Conjugation in Azines. Stereochemical Analysis of Benzoylformate Azines in the Solid State, in Solution, and in the Gas Phase†

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The stereochemistry of benzoylformate azines **3** was studied in the solid state (X-rays, IR), in solution (^{1}H-, ^{13}C-, and ^{15}N-NMR), and in the gas phase (ab initio theory). Benzoylformate azines are excellent systems to study phenyl conjugation because the ester substituent is electron-withdrawing *and* in a conformation that impedes π backdonation thereby causing the azine-C to be highly electron-deficient and an excellent potential acceptor for π-donation. The X-ray structure of ethyl benzoylformate azine (**3a**) is reported and compared to the crystallographic record. Azines **3** assume the N–N s-*trans* conformation and the *Z,Z* configuration. The phenyl groups are in the molecular plane of the C_i-symmetric azine while the carboxyl groups lie in planes that are nearly perpendicular. The solid-state structures are compared to optimized ab initio structures of geometrical isomers of **3**. RHF/6-31G*//RHF/3-21G energies indicate the ordering *Z,Z* > *E,Z* > *E,E* for the thermodynamic preferences and suggest that **3** prefers the same stereochemistry in the gas phase as in the solid state. Phenyl conjugation is shown to be of little importance. ^{1}H-, ^{13}C-, and ^{15}N-NMR spectroscopic analyses indicate the presence of one isomer in solution consistent with the stereochemical preferences found in the solid state and in vacuum. Infrared (calcd and exptl) and Raman (calcd) spectra show features characteristic of azines, but only the latter might be useful in stereochemical analyses. The stereochemical preferences differ markedly from those of the azines of esters, and an explanation is proposed.

Introduction

The addition of azines to isocyanates and maleic acid anhydride[2,3] are early examples of *criss–cross* additions, that is, 1,3-dipolar cycloadditions to form 1,5-diazabicyclo-[3,3,0]octanes.[4] Wagner-Jauregg pointed out that their importance for the synthesis of 5-membered rings parallels the significance of the Diels–Alder reaction in 6-ring chemistry. The scope of dienophiles[5] was greatly expanded[6] ever since.[7] The *criss–cross* addition is remarkable in that other related aza-derivatives always react in a Diels–Alder fashion.[8,9] Huisgen suggested azomethine imines as the key intermediate in the *criss-cross* addition[10] involving two [3 + 2] additions. This mechanism was supported by Tipping[11] and Burger,[12] while other mechanisms are operative in some cases.[13] The discovery of the [3 + 2] addition of azomethine imines to phosphaalkenes is related to the *criss-cross* addition,[14] and aldazines react with *C*-acetyl and *C*-(ethoxycarboxyl) nitrile imines as the "ene" to 5-membered heterocylces as [3 + 2] cycloadducts.[15] Azines become more important for CC bond formation to afford, for example, bis α,β-unsaturated azines and diazepines.[16]

Azines are easily synthesized[17,18] by reaction of carbonyls with hydrazines or hydrazones, and they have received increasing attention recently for their own sake. Some heterocyclic azines inhibit murin tumor growth[19] and act as fluorescent brightening agents and as photosensitizers,[20] and azines were developed for use as ion-selective optical

† Dedicated to Ernst Glaser on the occasion of his 60th birthday.

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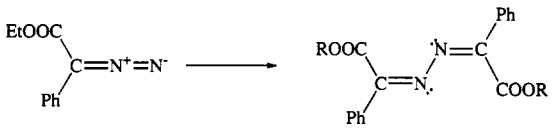
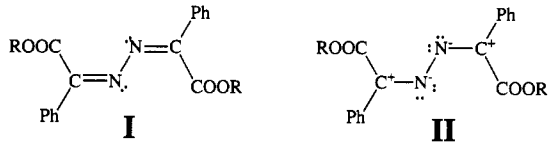
Scheme I



2 3a, R = Et

sensors.[21] Mixed azines between opioid anatagonists and steroidal ketones[22a] show various biological effects including ultralong opioid antagonist activity[22b] and specificity for the opioid δ receptor.[22c]

