Quantitative Measurement of *syn* Stabilization of Lithiated Aldimines

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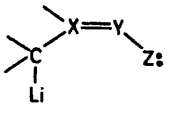
Summary The lithiation and alkylation of aliphatic aldimines has been shown to give *syn* and *anti* products in a ratio of 96:4 which is interpreted as representing a minimum value for the *syn* to *anti* ratio of the lithiated aldimine intermediates; the factor responsible for the preferential *syn* stabilization, though not yet identified, is determined to have a magnitude of at least 18 kJ mol^{-1}.

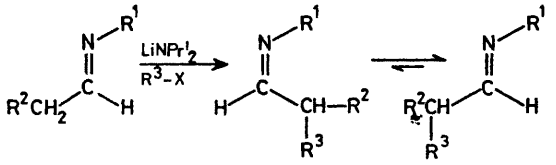
OVER the past few years evidence has been mounting which clearly establishes a thermodynamic preference for the *syn* forms of lithiated nitrosamines,[1] dimethylamides,[2] oximes,[3] their ethers,[4] and hydrazones,[5] all of which have the general formula (A).† We have recently shown that the *syn* configuration is also markedly favoured in lithiated ketimines[6] (A; Z = Pr^i). Since this result is not readily



(A)

rationalized by either orbital symmetry[7] or chelation arguments, it casts doubt on their validity in the other series as well. The magnitude of the *syn* effect in ketimines could only be assigned a lower limit of 7·5 kJ mol^{-1}. We here describe experiments which demonstrate the same *syn* stabilization for lithiated aldimines and establish its magnitude as a minimum of 18 kJ mol^{-1}.

We have examined the lithiation and alkylation of a number of aldimines (**1**), which in each case initially yield



(1) (2) (3)

the *syn* product (**2**), which isomerizes during purification to the more stable *anti* form (**3**). The stereochemical results and yields of products are given in the Table.

TABLE. The isomer distributions and yields of product in the lithiation and alkylation of the aldimines (**1**) (R^1 = CHMePh).

R^2	Isomer distributions (% *syn*) (**1**)	(**2**) (R^3–X)	(**2**) (at eq.)	% Yields of (**3**)
H	⩽ 0·5	89 (MeI)	⩽ 0·5	55
Me	⩽ 0·5	92 (MeI)[a]	⩽ 0·5	86
		91 ($PhCH_2Br$)	⩽ 0·5	94
		88 ($C_6H_{13}I$)	⩽ 0·5	88
Et	⩽ 0·5	96[a] (MeI)	⩽ 0·5	88

[a] This figure represents the only determination (±2%) of the *syn–anti* distribution in which a correction was made for equilibration during analysis by ^{13}C-n.m.r. spectroscopy. All reactions were carried out on a 3 mmol scale using tetrahydrofuran as solvent (0·2 M in aldimine). The yields represent pure distilled imines, characterized by mass and n.m.r. spectroscopy, and independent synthesis from the corresponding aldehyde. Since the ^{13}C spectra showed each reaction to be essentially quantitative, the yields of isolated product are indicative of some manipulative loss on this scale.

The most significant result of these alkylations is the continued predominance of *syn* product in spite of a large destabilizing steric effect. Accurate determination of the amount of *syn* isomer formed in the alkylation step required rapid measurement of the ^{13}C n.m.r. spectrum of each crude reaction mixture at −20 °C.‡ Even at this temperature some isomerization occurs, presumably by a base-catalysed mechanism as a lateral shift at nitrogen should not occur at this temperature.[8] This isomerization rate was measured in the methylation of propylideneamine by taking four consecutive spectra utilizing 600 scans (10 min each) and, assuming a first-order process, calculating the *syn*:*anti* ratio at zero time. This gave a value of 92% *syn* methylation, a minimum figure for the amount of *syn* product as any isomerization during removal of solvent or during n.m.r. sample preparation cannot be determined. The product of methylation of butylideneamine proved more stable to isomerization, allowing accumulation of 4000 scans, which showed the presence of a minimum of 96% of the *syn* isomer.§

If we assume methylation to be rapid relative to *syn–anti* interconversion of the lithiated aldimine¶ then the 96:4 ratio found in the methylation of butylideneamine (**1**; R^2 = Et) represents a difference in free energy of 5·2 kJ mol^{-1} in favour of the *syn* form. This effect is dominant in

† For lithiated nitrosamines and amides formula (A) represents the dipolar resonance structure in which X bears positive charge and Z bears negative charge.

‡ As in oxime ethers and hydrazones (see R. R. Fraser, K. L. Dhawan, and K. Taymaz, *Org. Mag. Resonance*, 1978, **6**, 269; P.Geneste, R. Durand, J. M. Karmeuka, H. Beierbeck, R. Martino, and J. K. Saunders, *Canad. J. Chem.*, 1978, **56**, 1940), the large difference in shieldings in the *syn* and *anti* isomers (*ca.* 10 p.p.m. for the nitrogen-bearing methine carbon and 5 p.p.m. for the carbon α to the imine group with both *syn* signals at higher field) permits ready differentiation of isomers.

§ In separate experiments, the relaxation times of the signals being measured were shown to provide peak intensities quantitatively related to within ±10%, which would affect the accuracy of value for the *anti* isomer by only ±1%, much less than the limit of accuracy (±1%) due to the base line noise.

¶ The disappearance of yellow colour within 1 min of the time of addition of methyl iodide indicates rapid alkylation. Such a reaction rate should be much faster than *syn–anti* interconversion.

spite of a strong steric effect whose magnitude in the lithiated aldimines can be expected to be at least as large as in the aldimine precursors. For all the aldimines studied the free energy difference (from the $>$ 99·5% *anti*) at 25 °C is at least 12·8 kJ mol^{-1}. Thus the electronic factor, whatever its origin, favours a *syn* lithiated aldimine by at least 18·0 kJ mol^{-1}.**

As in the case of ketimines, the origin of the stereochemical effect is at present unclear. The orbital symmetry explanation,[7] which requires involvement of 6 π electrons in the four-atom fragment and thus a hyperconjugative contribution of the measured amount does not appear plausible, and in aldimines the possibility of chelation is out of the question. The recent contrasting results of McIver *et al.*[9] on gas phase acidities of the but-2-enes compared with their solution values reported by Schlosser and Hartmann[10] has demonstrated the over-riding importance of solvent in determining the position of that equilibrium. The same influence of solvent may dominate in the present case.

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** It is assumed that entropy effects are negligible.

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