Comparative analysis of crystal structures of *E,E*-configured *para*-substituted acetophenone azines with halogen, oxygen, nitrogen and carbon functional groups

Rainer Glaser,* Grace Shiahuy Chen,[1a] Mitchell Anthamatten and Charles L. Barnes[1b]
Department of Chemistry, University of Missouri-Columbia, Columbia, Missouri 65211, USA

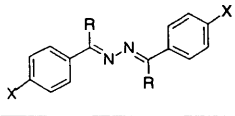
A comparative analysis is presented of the solid state structures of fifteen *E,E*-configured *para*-substituted acetophenone azines with halogen [–F (**1a**), –Cl (**1b**), –Br (**1c**)], oxygen [–OMe (**2**, **5** and **6**), –OH (**3**), –OCOEt (**4**)], nitrogen [–NMe_2 (**7**), –NH_2 (**8**), –NHCOMe (**9**), –NO_2 (**10**)] and carbon [–Me (**11**), –CO_2Et (**12**), –CN (**13**)] functional groups. The X-ray crystal structures of **2**, **7**–**10** and **12** were determined and are reported. The data allow us systematically to examine the structural effects of the nature of the *para*-substituent in a series of closely related azines and to assess and distinguish between intrinsic electronic and steric effects and consequences of crystal packing. Stereoelectronic effects of the *para*-substituents are discussed in terms of contributions of various resonance forms and structural parameters are identified that may serve as indicators of their importance. Analyses are presented of conformational properties and of crucial bond lengths of the azines **1**–**13**. The molecules also are analysed as *para*-disubstituted benzenes X–C_6H_4–Az and compared with X–C_6H_4–Z systems qualitatively to rank the electron-withdrawing ability of the Az group.

The *crisscross* addition,[2] the formation of 1,5-diazabicyclo-[3.3.0]octanes *via* tandem 1,3-dipolar cycloadditions[3] of azines with dienophiles, plays an important role for the construction of five-membered rings. The *crisscross* addition is remarkable in that all other closely related aza-analogues of dienes react in a Diels–Alder fashion.[4] Aside from the *crisscross* addition, azines react as the 'ene' component in [3 + 2] additions[5] and they are becoming increasingly important in synthesis of C–C bond formations.[6] Azines also are attracting increasing interest because of their special biological, chemical and physical properties.[7] For example, asymmetrical azines of the type D–C_6H_4–(R)C=N–N=C(R)–C_6H_4–A, azines with donor and acceptor groups at the ends of a π-conjugated backbone, hold promise as novel organic nonlinear optical materials.[8]

This great synthetic utility of azines as well as their special properties has resulted in continued interest in studies of their stereochemistry.[9] Questions of conjugative interactions are central to these discussions and these questions are usually addressed *via* analysis of solid-state structural data. Electronic structure analysis solely based on structural data of a particular azine suffers naturally from the lack of reference data. Secondly, the unambiguous identification of an intrinsic structural effect is complicated by packing effects. Furthermore, the magnitude of the structural effects, if any and if intrinsic, might be small and the effect might be difficult to identify unambiguously even if conjugation does occur. To overcome the first problem, examinations of electronic structure require comparative analysis of series of closely related molecules and evaluation of the changes of structural parameters. To overcome the second problem, examinations are required of the sensitivity of the structural parameters to crystal packing effects. Regarding the magnitude of the effects, additional independent information appears to be required unless the observed relative changes are large compared with typical standard deviations of the parameters examined.

We have been studying systematically the stereochemistry and the stereoelectronics of azines[10] with focus on *para*-substituted acetophenone azines. A comparative analysis of the symmetrical *para*-halogen substituted acetophenone azines, **1**, has recently been communicated and the implications were discussed of the polymorphism of the symmetrical *para*-methyl acetophenone azine, **11**. We now report the X-ray crystal structures of six symmetrical *para*-substituted acetophenone azines—the *para*-methoxy- (**2**), *para*-dimethylamino- (**7**), *para*-amino- (**8**), *para*-acetamidino- (**9**), *para*-nitro- (**10**) and *para*-ethoxycarbonyl- (**12**) systems—and present a comparative analysis of the azines **1**–**13** specified in Table 1. With the data for **1**–**13**, one can explore systematically (*a*) the effects of variations of the *para*-substituent from halogens over oxygen and nitrogen to carbon, (*b*) assess and distinguish between electronic and packing effects associated with H/Me-replacements in the oxygen and nitrogen substituted systems, and (*c*) to study the consequences of altering the electronegativity of the substituent through attachment of acceptor atoms.

Table 1 Scope and numbering of azines studied



	Methylated	Parent	Acceptor substituted
Halogen		**1** F (*a*), Cl (*b*), Br (*c*)	
Oxygen	**2** OMe	**3** OH	**4** OCOEt
	5 OMe (H)		
	6 $OCHF_2$ (H)		
Nitrogen	**7** NMe_2	**8** NH_2	**9** NHCOMe
			10 NO_2
Carbon		**11** CH_3	**12** CO_2Et
			13 CN

Table 2 X-Ray data and the experimental parameters for data collection

	2	7	8	9	10	12
Chemical formula	$C_{18}H_{20}N_2O_2$	$C_{20}H_{26}N_4$	$C_{16}H_{20}N_4O$	$C_{20}H_{22}N_4O_2$	$C_{16}H_{14}N_4O_4$	$C_{22}H_{24}N_2O_4$
Molecular weight	296.37	322.45	284.36	350.42	326.31	380.44
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$I2/a$	$I2/a$	$Pbcn$	$P2_1/c$
a/Å	6.3322(10)	6.9774(5)	16.5250(10)	16.723(4)	13.1571(6)	9.0291(7)
b/Å	7.3629(6)	7.7085(6)	9.4879(4)	4.810(2)	11.5898(9)	13.7583(5)
c/Å	16.945(3)	16.8119(13)	19.5320(20)	22.834(6)	20.0677(13)	8.2180(5)
β/°	97.385(6)	94.044(4)	96.126(3)	101.41(2)		102.474(3)
θ range	$20 \leq 2\theta/° \leq 30$	$40 \leq 2\theta/° \leq 50$	$40 \leq 2\theta/° \leq 50$	$40 \leq 2\theta/° \leq 50$	$20 \leq 2\theta/° \leq 30$	$40 \leq 2\theta/° \leq 50$
V/Å^3	783.48(20)	901.98(12)	3044.9(4)	1800.4(10)	3060.1(3)	996.78(10)
Z	2	2	8	4	8	2
D_x/g cm^{-3}	1.256	1.187	1.241	1.293	1.417	1.268
Radiation (λ/Å)	Mo-Kα (0.709 30)	Cu-Kα (1.540 56)	Cu-Kα (1.540 56)	Cu-Kα (1.540 56)	Mo-Kα (0.709 30)	Cu-Kα (1.540 56)
μ/cm^{-1}	0.8	5.2	5.3	6.2	1.0	7.6
T/K	293	293	293	293	293	293
Reflections measured	1197	1388	2334	1396	2139	2183
Independent reflections	1083	1337	2254	1352	2139	2054
Observed reflections	853, $I > 2.0\sigma(I)$	1207, $I > 3.0\sigma(I)$	1870, $I > 2.5\sigma(I)$	1108, $I > 2.0\sigma(I)$	1552, $I > 2.0\sigma(I)$	1837, $I > 2.0\sigma(I)$
h	$-6 \longrightarrow 6$	$-7 \longrightarrow 7$	$-18 \longrightarrow 18$	$-18 \longrightarrow 18$	$0 \longrightarrow 14$	$-11 \longrightarrow 11$
k	$0 \longrightarrow 8$	$0 \longrightarrow 8$	$0 \longrightarrow 10$	$0 \longrightarrow 5$	$0 \longrightarrow 12$	$0 \longrightarrow 17$
l	$0 \longrightarrow 18$	$0 \longrightarrow 18$	$0 \longrightarrow 21$	$0 \longrightarrow 25$	$0 \longrightarrow 22$	$0 \longrightarrow 10$
R; R_w; S	0.046; 0.069; 2.46	0.047; 0.088; 2.76	0.044; 0.065; 2.56	0.056; 0.083; 2.70	0.048; 0.065; 2.12	0.047; 0.080; 2.60
$F(000)$	316.12	348.91	1219.48	744	1360.64	405.24
Maximum Δ/σ	0.1%	0.5%	2.3%	0.1%	0.8%	1.7%
$\Delta\rho$ (max.; min)/e Å^{-3}	0.440; −0.210	0.210; −0.180	0.190; −0.220	0.260; −0.250	0.170; −0.160	0.170; −0.170