Considering the many applications of azines as well as their importance in synthesis, the stereochemical characterization of azines has received little attention. Azines are stereochemically versatile not only with regard to N–N conformation and C=N configuration, but also regarding questions of stereochemical manipulation via substitution. Phenyl-substituted azines play an especially important role in azine chemistry, and the effects of possible conjugation have not been explored in a systematic fashion. Theoretical and spectroscopic gas phase studies focused primarily on the N–N conformation of formaldazine, a series of larger azines were studied by X-ray crystallography, and a few reports on dynamic stereochemistry in solution were reported (*vide infra*). In this context, the stereochemical characterization of benzoylformate azines plays a special role for the examination of phenyl substitution in general. Do phenyl substituents interact strongly with the adjacent C=N bonds or is there a preference for π conjugation in the azabutadiene system? The ester substituent is electron-withdrawing *and* it assumes a conformation that impedes π back-donation (*vide infra*), and thus, *benzoylformate azines are excellent systems to study phenyl conjugation* and its potential structural effects since the azine-C is highly electron-deficient and an excellent acceptor for phenyl π-donation (**II**).



I II

In this paper, we discuss the stereochemistry of benzoylformate azines in the solid state, in solution, and in the gas phase. The crystal structure of methyl benzoylformate azine (**3b**) was known, and we report the X-ray structure of ethyl ester **3a** to substantiate the intrinsic structural properties in the solid state. As part of our studies of β,β-disubstituted vinyldiazonium ions, 1,[23] we prepared ethyl phenyl diazoacetic esters **2** and discovered that neat **2** forms **3a** (Scheme I) in a form suitable for X-ray analysis. We discuss the formation of **3a** from **2** and we compare the crystal structures of **3** to other azines. These X-ray data are used to judge the performance of molecular orbital calculations and we report ab initio results for geometrical isomers of **3**. The structural characterizations in the solid state via X-ray diffraction and IR spectroscopy and in the gas phase via ab initio theory are complemented by solution-phase ^{1}H-, ^{13}C-, and natural abundance ^{15}N-NMR spectroscopy. Substituent conformational preferences are studied for the configurational isomers. The stereochemical preferences are contrasted to those of azines of esters and an explanation for the differences is proposed.

Results and Discussion

Azine Formation via Thermal Diazoester Decomposition. Our interest in azines arose in our studies of *aliphatic* diazonium ions, the vinyldiazonium ions **1**. All of the stable ions[23] **1** known do not carry any α-substituent E ≠ H.[24] We are synthesizing α-substituted derivatives to explore the effects on the electronic structure with the goal of reversing the C=C bond polarity.[25] β,β-Dialkoxy-1 ions are prepared by alkylation of diazoacetic esters with trialkyloxonium salts.[26] In the course of the preparation[27] of **2**, the precursors for α-phenyl-1, by diazotization of phenyl glycine ester with isoamylnitrite, we discovered that neat **2**, a red oil, very slowly solidified to form pale yellow crystals of **3a** (Scheme I) when **2** was kept at room temperature and under air for more than 20 days. Even after 4 months, some unreacted **2** was still present. **3a** was previously synthesized by transesterification of **3b**, which was prepared from methyl benzoylorthoformate azine in acidic methanol[28] following a different route. The solid-state structure of **3b** was reported, and comparison of **3a** and **3b** allows one to examine the structural effects of the ester group.

Coupling of a hydrazone with a ketone fails for **3a** and **3b**. The attempted synthesis of **3b** via reaction of hydrazine with excess methyl benzoylformate in MeOH produced the azine only as a minor product.[29] Similarly, we made the ethyl phenylglyoxylate hydrazone by reaction of ethyl benzoyl formate with hydrazine hydrate in aqueous acetic acid, and no azine was formed. The hydrazone was prepared because it is the precursor of choice for the preparation of **2** by lead acetate oxidation.[30] The formation of only the *syn* hydrazone seemed like a plausible cause preventing azine formation because of intramolecular H-bonding with the carbonyl-O, but the ^{1}H NMR of the hydrazone of the ethyl ester shows a mixture of both

