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Prototropic Equilibrium of Imines. *N*-Benzylidene Benzylamines

Peter A. S. Smith* and Chi Van Dang

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

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The 1,3-prototropic shift of imines, exemplified in isomerization of unsymmetrically substituted *N*-benzylidene benzylamines, has been reexamined. Equilibrium constants for para-monosubstituted systems were determined by NMR methods; the constants do not show the anomalies reported in older work, and are adequately correlated by the Hammett equation ($\rho = 0.94$).

Recent investigations[1] of prototropic equilibration of nitrones Ia ⇄ Ib (Behrend rearrangement) in this laboratory invited a comparison with the corresponding imines, IIa ⇄ IIb. Imine isomerization had been investigated by Shoppee,[2,3]

$$\mathrm{ArCH_2{-}NX} \rightleftharpoons \mathrm{ArCH{=}NX}$$
$$\mathrm{CHAr'} \qquad\qquad \mathrm{CH_2Ar'}$$

Ia, IIa Ib, IIb

Ia, Ib, X = oxygen atom; IIa, IIb, X = electron pair

who brought about equilibration by heating *N*-benzylidene benzylamines with sodium ethoxide solution, over 40 years ago. His results on the effect of substituents, particularly alkyl groups, played a role in the early development of the theory of hyperconjugation.[4] Much later, the mechanism of isomerization was investigated by Cram and Guthrie,[5] who showed that it probably involved formation of a delocalized carbanion, rather than the synchronous process originally proposed.

In the ensuing years, uncertainties developed about the interpretation of the equilibrium constants reported by Shoppee. Baker in 1952 stated that the effects of substituents could not be satisfactorily assessed.[6] The effects of para substituents were not acceptably consistent with the correlations subsequently developed by Hammett, and could not be satisfactorily interpreted according to theories of electronic influences. The equilibrium constant for the *p*-methyl substituent, of particular importance for hyperconjugation in its earliest development, was especially inconsistent.

At the time of Shoppee's investigations, most instrumental methods of analysis had not been developed. As a consequence, he had to use an indirect and error-prone analytical method to determine the composition of the equilibrium mixtures of imines. He hydrolyzed the imines, converted the resulting benzaldehydes to dinitrophenylhydrazones, and compared the melting range of these mixtures with the phase diagram determined from known mixtures. Although this method is in principle sound, its reliability is vitiated if unsuspected traces of a third component should be present; it is also potentially sensitive to variations in yield of the conversion to dinitrophenylhydrazones. It therefore seemed desirable to reinvestigate the subject, not only for comparison with the Behrend rearrangement, but because of the importance of imine tautomerism in synthesis and in biological transamination.

We have prepared a series of para-substituted *N*-benzylidene benzylamines, all of which are known, by warming the corresponding benzaldehydes and benzylamines together. The purified imines consisted of but a single geometrical isomer, insofar as we could determine by infrared and NMR spectroscopy, consistent with Ossorio's report[7] that only the anti isomer is present significantly at equilibrium. We did not include the *p*-nitro substituent, although we would have liked to, because its reaction with sodium ethoxide is more complex (a nitronate salt is apparently formed, and is the basis for a microanalytical determination of benzylamine[8]).

We equilibrated the imines by refluxing them in a 1 M solution of sodium ethoxide in absolute ethanol for periods of 2–36 h. Analysis of the mixtures was accomplished with NMR spectroscopy. Neither the methylene nor the methyne hydrogens of the pairs of tautomers were sufficiently well resolved, unfortunately. However, the methyl signals of the mixtures from the *p*-methyl, *p*-methoxy, and *p*-dimethylamino systems allowed their compositions to be determined. For the *p*-chloro system, hydrolysis of the imines to the corresponding mixture of benzaldehyde and *p*-chlorobenzaldehyde was necessary; the signals of the aldehyde protons were separated by 2.5 Hz.

