

E-Z-Isomerism in Aldimines¹

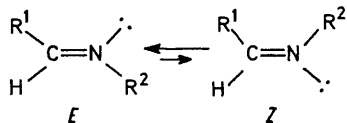
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A range of *ortho*-disubstituted *C*-aryl aldimines has been synthesized. N.m.r. spectroscopic analysis revealed a significant proportion of the *Z*-isomer at equilibrium in solution. The *E-Z*-isomer distribution is critically examined in terms of electronic, steric, and solvent effects. The effect of trace amounts of carboxylic acid on imine stereo-mutation is discussed.

THE barrier to *E-Z*-isomerization about a carbon-nitrogen double bond is very sensitive to the nature of the substituents.²⁻⁵ The barrier to interconversion in simple *N*-alkylimines is sufficiently large (>80 kJ mol⁻¹) for the latter process to be slow on the n.m.r. time-scale at ambient temperature. N.m.r. techniques have previously been applied in the detection and estimation of *E-Z*-ketimine isomer ratios at equilibrium.^{2,6} However, other studies⁷⁻⁹ using similar methods led to the conclusion that aldimines exist completely (>99%) in the *E*-configuration.



Z-Aldimines, which may be observed as transient intermediates after u.v. irradiation, spontaneously revert to the *E*-configuration⁵ and thus corroborate the independent observations of an exclusive preference for the *E*-aldimine configuration at equilibrium.⁷⁻⁹ *N*-Methylimines derived from benzaldehyde or mono-substituted benzaldehydes [imines (1)–(3) in Table 1] also show n.m.r. signals which may be attributed to a single *E*-isomer. However, imine derivatives of *ortho*-disubstituted benzaldehydes contain a minor stable component (in addition to the normal *E*-isomer) which can be identified as the *Z*-aldimine on the basis of the following evidence. (i) Immediately after dissolution of the crystalline imine no *Z*-isomer was detected by n.m.r. analysis. After a few minutes the signals due to a minor component appeared and increased up to an equilibrium value, while the concentration of the *E*-isomer decreased in concert. (ii) The *N*-methyl τ values for the minor components were similar to those reported for the corresponding *Z*-ketimines (Table 1).^{6a,8} The assignment of the higher field resonance to the *Z*-isomer

may be rationalized in terms of increased shielding of the *N*-alkyl group due to the proximate aryl ring. (iii) The magnitude and multiplicity of the HC=NCH coupling

TABLE 1
Equilibrium distribution of *E-Z*-aldimine isomers^a

Imine	Aryl	R	τ_{NR}^E	τ_{NR}^Z	%Z
(1)	R ¹ , R ² , R ³ , R ⁴ , R ⁵ = H	Me	6.56		<1
(2)	R ¹ , R ² , R ⁴ , R ⁵ = H; R ³ = Me	Me	6.54		<1
(3)	R ² , R ³ , R ⁴ , R ⁵ = H; R ¹ = Me	Me	6.55		<1
(4)	R ² , R ³ , R ⁴ = H; R ¹ , R ⁵ = Me	Me	6.49	6.96	6
(5)	R ² , R ⁴ = H; R ¹ , R ³ , R ⁵ = Me	Me	6.50	6.97	8
(6)	R ³ = H; R ¹ , R ² , R ⁴ , R ⁵ = Me	Me	6.47	7.00	17
(7)	R ¹ , R ² , R ³ , R ⁴ , R ⁵ = Me	Me	6.48	7.00	21
(8)	1-Naphthyl	Me	6.53		<1
(9)	9-Anthryl	Me	6.26	6.94	10
(10)	9-Anthryl	Et	6.12 ^b	6.82 ^b	9
			8.55 ^c	8.87 ^c	
(11)	9-Anthryl	Bz	4.87 ^b	5.68 ^b	8
(12)	9-Anthryl	CH ₂ Bu ^t	8.93 ^d	9.10 ^d	7
			6.33 ^b	7.07 ^b	
(13)	9-Anthryl	Pr ⁱ	8.57 ^e	8.96 ^e	6
			6.27 ^f		
(14)	9-Anthryl	Bu ^t	8.50		<1

^a Equilibrated imines were analysed at n.m.r. probe temperature (ca. 40°) in 1.0M solutions in CDCl₃. ^b CH₂. ^c CH₃. ^d Bu^t. ^e CMe₂. ^f CH.

constants (ca. 1.6 and 2.2 Hz for the major and minor components respectively) were in accord with the configurational assignment. (iv) The larger ¹⁵N=CH and ¹³CH coupling constants¹⁰ in the minor component [²J(HC=¹⁵N) ≈ -10, ¹J(¹³CH) ≈ +177 Hz] compared with those obtained for the *E*-isomer [²J(HC=¹⁵N) ≈ +4,

⁶ (a) J. Bjørge, D. R. Boyd, C. G. Watson, and W. B. Jennings, *J.C.S. Perkin II*, 1974, 757, and references contained therein; (b) unpublished data.