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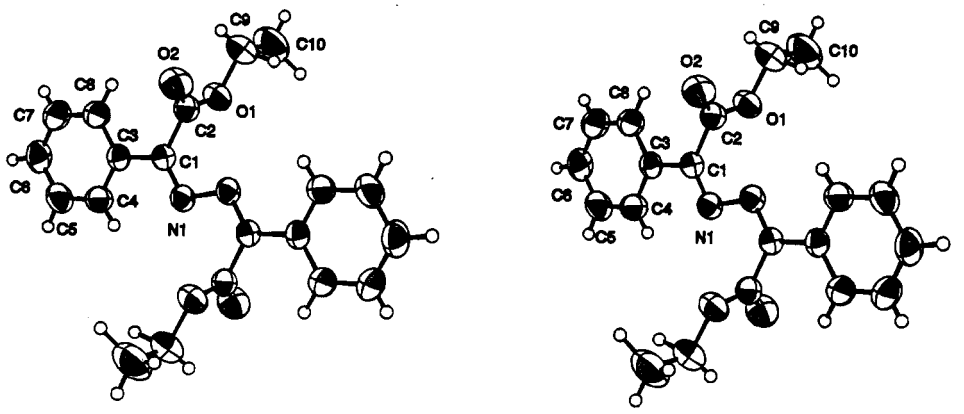

Figure 1. Stereoview of the molecule **3a** with numbering scheme. Thermal ellipsoids are drawn at the 50% probability level. Selected important bond lengths (in Å) include N(1)–N(1)a = 1.418(3), N(1)–C(1) = 1.28(2), C(1)–C(2) = 1.512(3), C(1)–C(3) = 1.473(2), important bond angles (in deg) include N(1)a–N(1)–C(1) = 111.5(2), N(1)–C(1)–C(2) = 121.7(2), N(1)–C(1)–C(3) = 120.3(2), and the pertinent torsional angles (in deg) are N(1)–C(1)–C(2)–O(1) = 89.12(2), N(1)–C(1)–C(2)–O(2) = –92.0(2), N(1)–C(1)–C(3)–C(4) = –6.4(2), and N(1)–C(1)–C(3)–C(8) = 175.3(2).

geometrical isomers[31] (their signals were assigned in analogy to the assignment reported for the methyl ester by Ciganek.[30])

Azines are known to be formed in decompositions of alkyl- and aryldiazomethanes by Lewis acids ZnX_2[32a,b] and Rh(II) acetate.[32c] The former reaction is thought to involve the initial formation of a carbenoid which is then added to diazoalkane while the latter formation more likely involves carbenes. In addition, two possible pathways for *thermal* azine formations have been discussed:[33] Unimolecular thermal formation of a free carbene from diazomethane followed by addition to the corresponding diazomethane (path A) and dimerization via the reaction (path B) involving addition of the nucleophilic methylene carbon of one diazomethane to the electrophilic N_β atom of another. The carbene addition to diazoalkane is a thermally allowed $[_\sigma 2_s + _\sigma 2_a]$ addition which is precedented in related $[_\sigma 2_s + _\pi 2_a]$ systems.[34] The azine formation from diazoalkanes in the presence of nonafluorobutanesulfonic anhydride[35] may be regarded as a variation of path B that involves diazoalkane addition to a sulfoxide-stabilized cation. Reports on the formation of azines from α-diazocarbonyl compounds are still rare,[33] and kinetic studies will have to show whether path A or B is preferred or whether other mechanisms, such as diazoalkane dimerization followed by N_2 extrusion, might be important.

Crystal Structure of Ethyl Benzoylformate Azine. An ORTEPII[36a] stereo drawing and a stereo PLUTO[36b] packing diagram are shown in Figures 1 and 2, and final positional parameters are given in Table I. **3a** assumes the N–N s-*trans* conformation with a torsional angle of $\tau = 180°$, and moreover, **3a** is planar and C_i symmetric. The energetic advantage associated with the planarity of the "*trans*" conformation is an interesting question because as many azines realize *gauche* conformations with τ angles $115° < \tau < 150°$ [28,37,38] as are known to have torsional angles of $\tau = 180°$, and in one case it was possible to crystallize two conformers of the azine of (3-acetyl-4-(2-chlorophenyl)-4-hydroxy-2-methoxycrotonic acid lactone).[39] Lai and co-workers pointed out that the C–N and N–N distances do not depend on the N–N conformation. For **3a**, the N(1)–N(1)a and the C(1)–N(1) bond lengths are 1.418 and 1.277 Å, respectively, and they fall within the typical ranges (1.38–1.42 Å for N–N, 1.27–1.30 Å for C–N[40]) and, if anything, indicate less conjugation in **3a**