For each substituent, equilibrium was approached from both sides, and values were determined at a series of times to be sure that equilibrium had been reached. The mean values

Table I. Equilibrium Constants for Tautomerism of Imines and Nitrones

p-$RC_6H_4CH{=}N(Y)CH_2C_6H_5 \rightleftarrows p$-$RC_6H_4CH_2N(Y){=}CHC_6H_5$
A B

	Imines (Y = e_2)			Nitrones (Y = O)
R	K (found)[a]	K (lit.[3])	Log K	K
$(CH_3)_2N$–	0.17	0.149	−0.77 ± 0.03	
CH_3O–	0.55	0.370	−0.26 ± 0.02	0.33
CH_3–	0.67	1.22	−0.17 ± 0.02	0.61
Cl–	1.64	1.13	0.214 ± 0.004	0.62

[a] K = B/A.

slope corresponding to ρ = 0.941 ± 0.008. Figure 1 also includes two values determined by Baker, Nathan, and Shoppee[4] for the *tert*-butyl and isopropyl groups, which they used in comparison with Shoppee's value for the methyl group to establish a relative order of hyperconjugation effects of alkyl groups.

One can conclude that tautomerism of imines is not anomalous, nor is the effect of the p-methyl group on it. The behavior of the system is adequately encompassed by the Hammett equation. The situation with analogous nitrones, Ia ⇄ Ib, has recently been analyzed in a way that implies that substituent effects operate in an ambivalent way with them, owing to the semipolar N–O bond, and that equilibrium constants for the Behrend rearrangement should not parallel those of imines.[1] This conclusion is consistent with the results reported here, as can be seen by comparing the values for nitrones and imines given in Table I.

Table II. Properties of Imines (Benzylidene Benzylamines)

$ArCH_2$–N=CHAr′

	Substituent on			NMR, δ, ppm (CCl_4, Me_4Si)			
Registry no.	Ar	Ar′	Mp, °C	–CH=N–	Arom CH	$-CH_2N$	$-CH_3$
24431-17-2	H	p-$(CH_3)_2N$	74–76 (lit.[3] 75)	8.13	7.10 (q, 4 H), 7.22 (s, 5 H)	4.67	2.94
31401-61-3	p-$(CH_3)_2N$	H	55.5–57 (lit.[3] 57)	8.02	6.70 (q, 4 H), 7.36 (m, 5 H)	4.60	2.76
622-72-0	H	p-CH_3O	42–43 (lit.[2] 42)	8.13	7.15 (q, 4 H), 7.16 (s, 5 M)	4.68	3.73
31490-38-7	p-CH_3O	H	Oil[2]	8.12	6.86 (q, 4 H), 7.40 (m, 5 H)	4.61	3.67
24431-15-0	H	p-CH_3	26–27 (lit.[3] 27)	8.11	7.15 (s, 5 H), 7.27 (q, 4 H)	4.67	2.32
41882-47-7	p-CH_3	H	bp 124 (0.2 mm) [lit.[3] 190–196 (20 mm)]	8.03	6.94 (s, 5 H), 7.1–7.7 (m, 4 H)	4.60	2.26
13540-93-7	H	p-Cl	34 (lit.[3] 34)	8.11	7.10 (s, 5 H), 7.11–7.7 (m, 4 H)	4.62	
15383-71-8	p-Cl	H	35–36 (lit.[3] 36–37)	8.28	6.71 (s, 5 H), 7.52 (q, 4 H)	4.77	

are given in Table I, along with the values reported by Shoppee. (The results of individual determinations are in Table III.)

Although our results differ quantitatively from those of Shoppee, the relative effects of substituents are the same if one omits the value for p-methyl, which is markedly out of line. A graphic comparison is given in Figure 1 as a Hammett plot vs. σ;[9] the weighted least-squares method[10] gave a line of