⁷ G. J. Karabatsos and S. S. Lande, *Tetrahedron*, 1968, 3907.

⁸ J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, 1967, 89, 2669.

⁹ K. A. W. Parry, P. J. Robinson, P. J. Sainsbury, and M. J. Waller, *J. Chem. Soc. (B)*, 1970, 700.

¹⁰ H. J. C. Yeh, H. Ziffer, D. M. Jerina, and D. R. Boyd, *J. Amer. Chem. Soc.*, 1972, 95, 2741.

¹ Preliminary communication D. R. Boyd, C. G. Watson, W. B. Jennings, and D. M. Jerina, *J.C.S. Chem. Comm.*, 1972, 183.

² C. G. McCarty in 'The Chemistry of the Carbon-Nitrogen Double Bond,' ed. S. Patai, Interscience, London, 1969, p. 363.

³ J. M. Lehn, *Fortschr. Chem. Forsch.*, 1970, 15, 311.

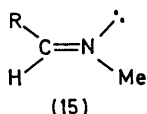
⁴ H. O. Kalinowski and H. Kessler, *Topics Stereochem.*, 1973, 7, 295.

⁵ G. Wettermark, *Svensk. Kem. Tidsskrift*, 1967, 79, 249; C. H. Warren, G. Wettermark, and K. Weiss, *J. Amer. Chem. Soc.*, 1971, 93, 4658.

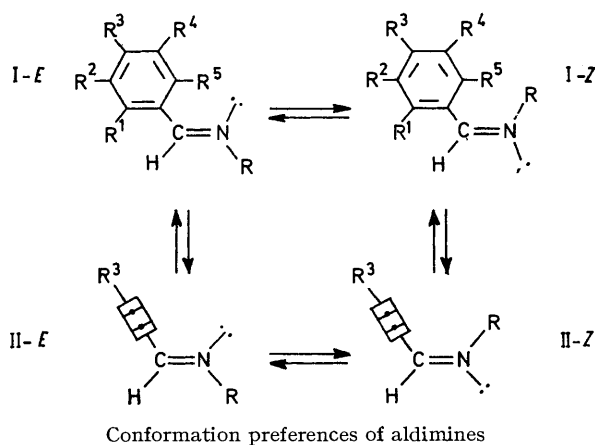
$^1J(^{13}\text{C}\text{H}) \approx +162 \text{ Hz}$] were in accord with a *Z*-configuration. Similar configurational assignments have been made for aldimine derived oxaziridines using $^{15}\text{N}=\text{CH}$ and $^{13}\text{C}\text{H}$ coupling constant data.¹¹ (v) Irradiation by u.v. light produced a higher proportion of the 'minor' isomer, which either disappeared completely [(1), (8), and (14)] or spontaneously reverted to a lower detectable equilibrium concentration.¹¹

The results in Table 1 show that *ortho*-disubstitution is necessary for a significant proportion (>5%) of the *Z*-isomer to be observed. However, concomitant *meta*- (or *meta*- and *para*-)substitution gives a more marked increase in this proportion. Since the '*ortho*-effect' has previously been discussed in a report on the equilibrium distribution of *C*-arylimines,^{6a} only a brief summary will be given in the present context.

The strong influence of classical non-bonded interactions between carbon and nitrogen substituents has been used to rationalize the observation of n.m.r.



signals for the *E*-imines only (>99%) which were derived from methylamine and alkylaldehydes [*e.g.* (15; R = Me)].^{7,8} The introduction of an aryl substituent (15; R = Ph) will render the effective 'size' of



the R group strongly conformation dependent, and will introduce conjugation or resonance stabilization effects (Figure).