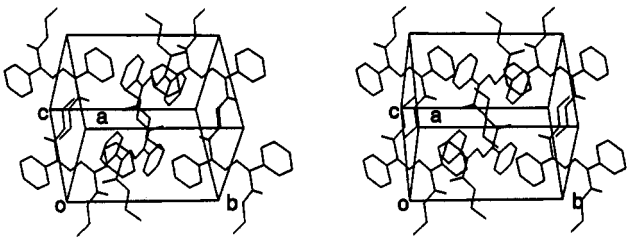

Figure 2. Stereoview of the packing interactions in ethyl phenyl benzoylformate azine (**3a**).

Table I. Positional and Equivalent Isotropic Thermal Parameters, with esd's in Parentheses[a]

	x	y	z	B_{iso}[b]
N(1)	0.4289(2)	0.9750(1)	0.0073(2)	3.75(7)
C(1)	0.4390(2)	0.9032(2)	0.1097(2)	3.36(7)
C(2)	0.5888(2)	0.8755(2)	0.1966(2)	3.87(8)
O(1)	0.6159(2)	0.9489(1)	0.3021(2)	4.81(6)
O(2)	0.6675(2)	0.7963(1)	0.1717(2)	5.80(8)
C(3)	0.3031(2)	0.8439(2)	0.1454(2)	3.59(7)
C(4)	0.1606(2)	0.8728(2)	0.0783(2)	4.57(9)
C(5)	0.0339(3)	0.8192(2)	0.1159(3)	5.4(1)
C(6)	0.0465(3)	0.7366(2)	0.2195(3)	5.5(1)
C(7)	0.1865(3)	0.7073(2)	0.2866(3)	5.9(1)
C(8)	0.3160(3)	0.7598(2)	0.2500(2)	4.9(9)
C(9)	0.7577(4)	0.9308(3)	0.3959(4)	6.9(1)
C(10)	0.7643(5)	1.0194(4)	0.5068(4)	8.7(2)

[a] There are symmetry-equivalent atoms. [b] B_{iso} is the mean of the principal axes of the thermal ellipsoid.[66]

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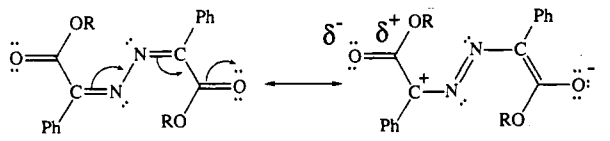
Scheme II



than in other azines. However, the structural argument alone mightnot reflect electronic factors because *shorter* N–N bonds were found for *gauche* than for planar *trans* azines.

Just like **3b**, **3a** is *Z,Z* configured, that is, the Ph group and the imine-N (N′) attached to the C=N bond are *trans*. Most 1,4-diphenyl azines have "*trans,trans*" structures although this fact is somewhat obscured by the *E/Z* nomenclature which assigns *E,E* to most 1,4-dialkyl-1-4-diphenylazines.[39,41] The available data suggest that the bulkier group generally is placed *trans* to N′ to reduce repulsive interactions with the N′ lone pair. Only in tetrachloropropiophenone azine,[28] the large $-CCl_2CH_3$ competes successfully with the Ph group for the *trans* position.

Some studies suggest low barriers for *E/Z* isomerization implying that the configurations in azines reflect thermodynamic preferences. *E/Z* isomerization requires rotation about the N–N bond and N-inversion. The interconversion between *E,E* and *Z,Z* isomers involves two rotation–inversion sequences. For the special case of bis-(dimethyl malonato)ketazine (A = B), this process becomes an automerization and its activation energy is only 8.7 kcal/mol,[32c] a value that is lower than $E_A \approx 21$ kcal/mol for the corresponding process in related hydrazones.[42] Also, the azine formed by diazoethane and α-diazo-*p*-nitroacetophenone results in a mixture of geometrical isomers,[43] and importantly, it was shown that the thermodynamically more stable *E* isomer can be obtained by heating the kinetic *Z* product (reflecting the hydrazone *syn* preference). On the other hand, Fleming and Harley-Mason[44] succeeded in the preparation of all three geometrical isomers of *ortho*-nitroacetophenone azine; their isomerization is slow and made possible the determination of the crystal structures of two of these.[45]