Experimental

General procedure for azines

Azines **2**, **7–10** and **12** were prepared by refluxing the appropriate *para*-substituted acetophenone with hydrazine hydrate in acidic ethanolic solution and precipitates formed after cooling.[11] Single crystals were grown by slow diffusion of hexane into the methylene chloride solutions. The acid catalysis is crucial for the reaction. Kolb *et al.*[7a] reported that no *para*-nitroacetophenone azine and only traces of *para*-methoxyacetophenone azine were obtained when the reaction was carried out at room temperature without the acid catalyst.

Preparation of *p*-dimethylaminoacetophenone, 7

The preparation of **7** in good yield has been a long-standing problem. The Friedel–Crafts acylation fails because aromatic amines always give very poor yields.[12] The Vilsmeier reaction of *N*,*N*-dimethylaniline also fails although *p*-dimethylaminobenzophenone could indeed be prepared in this way.[13] The introduction of the acyl group by oxidation of 1-(*p*-dimethylaminophenyl)ethanol is also not a successful synthetic route.[14] Consequently, synthetic approaches had to focus either upon the introduction of the dimethylamino function or on the methylation of the amino group in *p*-aminoacetophenone. The latter method is preferable because the nucleophilic aromatic substitution of *p*-chloroacetophenone by dimethylamine requires high pressure and high temperature conditions.[15] The reductive methylation (H_2, H_2CO) of *p*-aminoacetophenone works well and requires the Adams catalyst.[16] The methylation employed here is more economical and represents a modification of the preparation of *m*-dimethylaminoacetophenone reported by Rupe *et al.*[17] which consists of the direct methylation of *p*-aminoacetophenone with an excess of MeI in basic aqueous solution at moderate temperature. In contrast with the methylation of *m*-aminoacetophenone, attempts at methylating *p*-aminoacetophenone with MeI in a ratio of 1:2 gave predominantly the monomethylated product (3:1 ratio of mono- to di-methylated products). A larger excess of MeI afforded clean dimethylation.

p-Aminoacetophenone (0.01 mol) was mixed with Na_2CO_3 (0.03 mol) and dispersed in a suspension of MeI (0.04 mol) in 30 cm^3 H_2O. The mixture was refluxed for 5 h, after which saturated aqueous NaOH solution was added to destroy the excess of MeI. After addition of water to dissolve the precipitate, the clear yellow solution was extracted with CH_2Cl_2 three times. The combined CH_2Cl_2 fractions were dried with anhydrous Na_2SO_4. Pure *p*-dimethylaminoacetophenone was obtained in 43% yield after recrystallization from CH_2Cl_2–hexane solution.

Crystal structure determinations for azines 2, 7, 8, 9, 10 and 12

Data were collected on an Enraf-Nonius CAD4 diffractometer with Mo-Kα radiation (λ = 0.709 30 Å) for **2** and **10** and with Cu-Kα radiation (λ = 1.540 56 Å) for **7**, **8**, **9** and **12**. Crystal data and experimental parameters are summarized in Table 2. Selected bond lengths, angles, and torsion angles are listed in Table 3. Full lists of atomic co-ordinates, positional parameters and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).† Perspective ORTEPII[18] drawings of **2**, **7–10** and **12** with the numbering schemes are shown in Fig. 1 and stereo PLUTO[19] molecular packing diagrams are shown in Fig. 2. Azines **2**, **7–10** and **12** all assume *E*,*E*-configurations with regard to the C=N double bonds. As with all the other *para*-substituted acetophenone azines, the geometrical isomer preference is governed by the steric demand of the substituents at the azine-C atoms.[10,20]

† For details of the CCDC deposition scheme, see Instructions for Authors (1995), *J. Chem. Soc., Perkin Trans. 2*, 1995, Issue 1.

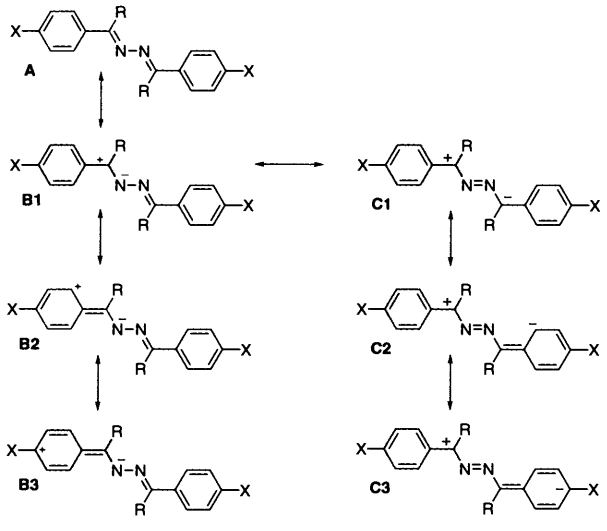
Table 3 Selected bond lengths (Å), angles (°), and torsion angles (°)