On the basis of classical steric interactions involving R¹ or R⁵ and the vinyl hydrogen or the NR group (Figure), *ortho*-substitution will tend to force the aryl ring to twist out of the imino-plane. This will be opposed by the conjugative stabilization of the coplanar conformations I-*E* and I-*Z*, and the resultant preferred ground-state conformation will reflect a compromise between these two effects. The *Z*-isomer will ex-

perience maximum steric interactions (involving R⁵ and the proximate NR group) in conformation I-*Z*. When both *ortho*-positions are substituted, the latter interaction cannot be avoided in this conformation and destabilization (relative to the *E*-isomer) is one possible consequence. The opposite effect is in practice observed, thus imines (4), (5), and (9) show an enhanced proportion of the *Z*-isomer compared with non- or mono-*ortho*-substituted aldimines (1), (2), (3), and (8). A possible rationalization of these results could be that the 2,6-dimethylphenyl, mesityl, or 9-anthryl groups are markedly 'smaller' than a phenyl group by adoption of a nonplanar conformation close to II-*E* or II-*Z*. The addition of *meta*- (6) or *meta*- and *para*- (7) substituents may prevent CR¹ and CR⁵ bond bending by a buttressing effect similar to that previously observed in hindered biphenyls.¹²

Comparison of the equilibrium ratios for the most substituted imines (6) and (7) with that for benzaldehyde *N*-methylimine (1) indicates that the conformational effect amounts to >8 kJ mol⁻¹. Similar effects have been observed in di-*ortho*-substituted *C*-arylimines,⁶ Thus imines derived from methylamine and 2,4,6-trimethylacetophenone,^{6a} 9-acetylanthracene,^{6a} or pentamethylacetophenone,^{6b} show 95, 95, and >99% *Z*-isomer respectively at equilibrium compared with 7% *Z* in acetophenone *N*-methylimine.

Consideration of the present data for aldimines in conjunction with the previous results for ketimines⁶ could suggest that a pentamethylphenyl or a 9-anthryl group may have a steric requirement between that of a methyl group and a hydrogen atom, but closer to the latter. It is difficult to reconcile this interpretation with conclusions drawn from an inspection of space filling molecular models representing the non-planar conformations II-*E* and II-*Z* (Figure), even after making due allowance for the limitations of such devices* (see later). Accordingly it is suggested that an additional interaction should be considered, *i.e.* *n*- π repulsion between the nitrogen lone-pair and the proximate aromatic π -cloud in conformation II-*E*.

It is noteworthy that the *N*-methyl τ values (Table 1) for the *Z*-isomer of imines (4)–(7) do not show a significant increase in parallel with the equilibrium distribution of this isomer. The position of the *N*-methyl signal in *Z*-imines should be sensitive to the conformation of the neighbouring aryl ring (ring current effect).⁶ This observation may indicate a very marked preference for the orthogonal conformation II-*Z* (Figure) for imines (4)–(7). The buttressing effect of *meta*-substituents in (6) and (7) may therefore be reflected in the proportion of conformation II-*E*. The significant increase in the proportion of *Z*-isomer could be attributed to an increase in *n*- π repulsion for the *E*-isomer owing to increasing orthogonality and π electron density. The conjugation

¹¹ W. B. Jennings, D. R. Boyd, C. G. Watson, E. D. Becker, R. B. Bradley, and D. M. Jerina, *J. Amer. Chem. Soc.*, 1972, **94**, 8501.

¹² E. L. Eliel in '*Stereochemistry of Carbon Compounds*,' McGraw-Hill, New York, 1962, p. 163.

* Exact reproductions from photographs of both Courtauld and Catalin space-filling models are given in ref. 6a.

energy would however also be decreased and would reduce the proportion of *E*-isomer at equilibrium.

The relative importance of classical non-bonded interactions (in conjunction with aryl conformation dependent steric and electronic effects) is evident from the decreasing proportion of *Z*-isomer associated with an increase in bulk of the *N*-alkyl substituent in aldimines (9)—(14) (Table 1).

In a recent communication¹³ an 'alternative explanation' of the *ortho*-effect in *C*-arylimines has been proposed. It was suggested that in ketimines containing an *ortho*-substituted phenyl or a 1-naphthyl substituent on the imino-carbon atom the aryl ring cannot be coplanar with the C=N group thereby reducing the steric interactions between the ring and a *cis*-*N*-methyl group. This suggestion appears to be identical to that proposed in our previous communication.¹⁴ However, Kyba¹³ further expressed the view that the *E*:*Z*-isomer ratios are about what would be expected based on the sizes of the three groups attached to the C=N linkage. As suggested earlier in this paper the latter interpretation is not in concurrence with our conclusions based on the visual inspection of space-filling models. When this report¹³ is considered in conjunction with the much more comprehensive data now available there appears to be little justification for dismissing the *n*- π effect as being 'at best of minimal importance.' In support of the latter conclusion it was suggested that an electronic effect resulting from aryl substitution of polar groups should be observable if *n*- π repulsions were operative.¹³ While this concept appears to have merit and has been considered for ketimines,^{6a} it should be recognized that the magnitude of the expected perturbation is uncertain and could readily be masked by the other effects of polar substituents, *e.g.* alteration of the preferred conformation of the aryl ring due to the resonance of the system and differential solvation effects.