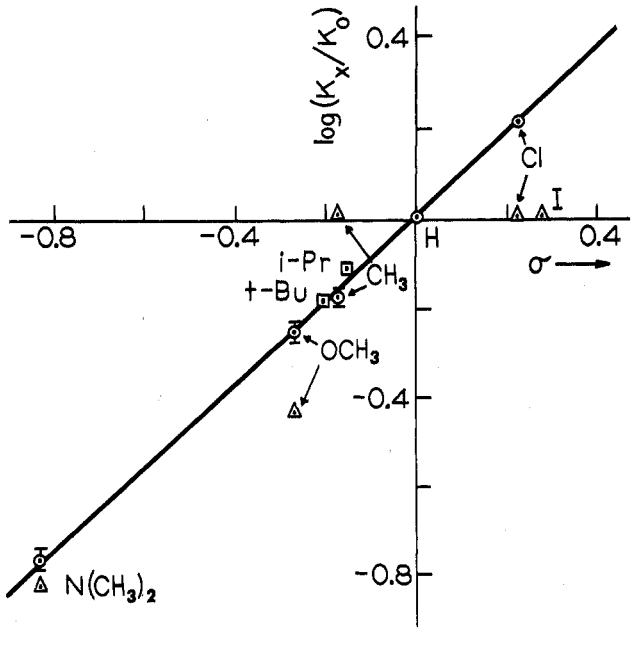

Figure 1. Hammett plot of equilibrium ratios in imine isomerizations: ⊙, data from present work; △, data of Shoppee;[3] □, data of Baker, Nathan, and Shoppee.[4]

Table III. Isomerization of Imines

p-$RC_6H_4CH{=}N$–$CH_2Ph \rightleftarrows p$-$RC_6H_4CH_2$–N=CHPh
A B

Initial imine			
R	A or B	Time, h	Product ratio, B/A
$(CH_3)_2N$	A	5	0.18
$(CH_3)_2N$	A	6	0.16
$(CH_3)_2N$	A	7	0.16
$(CH_3)_2N$	A	12	0.18
$(CH_3)_2N$	B	2.25	0.17
$(CH_3)_2N$	B	3.5	0.18
CH_3O	A	8–36	0.57[a]
CH_3O	B	5–12	0.53[a]
CH_3	A	5–13	0.69[a]
CH_3	B	4–5	0.65[a]
Cl	A	16–36	1.63[a]
Cl	B	20–29	1.64[a]

[a] Mean of values recorded after equilibrium was reached.

Experimental Section

Imines. The appropriate aldehydes and benzylamines (slight excess), all of which are commercial products, were heated for 30 min at 100 °C, essentially following the method of Shoppee.[3] The resulting crude imines were dissolved in ethyl ether and washed successively with two portions of 2% acetic acid, two portions of 10% sodium bicarbonate solution, and one portion of water. Evaporation of the dried (Na_2SO_4) solutions left the imines, which were recrystallized from petroleum ether or ligroin when possible. The identity of these known compounds was confirmed by their NMR spectra, all of which showed an upfield doublet and a downfield triplet with J = 1.3–1.5 Hz, at-

tributable to the $-CH_2N{=}CH-$ system, an aromatic region differentiated into 4 H and 5 H parts, and singlet signals appropriate to the substituents. These data are collected in Table II.

Isomerization. Solutions of 0.3 g of imine in 20 ml of 1 N ethanolic sodium ethoxide were heated under reflux (solution temperature 82 °C). Reaction was quenched at a determined time by rapid cooling with cold water and dilution with 20 ml of distilled water. The resulting mixtures were extracted twice with chloroform, and the extracts were washed twice with water and then dried over sodium sulfate.

Analysis. The dried chloroform solutions were evaporated under vacuum and the residue was dissolved in carbon tetrachloride containing 1% Me_4Si. NMR spectra were determined on a Varian T-60 instrument. Addition of a drop of Me_2SO-d_6 or CD_3OD enhanced the resolution of the signals of the pairs of isomers present. The intensities of the methyl signals (where present; see Table II) were compared to obtain the ratios reported in Table III. In general, three to five samples of each imine were used; except for the *p*-dimethylamino pair, for which all samples are reported, only the mean values are shown.

The mixtures with a *p*-chloro substituent were first hydrolyzed by emulsifying with a small amount of methanol–water mixture and heating with 30 ml of 2 N sulfuric acid at 100 °C for 30 min. The cooled mixture was then extracted with ether, the dried extracts were evaporated to dryness, and the residue was taken up in carbon tetrachloride for NMR analysis by comparison of the aldehydic CH signals.

The reliability of the methods was examined by using mixtures of known compositions. For the pair *N*-benzylidene-*p*-methylbenzylamine/*p*-methylbenzylidenebenzylamine, the results follow: known, 59.5/40.5 (found, 59.8/40.2); known, 58.2/41.8 (found, 59.5/40.5); known, 55.9/44.1 (found, 56.1/43.9). For benzaldehyde/*p*-chlorobenzaldehyde mixtures derived from the *p*-chloro tautomeric imines, the results follow: known, 61.1/38.9 (found, 62.0/38.0); known, 62.4/37.6 (found, 63.0/37.0).