		2	7	8[a]	9	10[a]	12
X1–C5		1.364(3)[b]	1.369(2)[g]	1.388(4)	1.415(3)[h]	1.456(4)	1.491(2)[i]
X2–C13				1.370(3)		1.467(4)	
N1–N2		1.409(4)[c]	1.401(3)[c]	1.409(2)	1.395(5)[c]	1.398(3)	1.404(2)[c]
N1–C1		1.281(3)	1.286(2)	1.287(3)	1.292(4)	1.280(4)	1.274(2)
N2–C9				1.289(3)		1.273(4)	
C1–C2		1.479(3)	1.472(2)	1.478(3)	1.483(4)	1.491(4)	1.487(2)
C1–C8		1.492(4)	1.495(3)	1.504(3)	1.493(4)	1.500(4)	1.497(2)
C9–C10				1.474(3)		1.482(4)	
C9–C16				1.502(3)		1.493(4)	
N2–N1–C1		114.0(2)[d]	114.2(1)[d]	116.3(2)	113.7(2)[d]	115.0(2)	114.2(1)[d]
N1–N2–C9				115.5(2)		115.2(2)	
N1–C1–C2		116.1(2)	116.7(1)	117.5(2)	115.3(2)	115.1(2)	116.1(1)
N1–C1–C8		124.1(2)	124.3(2)	123.3(2)	124.2(3)	125.2(3)	125.7(1)
C2–C1–C8		119.8(2)	119.0(2)	119.2(2)	120.5(2)	119.7(3)	118.2(1)
C1–C2–C3		120.7(2)	122.9(2)	121.7(2)	120.9(2)	120.9(2)	121.7(1)
N2–C9–C10				118.0(2)		115.8(2)	
N2–C9–C16				122.4(2)		124.7(3)	
C10–C9–C16				119.6(2)		119.5(2)	
C9–C10–C11				121.3(2)		120.2(2)	
C1–N1–N2–C9	τ	180.0[e]	180.0[e]	131.1(2)	180.0[e]	152.0(3)	180.0[e]
N2–N1–C1–C8	φ_{1a}	−1.1[f]	−1.0[f]	−3.3(1)	−0.3[f]	−3.1(1)	0.0[f]
N1–N2–C9–C16	φ_{2b}			−4.0(1)		−3.5(1)	
N1–C1–C2–C7	θ_{1a}	168.9(3)	−14.2(1)	−15.1(1)	2.8(2)	1.2(2)	12.0(1)
N1–C1–C2–C3	θ_{1b}	−10.7(1)	164.9(2)	161.4(3)	−177.9(3)	−180.0(4)	−168.0(2)
N2–C9–C10–C15	θ_{2a}			−0.2(1)		−168.0(3)	
N2–C9–C10–C11	θ_{2b}			179.3(3)		14.0(2)	

[a] X1 = N3, X2 = N4. [b] O–C5. [c] N1–N1a. [d] N1a–N1–C1. [e] C1–N1–N1a–C1a. [f] N1a–N1–C1–C8. [g] N2–C5. [h] N2–C5. [i] C5–C9.

Electronic structures and azine geometries

Resonance form **A** represents the principal resonance form for azines and various others need to be considered in electronic structure discussions. Forms **B** reflect the polarity of the C=N bond (**B1**) and possible delocalizations of positive charge onto the *ortho* (*o*-**B2** and *o'*-**B2**) and *para* positions (**B3**). Forms **C** and **C'** also need to be considered. If these sets of resonance forms all have pairwise equal weight, that is **B** and **B'** (or **C** and **C'**) are degenerate, then the resulting wavefunction will be symmetric (but this does not have to be the case). Of course, if the azine structure is not C_i symmetric, then the pairs **B** (or **C**) and **B'** (or **C'**) are not degenerate. Structural and electronic consequences of asymmetrical substitution of the azines, as in the systems D–C_6H_4–(R)C=N–N=C(R)–C_6H_4–A mentioned in the introduction, differ from the symmetrical azines fundamentally in that the (near) degeneracy of these pairs **B** (or **C**) and **B'** (or **C'**) is purposely eliminated.

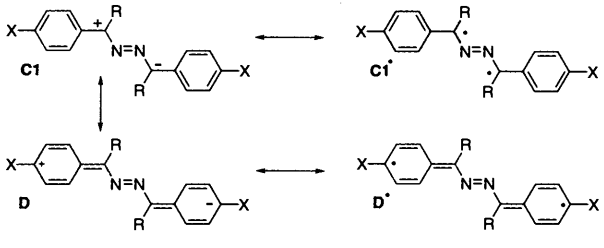


Scheme 1

are derived from **B1** by shifting π-electrons in such a fashion that negative charge is delocalized from the N atom onto the azine C atom (**C1**), the *ortho* position (*o*-**C2** and *o'*-**C2**), and the *para* position (**C3**). The **C**-forms disperse negative charge from an N-atom onto C-atoms, while a positive charge is placed on an sp^2-hybridized C atom in all of the **B**-forms. One might thus expect large contributions from **B**- than from **C**-forms.

All of these resonance forms **B** and **C** are shown in Scheme 1 for one half of the molecule and their symmetry related counterparts (delocalization into the other ring system) **B'** and

Aside from **B** and **C**, many more resonance forms need to be considered in which the types of shift leading to **B** and **C** both occur and, in Scheme 2, **D** is shown as just one such example. **C1**



Scheme 2

and **D** were selected in Scheme 2 to illustrate another important aspect. Linear combinations of equal contributions of **C1** and **C1'** or **D** and **D'** result in the radical resonance **C1'** and **D'** and all of the radical resonance forms resulting from π-electron shifts in the ones shown might also contribute. Sinha suggested that such diradical resonance forms contribute to the ground state of benzaldazine.[21] If these diradical resonance forms were indeed important, one would expect to find N–N *trans* conformations and shortened C_{ipso}–C_{azine} bond for azines with radical-stabilizing X groups (*e.g.*, NMe_2, NH_2, OMe, OH, CN).[22] The discussion below will show that **3** and **8** in fact

