addition of 2·0 equiv. of hexamethylphosphoramide (HMPA) at −78 °C followed by warming gave solutions of these anions. Alternatively, anion solutions could be obtained in method (B) by adding HMPA at −78 °C before addition of the DMH in a procedure otherwise identical to method (A).

Solutions of the anions (**2a**, **c**, and **d**) were stable at room temperature under nitrogen for several hours but solutions of (**2b**) in THF containing HMPA decomposed rapidly (n.m.r.) at 16 °C to form unknown products. However, the anion (**2b**) was stable for at least 30 min at −12 °C or below.

Because of interference from solvent protons, we were only able to observe the formyl proton signal for the anions (**2a**—**d**) and the benzyl and phenyl protons for the anion (**2c**). In every case, the formyl proton signal indicated the presence of more than one stereoisomer. Our spectral and chemical results suggest that C(1)–C(2) bond rotation is slow and that C–N bond rotation is also slow on the n.m.r. time scale (*vide infra*), and show the presence of significant amounts of more than one of the low-energy stereoisomers of (**2**) shown (Y = NMe_2).

The n.m.r. spectrum of (**2a**) prepared by either method (A) or (B) consists of two sets of doublets of doublets for the formyl proton in a ratio of *ca.* 8 : 1. The larger set of peaks at δ 6·6 has the expected coupling constants, J_{cis} 7·9 Hz, J_{trans} 13·8 Hz; the smaller set of peaks at δ 6·9 has similar coupling constants of *ca.* 8 and 15 Hz. We have assigned the (*Z*)-structure to the major (**2a**) stereoisomer for two reasons. First, both theory† and experimental results[3] on similar systems suggest that the (*Z*) isomer should be lower in energy than the (*E*) stereoisomer. Second, treatment of (**2a**) with chlorotrimethylsilane gives two isomers of (**1d**) in a ratio of *ca.* 7·5 : 1 (n.m.r.) which, either on standing or on pyrolysis in g.l.c., are converted into what was initially the minor isomer. This isomerization and the n.m.r. spectra‡ of the two products suggest that the (*Z*) isomer of (**1d**) predominated initially.


(*E,Z*)-(2)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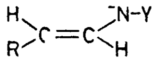
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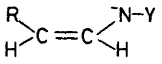
(*Z,E*)-(2)

The n.m.r. spectrum of (**2b**) generated by method (A) at −12 °C contains broad doublets at δ 6·2 (*J* 12·5 Hz) and at δ 6·6 (*J* 7·7 Hz) with relative areas of 2·9 : 1·0. Some minor peaks are also present in this region. Assuming that the stereochemistry about the C–N bond is predominantly (*Z*) as in (**2a**), this spectrum indicates that (**2b**) is formed as a mixture of (*E,Z*)-(**2b**) (major) and (*Z,Z*)-(**2b**) (minor) stereoisomers. When (**2b**) was formed using method (B) at −33 (±5) °C, a mixture of (*E,Z*)- and (*Z,Z*)-(**2b**) in a ratio of 1·0 : 2·0 was formed within 10 min. The spectra of these mixtures did not change after 1 h at −33 °C.§

The formyl proton signals in the ^{1}H n.m.r. spectra of both (**2c**) and (**2d**) consist of two doublets with *trans* coupling constants [(**2c**): δ 7·3 (*J* 12·1 Hz) and 8·0 (*J* 13 Hz), ratio 7 : 1; (**2d**): δ 6·4 (*J* 15·6 Hz) and 7·2 (*J* 16·4 Hz), ratio 4 : 1]. As in (**2a**), the larger of the two signals in each case is upfield and we have, for the reasons discussed above, assigned the (*E,Z*)-structure to the major component and the (*E,E*)-structure to the minor component of these stereoisomeric mixtures. The Table summarizes these results.

TABLE. Structures of DMH anions (2) at 30—35 °C

Compound	Method[a]	% Composition of isomers[b] (*E, Z*)	(*Z, Z*)	(*E, E*)	(*Z, E*)
(**2a**)	A	89 (*Z*)		11 (*E*)	
(**2b**)[c,d]	A	74	26	0	0
(**2b**)[d,e]	B	33	67	0	0
(**2c**)	A or B	87	0	13	0
(**2d**)	A or B	81	0	19	0

[a] See text for description of methods. [b] Estimated errors are ±5%. [c] −12 ± 5 °C. [d] Estimated errors are ±10%. [e] −33 ±5 °C.