Thus it is still our view that, on the basis of the present and other⁶ data, the *n*- π effect of the nitrogen lone-pair provides one possible alternative to considering that a non-planar di-*ortho*-substituted aryl ring is considerably 'smaller' than a methyl group. The importance of the latter effect is based upon the assumption that the equilibrium position will be dominated by repulsive interactions. Among other contributing factors the possibility of attractive nonbonded interactions¹⁵ between the aryl and *N*-alkyl groups (which will lead to stabilization of the *Z*-form) should be considered.

The *E*:*Z*-isomer ratios for imines (7) and (9) have been determined in a series of solvents (Table 2). While solvent choice appears to be a relatively important factor in imine equilibrium distribution, the most significant effect is the considerable increase in the proportion of the *Z*-isomer in *t*-butyl alcohol. A possible explanation of this phenomenon may lie in a propensity for the bulky *t*-butyl alcohol molecules to hydrogen-bond more readily

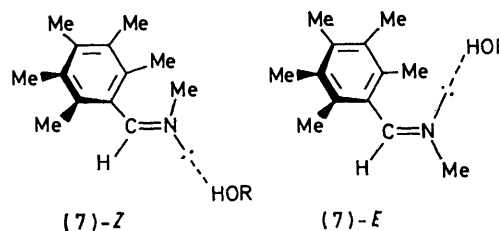
to the less sterically hindered nitrogen lone-pair in the *Z*-isomer. The lack of a similar effect in methanol may

TABLE 2
Solvent effects on equilibrium distribution of *E*-*Z* aldimine isomers (7) and (9) *

Solvent	<i>Z</i> %	
	(7)	(9)
Bu ^t OH	31	18 †
CDCl ₃	21	10
CCl ₄	21	5 †
CD ₃ OD	18	7 †
C ₆ D ₆	18	7 †
1,2,4-C ₆ H ₃ Cl ₃	14	5
C ₆ H ₅ N	14	4

* See footnote a in Table 1. † Saturated solutions (<1.0M).

be due to an ability of the smaller methanol molecules to hydrogen-bond more effectively with both isomers.



A similar dramatic effect for *t*-butyl alcohol was not found for the analogous *E*:*Z* ketimine ratios.^{6a} The degree of steric hindrance encountered during hydrogen-bonding by *t*-butyl alcohol would be less diverse in those *E*- and *Z*-ketimines considered in ref. 6a than in the corresponding aldimines.

All solid imines in Table 1 were found to crystallize from solution in the pure *E*-configuration. When the freshly recrystallized imines (6), (7), and (9)—(13) were dissolved the n.m.r. signals of the *Z*-isomer rapidly appeared and increased to an equilibrium value. The half-life was observed to be *ca.* 1 min for (7) and *ca.* 4 min for (9) in benzene solution at 35 and 42° respectively. This corresponds to a free energy of activation (ΔG^\ddagger) of 89 and 96 kJ mol⁻¹ respectively (mean of the forward and reverse reactions). This is a remarkably low value for imines of this type since *N*-alkylketimines have been shown by dynamic n.m.r. spectroscopy to have $\Delta G^\ddagger \approx 110$ —120 kJ mol⁻¹ at 200° in biphenyl solution.^{1,16} A large solvent effect or a large negative entropy of activation would not be expected for an intramolecular nitrogen inversion process. It appears probable that the isomerization process is being catalysed by trace amounts of carboxylic acid produced by autoxidation of the corresponding aldehydes. The aldehydes may have been present as trace impurities from the aldimine synthesis (despite purification by sublimation and recrystallization) or from partial hydrolysis of the aldimine.

¹⁵ N. D. Epiotis, D. Bjorkquist, L. Bjorkquist, and S. Sarkanen, *J. Amer. Chem. Soc.*, 1973, **95**, 7559.

¹³ E. P. Kyba, *Tetrahedron Letters*, 1973, 5117.

¹⁴ J. Bjørge, D. R. Boyd, C. G. Watson, and W. B. Jennings, *Tetrahedron Letters*, 1972, 1747.

¹⁶ W. B. Jennings and D. R. Boyd, *J. Amer. Chem. Soc.*, 1972, **94**, 7187.