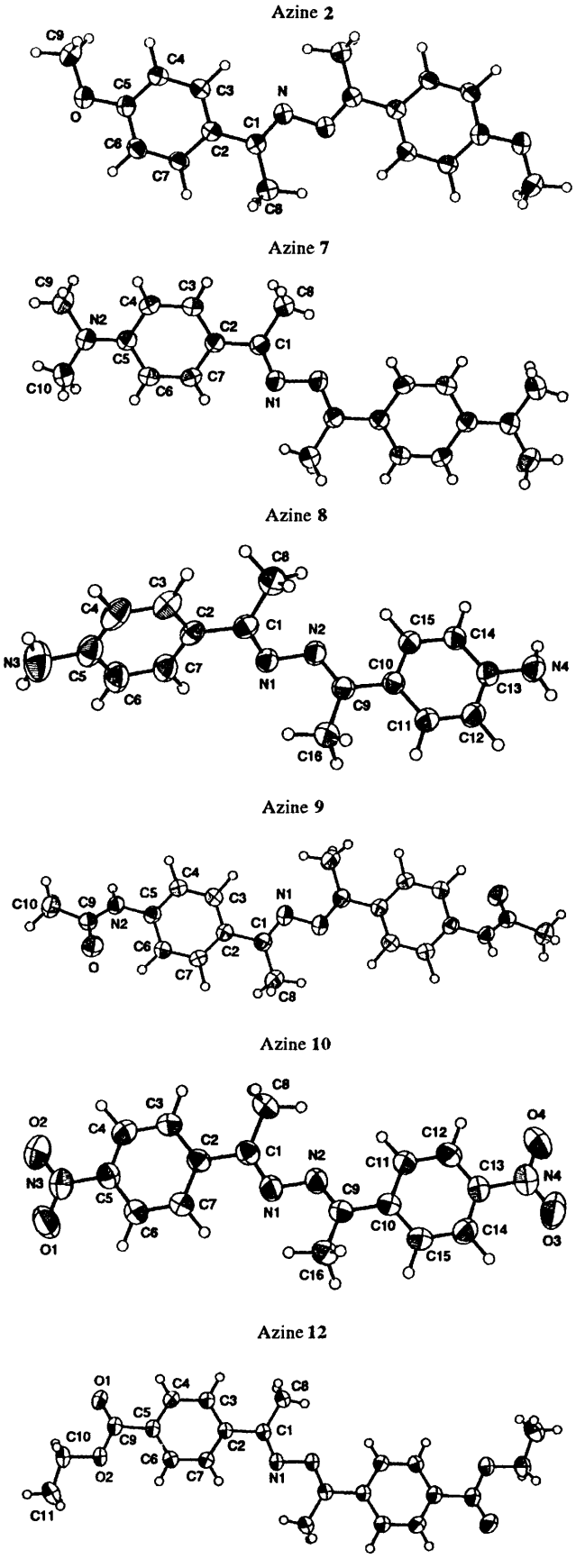


Fig. 1 ORTEPII stereodrawings of the azines **2**, **7**–**10** and **12** with the numbering scheme

assume *gauche* conformations and, more significantly, that the N–N and C_{ipso}–C_{azine} bond lengths do not follow patterns consistent with radical involvement. Consequently, we focus on discussions of the closed-shell resonance forms.

How are these resonance forms to be related to the azine geometries? Significant contributions from **B** will result in longer C=N bonds and shorter C_{ipso}–C_{azine} bonds (**B1**–**B3**). In addition, the **B** forms should result in shorter X–C bonds (**B3**) if X is donating. Significant contributions from **C** will result in shorter N–N bonds and shorter C_{ipso}–C_{azine} bonds (**C1**–**C3**) and, if X is withdrawing, then shorter X–C bonds (**C4**) should also occur. Thus, the changes in the C_{ipso}–C_{azine} bonds indicate whether charge dispersal (of either type) occurs and the relative C–X bond length should indicate whether the dispersed charge is positive or negative. The N–N bond length should shorten only if significant negative charge dispersal occurs. Such negative charge dispersal onto the phenyl rings would be favoured in N–N *trans* conformations. In contrast, significant contributions by the **B** forms would lead to an N–N *gauche* preference for reasons of electron–electron repulsion. Finally, any significant conjugative interaction of the X substituent should favour coplanarity of the phenyl ring with the –CR=N– group.

For clarity, we have summarized in Table 4 the most important structural parameters for the azines **1**–**13**. Their analysis allows one to examine in a systematic fashion the possible relationship between the nature of the X-substituent and stereochemistry. We begin with a conformational analysis, examine intermolecular packing effects in the process, and then turn to a comparative analysis of the 'hard' bond length data.

Intrinsic conformational preferences and packing effects

Conformational analysis of oxygen substituted azines. Azine **2** assumes the s-*trans* conformation and it is C_i symmetric since the phenyl rings both are twisted by ∠(N1–C1–C2–C3), θ_{1b} = −10.7°. Importantly, the crystal of **2** does not contain lattice water and the methoxy groups do not allow for any of the intermolecular interactions that occur for *p*-hydroxyacetophenone azine **3**,[23] and *p*-(difluoromethoxy)benzylideneazine, **6**.[24] Azine **6** is inversion symmetric with both phenyl groups twisted by 11.6°. The acidic H-atom of the $OCHF_2$ group is involved in an H-bond (H···F = 2.46 Å). Azine **3** is *gauche* with τ = 148° with phenyl ring twists of 13° and 20°, respectively, and **3** engages in two types of intermolecular H-bonding. The H- and O-atoms of both OH groups in **3** all are H-bonding to lattice water with OH···O_{water} distances of 1.57 and 1.68 Å and one of the azine nitrogens also is engaged in H-bonding to lattice water with OH_{water}···N = 1.89 Å. These strong H-bonds certainly affect the N–N conformation significantly. Supporting the argument is the observation that the closely related *p*-ethoxy-*o*-hydroxyacetophenone azine[25] shows the s-*trans* conformation with phenyl group twist angles of 4.5°. This azine does not have the types of H-bonding interactions occurring in **3**, but there are intramolecular H-bonds between the OH groups and the azine nitrogens and face-to-face phenyl interactions occur as well.

The crystal structure of anisaldehyde azine, **5**,[26] shows a near N–N s-*trans* conformation (τ = 175.6°) and the phenyl groups are only slightly twisted by 1.8° and 5.2°, respectively. However, the packing diagram shows that the phenyl rings of each molecule of **5** are stacked with the phenyl rings of neighbouring azines. While this stacking interaction might provide an incentive for the near-*trans* conformation of **5**, the *trans* structure of **2** clearly indicates that both **2** and **5** have an intrinsic preference for the *trans* conformation.

The unit cell of *p*-ethylcarbonyloxyacetophenone azine, **4**,[27] contains two symmetry independent C_i symmetric molecules with N–N s-*trans* conformations that differ marginally in their phenyl ring twists (9° *vs.* 11°). The crystal contains layers of