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† A qualitative extension of the arguments presented by Epiotis (N. D. Epiotis, *J. Amer. Chem. Soc.*, 1973, **95**, 3087; N. D. Epiotis and R. L. Yates, *ibid.*, 1976, **98**, 461) for 1,2-difluoroethene leads to the prediction that the (*Z*)-(**2a**) isomer will be favoured over the (*E*)-(**2a**) isomer. This line of reasoning has been used to rationalize results in similar systems (refs. 3a and b).

‡ The n.m.r. spectrum of the initial mixture of (**1d**) contains a doublet for the methylene peaks of the major isomer which is 0·3 p.p.m. downfield from that of the minor isomer. The α-proton signals in the n.m.r. spectrum of the (*Z*) isomers of related systems occur downfield from those of the (*E*) isomers (ref. 3).

§ The variation in anion isomer population observed when HMPA is added to a base solution before deprotonation was first reported by Ireland for ester enolates (R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Amer. Chem. Soc.*, 1976, **98**, 2868; R. E. Ireland and A. K. Willard, *Tetrahedron Letters*, 1975, 3975).

On the basis of these spectra and chemical data we can assign some limits to the energy barriers for rotation about the C(1)–C(2) and C–N bonds in these compounds. Since two distinct coupling constants and sharp peaks are observed for the formyl proton of (**2a**), the energy barrier for C(1)–C(2) rotation in this case must be at least 68 kJ/mol (16 kcal/mol). A similar minimum energy barrier of 77 kJ/mol (18 kcal/mol) can also be estimated for (**2b**) since spectra of (**2b**) generated by method (A) and (B) were not altered within 1 h at −12 or −33 °C. These results correspond to previous observations in other enolates.[4] The energy barrier for C–N bond rotation was somewhat higher than we expected. For the anions (**2a**, **c**, and **d**), this rotational barrier is greater than 60—63 kJ/mol (14—15 kcal/mol) since the respective n.m.r. spectra are at the slow exchange limit. The apparent difference in stereochemistry between the anions (**2a**, **c**, and **d**) and the corresponding DMH's (**1a**, **c**, and **d**) [(**1a**) and (**1c**) appear to be homogeneous (*E*)-isomers (g.l.c., n.m.r.) and (**1d**) is a mixture in which the (*E*) isomer predominates] suggests that isomerization about the C–N bond has occurred during deprotonation. If this isomerization is assumed to be due to a rotational process, an upper limit to the C–N rotational barrier of *ca.* 90 kJ/mol (22 kcal/mol) can be estimated.

Alkylations and acylations of other stabilized carbanions are known to occur readily, typically going to completion within 30 min at −78 °C with activation free energies of $<$ 58 kJ/mol (14 kcal/mol).¶ Although detailed kinetic studies are not available for DMH anions, similar activation barriers could be expected in their reactions. Comparison of these activation free energies with the minimum free energy barriers to rotation estimated above show that electrophilic attack on a DMH anion occurs faster than either C(1)–C(2) or C–N bond rotation. This conclusion indicates that a complete explanation of the origins of stereoselectivity in reactions of DMH and related anions must include a description of the stereochemistry and the relative population of the various intermediate diastereomeric anions.

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¶For example, oxazoline anions are alkylated with Bu^{n}I within 20 min at −105 °C (A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Amer. Chem. Soc.*, 1976, **98**, 567) and other enolates react with ketones within 5 s at −72 °C (W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Amer. Chem. Soc.*, 1977, **99**, 247).

[1] (a) E. J. Corey and D. Enders, *Tetrahedron Letters*, 1976, 3; (b) E. J. Corey, D. Enders, and M. G. Bock, *ibid.*, p. 7; E. J. Corey and D. Enders, *ibid.*, p. 11; E. J. Corey and S. Knapp, *ibid.*, pp. 3667 and 4687.

[2] D. Enders and H. Eichenauer, *Tetrahedron Letters*, 1977, 191.

[3] For example: (a) T. A. Spencer and C. W. Leong, *Tetrahedron Letters*, 1975, 3889; (b) M. E. Jung, P. A. Blair, and J. A. Lowe, *ibid.*, 1976, 1439; (c) R. E. Lyle, J. S. Saavedra, G. G. Lyle, H. M. Fribush, J. L. Marshall, W. Lijinsky, and G. M. Singer, *ibid.*, p. 4431.

[4] See examples in H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, Menlo Park, California, 1972, ch. 9.