This conclusion is supported by the following observations. (i) Small amounts of benzoic acid were found to accelerate the equilibration of several aldimines and ketimines. This process is bimolecular and appears to have the expected large negative entropy of activation, thus the catalysed process can compete more efficiently with the intramolecular process at 35 than at 200°.* (ii) The half-life for equilibration of (7) or (9) at 35° in benzene can be increased to several hours by prior recrystallization of the sample from methanol containing a trace of sodium methoxide. (iii) The photoenhanced *Z*-aldimine concentration in deuteriomethanol has a much longer half-life in the presence of a trace of sodium deuteriomethoxide.¹⁰ (iv) Ketimines prepared by similar routes were uncontaminated by carboxylic acid since analogous autoxidation problems are not encountered with ketones, thus the ΔG^\ddagger values obtained by direct thermal stereomutation were very similar to those found by dynamic n.m.r. methods.¹⁶

EXPERIMENTAL

The aldimines were synthesized from the corresponding aldehydes and amine either in the presence of an excess of amine or in ethanol solution. Physical properties and microanalytical data are presented in Table 3.

N.m.r. spectra were obtained using Varian HA-100, XL-100, A-60, or Perkin-Elmer R-12 instruments.

* Quantitative investigations are in progress and will be reported at a later date.

¹⁷ R. B. Moffett, *Org. Synth.*, 1954, **34**, 65.

¹⁸ A. R. Surrey and W. G. Webb, U.S.P. 3,328,418/1967 (*Chem. Abs.*, 1968, **68**, 68,977h).

TABLE 3

Physical and analytical data for imines (1)–(14)

Imine	Physical and analytical data
(1)	B.p. 74° at 16 mmHg (lit., ¹⁷ 92–93° at 34 mmHg)
(2)	B.p. 73° at 2–3 mmHg (lit., ¹⁸ 48–52° at 0.5 mmHg)
(3)	B.p. 51–52° at 0.45 mmHg (lit., ¹⁸ 42–48° at 0.5 mmHg)
(4)	B.p. 40–42° at 0.1 mmHg (Found: C, 81.3; H, 8.9; N, 9.3. C ₁₀ H ₁₃ N requires C, 81.6; H, 8.9; N, 9.5%)
(5)	B.p. 50–52° at 0.05 mmHg (Found: C, 81.9; H, 9.55; N, 8.6. C ₁₁ H ₁₅ N requires C, 81.9; N, 9.4; N, 8.7%)
(6)	M.p. 58–59° (Found: C, 82.1; H, 9.85; N, 7.8. C ₁₂ H ₁₇ N requires C, 82.2; H, 9.8; 8.0%)
(7)	M.p. 60–61° (Found: C, 82.5; H, 10.1; N, 7.4. C ₁₃ H ₁₉ N requires C, 82.4; H, 10.1; N, 7.4%)
(8)	B.p. 162–164° at 17 mmHg (Found: C, 85.3; H, 6.8. C ₁₂ H ₁₁ N requires C, 85.2; H, 6.5%)
(9)	M.p. 113° (Found: C, 87.3; H, 5.9; N, 6.1. C ₁₆ H ₁₃ N requires C, 87.7; H, 5.9; N, 6.4%)
(10)	M.p. 76–77° (Found: C, 87.4; H, 6.6; N, 5.8. C ₁₇ H ₂₅ N requires C, 87.5; H, 6.5; N, 6.0%)
(11)	M.p. 72–73° (Found: C, 89.3; H, 5.8; N, 4.65. C ₂₂ H ₁₇ N requires C, 89.45; H, 5.8; N, 4.7%)
(12)	M.p. 72–73° (Found: C, 87.2; H, 7.7; N, 5.0. C ₂₀ H ₂₁ N requires C, 87.2; H, 7.7; N, 5.1%)
(13)	M.p. 111–112° (Found: C, 87.4; H, 7.1; N, 5.45. C ₁₈ H ₁₇ N requires C, 87.4; H, 6.9; N, 5.7%)
(14)	M.p. 93–95° (Found: C, 87.3; H, 7.4; N, 5.3. C ₁₉ H ₁₉ N requires C, 87.3; H, 7.3; N, 5.4%)

Imine equilibrium ratios were estimated after duplicate experiments and n.m.r. integration ($\pm 2\%$).

We are indebted to Messrs W. J. Swindall and H. B. McKnight for microanalyses, Dr. L. Waring and Mr. I. Jack for Varian HA-100 n.m.r. spectra, and the Queen's University of Belfast for demonstratorships to J. B. and C. G. W.

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