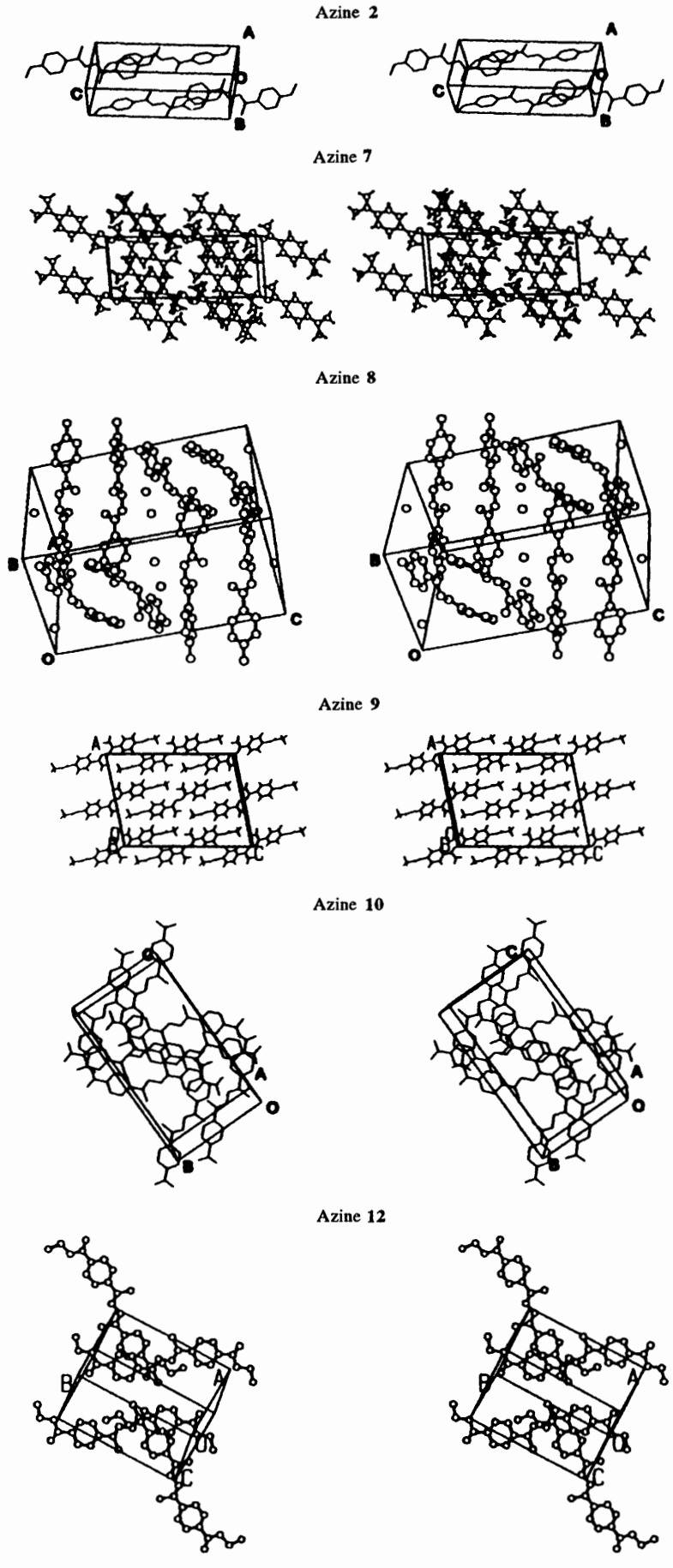


Fig. 2 Packing diagrams: azines **7** and **9** are viewed down the *b* axis

Table 4 Comparison of pertinent structural data

	X	EN	σ_p	R	C–X	C_{ar}–X	Δ(C–X)	C–N–N–C	Ph twist	C=N	N–N	C_{ipso}–C	Note
1a	F	3.95	0.06	−0.39	1.356, 1.358	1.363	0.007, 0.005	138.0	1.9, 18.6	1.284, 1.285	1.396	1.475, 1.476	10(*b*)
1b	Cl	3.03	0.23	−0.19	1.742, 1.743	1.739	−0.003, −0.004	134.7	30.5, 29.3	1.282, 1.288	1.398	1.475, 1.476	10(*b*)
1c	Br	2.80	0.23	−0.22	1.891, 1.904	1.899	0.008, −0.005	124.6	27.2, 20.9	1.264, 1.269	1.383	1.477, 1.478	10(*b*)
2	OMe	3.7	−0.27	−0.56	1.364	1.370	0.006	180	10.7	1.281	1.409	1.479	This work
5	OMe (H)				1.389, 1.395			175.6	1.8, 5.2	1.265, 1.300	1.410	1.480, 1.510	26
3	OH	3.7	0.57	−0.42	1.379	1.362	−0.017	148	13 20	1.278, 1.282	1.417	1.495, 1.499	23
4	OCOEt (A)		0.31[a]	−0.11[a]	1.41	1.401	−0.009	180	9	1.27	1.41	1.51	27
	OCOEt (B)				1.42			180	11	1.288	1.402	1.50	
6	$OCHF_2$ (H)		0.18	−0.19	1.397			180	11.6	1.276	1.413	1.471	24
7	NMe_2	3.0	−0.83	−0.98	1.369	1.371[c]	0.002	180	14.2	1.2855	1.401	1.4722	This work
8	NH_2	3.35	−0.66	−0.74	1.370, 1.388	1.355[d]	−0.015, −0.033	131.1	15.1, 0.3	1.287, 1.289	1.409	1.474, 1.478	This work
9	NHCOMe		0.00	−0.31	1.415	1.419[e]	0.004	180	2.8	1.292	1.395	1.483	This work
10	NO_2	3.4	0.78	0.13	1.456, 1.467	1.468	0.012, 0.001	152	14.0, 1.2	1.273, 1.280	1.398	1.482, 1.491	This work
11	CH_3 (A)	2.3	−0.17	−0.18	1.509	1.506	−0.003	180	23.7	1.279	1.405	1.482	10(*c*)
	CH_3 (B)				1.511, 1.520		−0.005, −0.014	142.8	0.4, 19.9	1.277, 1.282	1.407	1.481, 1.493	10(*c*)
12	CO_2Et	2.85[b]	0.45	0.11	1.491	1.487	−0.004	180	12.0	1.274	1.404	1.487	This work
13	CN	3.3	0.66	0.15	1.435	1.443	0.008	180	0.5	1.277	1.397	1.475	10(*b*)

[a] Value for OCOMe. [b] Mutually consistent group electronegativity for CO_2H or CO_2^-. [c] The bond lengths are 1.371 and 1.426 Å for planar and pyramidal NR_2, respectively. [d] The C_{ar}–NH_2 bonds of planar and pyramidal NH_2 are 1.355 and 1.394 Å, respectively. [e] The C_{ar}–NHR bonds are 1.353 and 1.419 Å for N_{sp^2} and N_{sp^3}, respectively.

stacked molecules in which the molecules are parallel to each other. Ciajolo *et al.* mentioned that the phenyl rings might be twisted out of the azine plane because of repulsion between the phenyl ring and the proximate azine methyl group. Several observations argue against this claim. We have shown that *p*-cyanoacetophenone azine, **13**,[2b] *does* assume a C_{2h} structure. Moreover, the phenyl rings in **5** and **6** are also twisted out of the azine planes even though the substituents on the azine-C are hydrogens. Ciajolo's explanation is inconsistent with our findings which suggest that the variations of the torsion angles of phenyl groups more likely reflect electronic or packing effects.

Conformational analysis of nitrogen substituted azines. Azine **7** assumes the N–N *trans* conformation, it is inversion symmetric, and the phenyl rings are twised by 14.2°. Importantly, **7** does not engage in intermolecular H-bonding and there are only ring–face interactions. In contrast, the parent system **8** shows the *gauche* conformation (τ = 131.1°) and the phenyl rings are twisted by 0.2° and 15.1°. The NH_2 groups in **8** do not form intermolecular H-bonds as in the case of the hydroxy analogue **3** or between the NH_2 groups in crystals of *p*-aminoacetophenone,[28] but H-bonding occurs between the azine-N of **8** and a lattice water [OH · · · N is 2.01 Å, ∠(O–H · · · N) is 168.5°]. The N–N conformation of **8** is likely to be affected by this H-bonding since the *gauche* form allows for optimal orientation of the azine N lone pair toward the H-bonding acceptor. Azine **9** shows the N–N s-*trans* conformation and the phenyl groups are coplanar with the azine fragment. However, only C_i symmetry results because the amide groups are twisted out of the plane of the aromatic rings by 41.0° to engage in intermolecular C=O · · · H–N hydrogen bonds along the *b*-axis (N2 · · · O is 2.997 Å). Azine **9** is closely related to *p*-acetamidinobenzoic acid[29] in which the amide group also is rotated by 40.4° against the benzene ring to allow for such amide–amide H-bonding.[30]