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Occurrence of N-Alkylation during the Acidolytic Cleavage of Urethane Protecting Groups[1a,b]

A. R. Mitchell* and R. B. Merrifield

The Rockefeller University, New York, New York 10021

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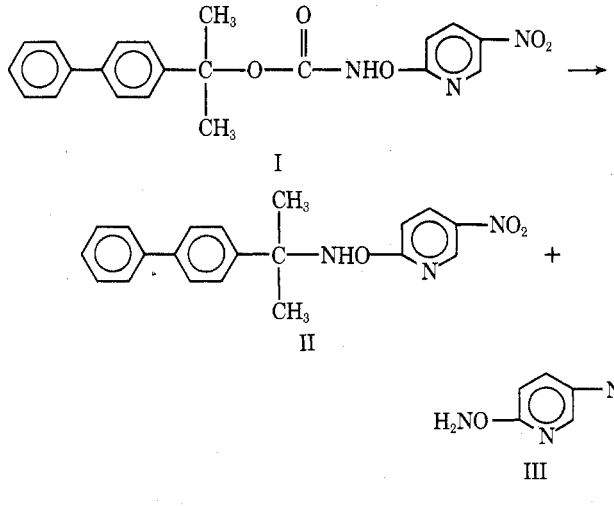
The occurrence of N-alkylation as a side reaction during the acidolytic cleavage of urethane protecting groups by trifluoroacetic acid has been investigated under the conditions of solid phase peptide synthesis. N-Alkylation did not occur when the protecting group was *tert*-butyloxycarbonyl (Boc) as treatment of Boc-Gly-Lys(Z)-resin with 50% CF_3COOH–CH_2Cl_2 did not produce *t*-Bu-Gly-Lys(Z)-resin (<0.05%). This novel side reaction did occur when the protecting group was benzyloxycarbonyl (Z). When Boc-Lys(Z)-resin was treated with 50% CF_3COOH for 14 h (25 °C) the Z group was partially removed and gave rise to 0.6% N^{ϵ}-benzyllysine-resin. The use of a more acid stable N^{ϵ} protecting group (2,4-Cl_2Z) suppressed N-alkylation to less than detectable levels (<0.1%). The acidolytic removal of the benzyloxycarbonyl group from Z derivatives in solution was also studied. Treatment of Z-Gly and Lys(Z) (0.1 M) in refluxing CF_3COOH (30 min) gave 1.1% Bzl-Gly and 3.3% Lys(Bzl), respectively. The addition of 20% anisole gave 0.5% Bzl-Gly and 2.1% Lys(Bzl) from the same Z derivatives. The use of CF_3SO_3H–CF_3COOH–anisole (30 min, 25 °C) allowed the formation of 1.2% Bzl-Gly from Z-Gly and 3.1% Lys(Bzl) from Lys(Z). No N-alkylation could be detected when amino acid resins or free amino acids containing Z protecting groups were cleaved with anhydrous HF.

The most widely used amino protecting groups in peptide synthesis are the benzyloxycarbonyl (Z)[2] and *tert*-butyloxycarbonyl (Boc)[3] groups. A recent addition to this family of urethane-type protecting groups is the relatively acid-labile biphenylisopropyloxycarbonyl (Bpoc)[4,5] group. A report[6] of N-alkylation during the acidolytic cleavage of a Bpoc group from a derivative of hydroxylamine initially prompted the present study as a possible explanation of a rise in background observed with picrate monitoring during solid phase peptide synthesis.[7]

The unexpected formation (20%) of *N*-2-(*p*-biphenylyl)-isopropyl-*O*-(5-nitro-2-pyridyl)hydroxylamine (II) occurred when 2-(*p*-biphenylyl)isopropyl *N*-(5-nitro-2-pyridyloxy)-carbamate (I) was treated with acetic acid in nitromethane.[6] Attack of III by *p*-biphenylyldimethyl carbonium ion could give rise to II. Attack of the carbonium ion on the carbamic acid formed from I, with simultaneous decarboxylation, was also considered a possible route to II.



Our initial interest was focused on the possible occurrence of an analogous reaction with the Boc group under conditions of solid phase peptide synthesis. The formation of a small amount (ca. 0.1–1%) of N^{α}-*tert*-butyl peptide (V) during each