The NH_2-[31] and NH-hydrogens were refined for **8** and **9** and the *N*-methyl conformations were determined for **7**. The NH_2 groups in **8** both are nearly planar around N (angle sum at N ≈ 358° and 351°) and they differ somewhat regarding the twisting about the C–N bonds (dihedral angles C4–C5–N3–H 7.2° and 172.9°; C14–C13–N4–H −18.9° and 165.6°). The amide-N atoms in **9** are planar (angle sum at N ≈ 359°). In the methylated system **7**, the amino-N atoms are also essentially sp^2 hybridized and the NMe_2 groups almost are coplanar with the phenyl planes (C6–C5–N2–C10 and C4–C5–N2–C10 are −0.8° and 178.7°) even though the NMe_2 methyl groups are just within van-der-Waals distance of the *ortho*-H atoms (vdW radius of H is 1.2 Å).

The nitro-substituted azine **10** is *gauche* with τ = 152.0° and the two phenyl ring twists of 1.2° and 14.0° are markedly different. There are no specific intermolecular interactions in **10** and the molecules align with alternating stacking direction. The *E,E*, *E,Z* and *Z,Z* isomers[11] of *o*-nitroacetophenone azine, **10b**, were isolated and the X-ray structures of the *E,E*-**10b** (τ = 180°) and *E,Z*-**10b** (τ = 166.1°) were determined.[32] The C_{ipso}–C_{azine} bond and the C=N bond lengths are very close for **10** and both isomers of **10b**. However, the N–N and the C–NO_2 bond lengths of azines **10b** are longer by 0.022 Å and 0.024 Å, respectively, than those of **10**. In *E,E*- and *E,Z*-**10b**, the phenyl rings twist from the azine fragment by 38.5° and 37.0°, respectively, and the best planes of the NO_2 groups and the corresponding phenyl rings enclose angles of 52.0° and 59.2°. Hsu *et al.*[32] suggested that these deviations in **10b** are caused by steric repulsion between the NO_2 group and the azine N-atoms. The structures of **10b** thus do not allow the assessment of intrinsic conformational preference. In **10**, however, no such intramolecular neighbouring groups are possible and in their absence, we find that the NO_2 group prefers near-coplanarity with the phenyl rings and the twisting about the C_{ipso}–C_{azine} bonds is much smaller than in **10b**. Note that the phenyl rings remain twisted in **10**, that is, the phenyl rings in **10** do not show a

clear and strong preference for coplanarity with the –CMe=N– fragment even in the absence of intramolecular steric repulsion.

Conformational analysis of carbon substituted azines. Polymorphism realizes both the s-*trans* and *gauche* conformations for **11**.[10c] The phenyl rings twist by 23.7° in the C_i symmetric molecule and they twist by 0.5° and 19.9° in the *gauche* structure with τ = 142.8°. *Ab initio* calculations at the RHF/6-31G*//RHF/3-21G level showed a *trans* preference while our more recently refined studies at the RHF/6-31G* level indicate that a *gauche* structure with τ = 164.6° is 0.75 kJ mol^{-1} more stable than the *trans* structure.[33] Independent of the theoretical level, it is the most important result of the theoretical analysis that the energy required for the deformation to the *gauche* structure is less than 2.0 kJ mol^{-1}.

There are no intermolecular H-bond interactions in the crystal structures of the acceptor-substituted azines **12** and **13**. Both of these azines realize N–N s-*trans* conformations but only **13** is C_{2h} symmetric. In **12**, the carboxy groups are in nearly ideal conformations to conjugate with the phenyl rings [∠(O1–C9–C5–C4) = 5.3° and ∠(O2–C9–C5–C4) = 175.0°], but the phenyl rings twist by 12.0° about the C_{ipso}–C_{azine} bonds in the C_i symmetric structure of **12**.

N–N conformation and stereoelectronic substituent influence. Forms **B** might be expected to predominate in azines with substituents capable of stabilizing electron deficiencies *via* π-donation (**1**, **2**, **3**, **5**, **7** and **8**) and cause N–N *gauche* conformations. On the other hand, **C** could be more important for **10**, **12** and **13** and tend to favour N–N s-*trans* conformations. The halogenated systems **1** as well as the parent hydroxy and amino systems, **3** and **8**, do assume *gauche* conformations. However, our analysis demonstrates that this finding *cannot* be taken as evidence for the importance of **B**. Our careful analysis suggests an intrinsic preference for the N–N *trans* conformation in RO- and R_2N-substituted azines which might be obscured by packing and specific intramolecular interactions. Similarly, the NO_2 group is the strongest π-withdrawing group but **10** assumes the *gauche* conformation nevertheless. The comparative analysis of the large set of X-ray data provides compelling evidence that the N–N conformation *is not* a good indicator of intrinsic electronic preferences because of the low energy requirements for N–N conformational deformations and the clearly demonstrated dependence on intermolecular interactions in the solid state.

Phenyl ring twisting about the C_{ipso}–C_{azine} bonds. Remarkably, among all of the symmetrical acetophenone azine crystal structures known to date, the cyano-system **13** is the only one with C_{2h} symmetry. Aside from **13**, azine **9** is the only other system in which the phenyl rings are coplanar with the azine function. All the other N–N s-*trans* azines **2**, **4**, **6**, **7**, **11** and **12** are inversion symmetric only because of twisting of the phenyl rings out of the best plane of the azine functional group. The same is true for the N–N *gauche* structures; the data in Table 4 show that the phenyl groups in the *gauche* azines are twisted similarly.[34] *The placement of the phenyl ring in strict coplanarity with the azine functional group thus is the exception rather than the rule.* We showed that the Ph–C rotational barrier in HO_2C–C(Ph)=N–N=CH_2 [10a] is less than 21 kJ mol^{-1} and this value represents an upper limit for acetophenone azines because of the electron-withdrawing nature of the CO_2H group. The phenyl rotational barriers in *para* X-substituted acetophenones, *para*-X–Ar–COMe, are 18–35 kJ mol^{-1} (18.4 for X = NO_2, 22.4 for X = H, 27.6 for X = OMe and 34.7 for X = NMe_2)[35] and the direction of the substituent effects are as expected. We conclude that the conjugation between the azine group and the phenyl ring is *less* than the respective interaction in the carbonyls and that the twists of the phenyl rings in the acetophenone azines are strongly affected by the stacking in the solid state. Hence, the C_{2h} symmetry of **13** in the solid state cannot be taken as evidence for an intrinsic preference but more likely is beneficial to the packing of the layers of stacked azines.

Bond length variations as probes for substituent effect in azines

Data pertinent to the analysis of azine bond lengths are collected in Table 4 and include mutually consistent group electronegativities EN,[36] Hammett substituent constants σ_p and resonance factors R,[37] and the average crystallographic C_{ar}–X bond lengths.[38] We consider first the response of the azine functional group to variations of the X substituent and subsequently examine the sensitivity of the C–X bonds on the nature of the *para*-substituent.

Substituent effects on N–N, C=N and C_{ipso}–C_{azine} bond lengths

The N–N bonds of **1–13** fall in the range 1.383–1.417 Å and the C=N bond lengths are in the range 1.264–1.300 Å and near the standard C_{sp^2}–N distance of 1.279 Å.[38a] The C_{ipso}–C_{azine} bonds are in the range 1.471–1.510 Å and close to the typical C_{sp^2}–C_{sp^2} single bond length of 1.485 Å.[39] Most importantly, *none of the variations of these bond lengths correlate with the properties of the X-substituents in any systematic fashion for all of the azines* **1–13**.

The C=N and C_{ipso}–C_{azine} bond lengths within the two halves of **5** differ dramatically. In the fragment with θ_1 = 1.8°, the C=N and C_{ipso}–C_{azine} bonds of 1.265 and 1.510 Å, respectively, are 0.035 Å shorter and 0.030 Å longer, respectively, than those in the fragment with θ_2 = 5.2° (1.300 and 1.480 Å). This difference in the C=N distances in **5** is entirely due to packing effects and it is nearly twice as large as the entire range in the C=N distances in **1–13**!

The *para*-MeO azines **2** and **5** are very similar and they merely differ in the azine-C atoms' substituents which are Me or H in **2** and **5**, respectively. One would reasonably assume to find this close similarity reflected in the solid-state data since both of the crystals exhibit no strong intermolecular interactions and show (nearly) *trans*- N–N conformations. But the structural characteristics of **2** and **5** differ dramatically. The C=N bonds in C_i-**2** are equal, while crystal packing distorts **5** so drastically that one of the C=N bonds is ≈0.02 Å longer and the other is shorter by the same amount. The two phenyl systems respond differently to these C=N bond changes but both MeO–C bonds in **5** are longer by 0.03 Å than those in **2**. Azine **6** is symmetric and shows similar structural parameters to **2** with one exception: the F_2CHO–C bond lengths are 0.033 Å longer in **6** than in **2**. *The replacement of the* MeO *group in* **2** *by the electronically quite different* F_2CHO *group in* **6** *leads to comparable* O–C *bond length changes as occur between* **2** *and* **5** *as the result of mere packing differences.* These comparisons of **5** and **6** with **2** show beautifully just how treacherous the interpretation of structural data can be!

Bond lengths in general are essentially the same for **7** and **8** except for the C_{para}–N bonds which are slightly (< 0.01 Å) shortened upon methylation. The C=N and the C_{ipso}–C_{azine} bonds within the two halves of the nitro compound **10** are somewhat shorter and longer, respectively, than those in **7** and **8**, whereas the C_{para}–N bonds are much longer (> 0.08 Å). Azine **7** assumes the s-*trans* conformation which would allow for conjugation over the entire azine system.[40] However, the C=N, N–N and C_{ipso}–C_{azine} bond lengths do not show structural evidence for such conjugation. Azine **8** assumes the *gauche* conformation and its two phenyl rings are twisted to different extents. Yet, the C=N and C_{ipso}–C_{azine} bonds within the two halves of **8** are identical and this finding indicates that there is no significant conjugation even within either of the Ar–C=N fragments. Moreover, the C=N, N–N, C_{ipso}–C_{azine} and C–NR_2 (R = Me, H) bond lengths in **7** and **8** are almost the same. In fact, the analysis of **1–13** demonstrates in a compelling fashion

that the C=N–N=C conformation essentially does not affect the bond lengths and this important result confirms and strengthens the deduction made earlier in the discussion of the polymorphism of *p*-methylacetophenone azide.[10c]

The examples show clearly that the changes associated with intrinsic electronic effects are easily dominated by packing effects. The lack of systematic structural variations as a function of X is one consequence. We conclude that the solid-state data do not and cannot be expected to provide convincing structural evidence for or against conjugation of the phenyl rings with the entire azine fragment or within the N-analogue vinylbenzene subsystems.

C–X bond lengths and 'typical' values. The Δ(C–X) values in Table 4 specify the differences between the C–X bonds in the azines compared with typical C_{ar}–X bonds. For most substituents, the Δ(C–X) values are lower or of the same magnitude as the standard deviations seriously limiting or impeding any deductions regarding electronic structure. Larger |Δ(C–X)| values, such as for **3** and **8**, are also difficult to interpret rigorously. For **3**, specific intermolecular interactions affect the C–O bond and Δ(C–O). The Δ(C–N) value for **8** is free of such packing effects, but in this case questions about the reference remain. The negative values for the NH_2 group do not indicate the absence of conjugation but rather they indicate less conjugation than in the molecules used to determine the reference for the planar NH_2 group. Ideally, one would want to compare the N–C bond in **8** to the N–C bond in aniline with *the same* NH_2 conformation. Unfortunately, this is not possible since aniline crystallizes with a pyramidal NH_2 group.[38b] Note however that the C–N bonds in **8** are, on average, somewhat shorter than in aniline.

X–C correlation with LFER substituent parameters. The *R* values of the *O*-substituents show that the electron-donating ability of the *O*-substituents decreases in the order MeO > HO > F_2HCO > RCOO and it is found that the *para* C–O bonds become longer with decreasing π-donating ability. According to the *R* values, NMe_2, NH_2 and NHCOMe are all π-electron donating, and more so for NMe_2, while NO_2 is electron-withdrawing. As with the *O*-substituents, we find that the C_{para}–N bonds become longer with decreasing π-donating ability of X.[41] Note that there is no simple relationship between the substituent σ_p and the C–X bond lengths.

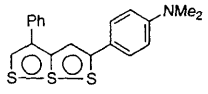
Characterization of the azine function as a benzene substituent

So far, we have viewed **1–13** as 'phenyl substituted azines'. We now change perspective and consider these molecules as '*para*-disubstitued benzenes' in which X is one substituent and an azine function is the other. The –CMe=N–N=CMe(C_6H_4–X_{para}) group varies but the changes due to X are so small (*vide supra*) that it is fully justified to refer to all the azine groups simply as the azine group –CMe=N–N=CMePh, or –Az for short. We have reviewed the X-ray crystallographic data published for a variety of X–C_6H_4–Z compounds. Comparisons of the X–C bond variations in X–C_6H_4–Z and X–C_6H_4–Az allow one to examine the sensitivity of the C–X bonds on the nature of the *para*-substituent and to rank the electron-withdrawing ability of the Az group.

C–X bonds in halogen-substituted azines. The X–C bond lengths in the *para*-halogen substituted acetophenone azines are nearly identical (considering the estimated standard deviations) with those in the corresponding *para*-halogen substituted benzoic acids. For the fluoro- and chloro-substituted benzoic acids the C–X bond lengths were established in several independent X-ray investigations. The F–C bonds are 1.356(3) and 1.358(3) Å in **1a** and values of 1.360(4)[42a] or 1.364(3)[42b] Å were reported in two studies of *para*-fluorobenzoic acid. The Cl–C bonds are 1.7420(22) and 1.7426(24) Å in **1b** and they are close to the Cl–C distances of 1.7352(7),[43a] 1.736(2)[43b] or 1.744(5)[43c] Å determined in three X-ray analyses of *p*-chlorobenzoic acid. The Br–C bonds are 1.904(5) and 1.891(5) Å in **1c** and 1.902(10) Å in *p*-bromobenzoic acid.[44] These halogen–C bond lengths indicate that the electron-withdrawing ability of the azine group is close to that of a carboxylic acid group.

C–X bonds in oxygen-substituted azines. The O–C bonds indicate that the Az function is less electron-withdrawing than are the carbonyl and oxime groups. The HO–C bond of 1.379 Å in **3** is longer than the bond of 1.358 Å in *p*-hydroxybenzaldehyde[45] and that of 1.3607 Å in (*E*)-4-hydroxybenzaldehyde oxime.[46] Similarly, the MeO–C bonds in **2**, **5** and **6** also are longer compared with the MeO–C bond of 1.355 Å in 2-chloro-4'-methoxyacetophenone.[47]

C–X bonds in nitrogen-substituted azines. The C–NMe_2 bond lengths are 1.369 Å in **7** and very close to the bond lengths of 1.361 Å in the 2-(*p*-dimethylaminophenyl)-4-phenyl-6a-thiathiophthene[48] shown and of 1.365 Å is one of the two



molecules of *N*,*N*-dimethyl-*p*-nitrosoaniline.[49] This close similarity provides strong evidence that *the azine substituent is a very potent electron-withdrawing functional group capable of engaging in strong push–pull interactions.* In **8**, the C–NH_2 bonds are 1.370 and 1.388 Å long and their average is close to the length of 1.376 Å in *p*-aminoacetophenone.[28] These bonds are longer than the C–NH_2 bond length of 1.36 Å in *p*-nitroaniline.[50] In comparison with the RO-substituted systems, the nature of the electron-withdrawing group *para* to the amino group affects the C–NR_2 bonds less. The amino groups interact with the phenyl system in all cases, while the hydroxy groups are 'good π-donors' only if strong electron-withdrawing groups are present 'to pull'. The C_{para}–N bonds in **9** are almost the same as the C–N bond in *p*-acetamidinobenzoic acid[29] (1.415 Å in **9** and 1.42 Å in the acid) and similar to those in other *N*-aromatic amides.[51]

The C–NO_2 bond lengths in **10** are 1.456 and 1.457 Å and somewhat shorter than the bond length of 1.466 Å in *p*-nitroacetophenone[52] but, as expected, much longer than in *p*-nitroaniline (1.39 Å). With the O–C analysis above, these data are consistent with assigning the azine function a slightly lower withdrawing ability compared with the carbonyl group.

C–X bonds in carbon-substituted azines. There are no strong intermolecular interactions in the *para*-carbon substituted azines. As expected, the C_{sp^2}–C_{sp^3} C_{para}–Me bond lengths in **11** are longer than the C_{sp^2}–C_{sp^2} C–CO_2Et bonds in **12** and the C_{sp^2}–C_{sp} C–CN bonds in **13**. The C–Me bonds in **11A** and **11B** are all longer than that of 1.485 Å in *p*-azotoluene.[53] The C–CO_2Et of 1.491 Å is close to those of 1.497 and 1.501 Å in ethyl *p*-azoxybenzoate.[54] Two crystal-structure determinations have been reported for *p*-dicyanobenzene which resulted in C–CN distances of 1.438(3)[55a] and 1.451(13) Å.[55b] The refinement by Drück and Littke gives the slightly better *R* factor but it is based on fewer independent reflections compared to Rij and Britton and the results of both studies are therefore of about equal quality. Thus, the C–CN bond length of 1.435(5) Å in **13** is very close to the respective value in the *p*-dicyanobenzene.

Conclusion

Potential conjugative interactions are pivotal to discussions of the stereochemistry and of the electronic structure of azines. In valence-bond terms, this question reduces to the assessment of the X substituents' abilities to stabilize positive (**B** forms) or

negative (**C** forms) charge. Both modes of charge dispersal would lead to C=N bond polarity reduction. Structural parameters were identified that may indicate the relative significance of the various resonance forms.

Strong conjugative interactions of the aromatic rings with the azine (or imino) functional group(s) would be expected to find manifestation in C_{ipso}–C_{azine} conformations allowing for optimal conjugation ($\theta = 0°$). For azines with $-M$ substituents one might expect N–N s-*trans* conformations and consequently overall planar structures. Only one of all the azines, **13**, realizes C_{2h} symmetry and there is evidence to suggest that this symmetry is beneficial for its packing. In both the N–N s-*trans* or *gauche* structures, the C_{ipso}–C_{azine} $\theta = 0°$ conformations are the exception rather than the rule. The C_{ipso}–C_{azine} rotational barrier is *lower* than in the respective carbonyls and the θ twists in the azines are strongly affected by the crystal packing. The N–N conformation is *not* a good indicator of intrinsic electronic preferences because of the low energy requirements for τ variations and its dependence on intermolecular interactions.

Among the 'hard' parameters, the X–C, N–N, C=N and C_{azine}–C_{ipso} bonds are critical and the analysis shows that none of the variations of these bond lengths correlate with the properties of the X-substituents in any systematic fashion for all the azines **1**–**13**. Several examples clearly illustrate that the *modest changes associated with intrinsic electronic effects can be and often are completely dominated by packing effects*. There is evidence that the C–O and the C_{para}–N bonds lengthen with decreasing π-donating ability of X and this finding is consistent with positive charge dispersal in the azines (**B** forms). From the analysis of the solid-state structures of a series of acetophenone azines, we must conclude that there is no convincing structural evidence either for or against conjugation between the phenyl rings with the entire azine fragment or within the N-analogue vinylbenzene subsystems.

The analysis of **1**–**13** as '*para*-disubstituted benzenes X–C_6H_4–Az' in comparison with compounds X–C_6H_4–Z allows us to rank the electron-withdrawing ability of the Az group. It is found that the electron-withdrawing ability of the azine functional group is comparable to the carboxy (hal–C bond analysis), nitroso (N–C bond analysis), azoxy and cyano (C–C bond analysis) groups, less compared with the carbonyl (O–C and N–C bond analysis), oxime (O–C bond analysis), and azo (C–C bond analysis) groups and significantly less than the nitro group.

Since the observed relative changes are of the same magnitude as are the typical standard deviations of the parameters examined, additional information is required to address questions concerning the underlying electronic structures. The experimental determination of electron density distributions does provide such additional information but these experiments remain difficult and expensive and the technique is not generally available. On the other hand, the reliable computational determination of electron density distributions at high levels has matured and this technique has become widely available due both to progress in hardware performance and significant advances in quantum-mechanical software development. We have thus begun *ab initio* studies of azines in the gas phase and in the solid state in the quest to a better understanding of the stereochemical preferences and the electronic structures of azines.

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