In both **3a** and **3b**, the carboxyl groups lie nearly perpendicular to the best molecular plane while the Ph groups are placed in the molecular plane. Resonance forms illustrate well why carboxyl conjugation is not to be expected. In Scheme II, one of the two degenerate resonance forms is shown that result from delocalization of a π-electron pair from the azine system onto one of the ester groups. Such delocalization places a formal + charge on the azine-C at the other end of the chain adjacent to the electron-deficient carboxyl-C (indicated by the C=O polarity) and thus would not be expected to contribute significantly. On the other hand, Ph groups can act as electron donors leading to resonance forms with negative formal charges placed on the N atoms. This type of conjugation would be reflected in shorter Ph–C and longer N=C bonds, but the C=N data (Table II) show no such effect and the C(1)–C(3) bond length in **3a** is 1.473 Å and it also gives no indication for conjugation.

The staggered Et group in **3a** is *cis* relative to the carbonyl bond, as with **3b**, and **3a** assumes the C–O s-*trans* conformation with regard to the $O-C_2H_5$ bond. There are no significant differences in bond lengths ($\Delta < 0.01$ Å) and angles ($\Delta < 1°$) between **3a** and **3b**.

The comparison of **3a** and **3b** clearly shows that the structure of **3** depends but marginally on the nature of the ester group and, hence, our discussion substantiates the intrinsic structural properties in the solid state.

Azine Stereochemistry: Manipulation via Substitution Patterns? IR and Raman studies[48] and an electron diffraction[49] show that formaldazine, **4**, exists "as a mixture of s-*trans* and [*cis*-] *gauche* conformers with the *trans* the more stable" (75% *trans* at 225 °C). Vibrational spectroscopy shows that acetone azine assumes the N–N *trans* conformation (C_{2h}),[50a] and PE spectroscopy[50b] suggests the same conformation also for alkyl azines. The N–N rotational profile was discussed[51] by Shancke (RHF/DZ), Bock *et al.* (RHF/6-31G*), Bachrach and Liu (MP2/6–31G*//RHF/6–31G*), Oberhammer *et al.* (MP2/6–31G**//RHF/6–31G**), and by Wiberg *et al.* (MP3/6–311++G**//MP2/6–31*). These studies consistently show that the potential energy surface is rather flat in the region with $\tau \approx 90°$. The best estimate for the relative energy of *cis*-**4** compared to *trans*-**4** is 15.9 kcal/mol, and the "*gauche* region" is over 2 kcal/mol less stable than *trans*-**4**. Effects of solvation were examined at the RHF level with the reaction field model using $\epsilon = 80$, and the results suggest that solvation would stabilize *cis*-**4** somewhat compared to *trans*-**4** while the structures in the "*gauche* region" are destabilized.

Theory and experiment thus agree that *trans*-**4** is the most stable structure, that *cis*-**4** is a transition state significantly higher in energy, and that a wide region around $\tau \approx 90°$ is essentially isoenergetic and modestly higher in energy than *trans*-**4**. Crystallography contributes to the discussion on the N–N conformation in that the crystallographic record shows but little of an energetic advantage for the *trans* conformation with $\tau = 180°$: as many substituted azines realize *gauche* conformations with $115° < \tau < 150°$ as there are known *trans* structures (Table II).[52] Clearly, *the stereochemistry of the parent system does not carry over to substituted azines in the solid state.*

The N–N conformation depends on small effects, and azines thus show potential for stereochemical manipulation

(40) The C=N bonds are typically 1.29–1.31 Å long, and conjugation of the type C=CC=N is known to effect this bond length insignificantly. Typical N–N single bonds are quoted as 1.47, and ours is shorter as expected for this sp^2 hybridization. See, for example: Sandorfy, C. *General and Theoretical Aspects* in *The Chemistry of the Carbon–Nitrogen Double Bond*; Patai, S., Ed.; Interscience Publishers: New York, 1970, p 2.

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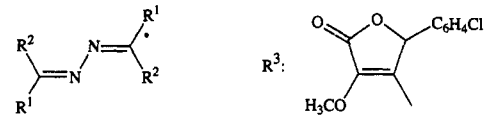
Table II. Comparison of Structural Features of Various Azines



R^1	R^2	C=N	N-N	C-N-N-C	Ph twist	ref
H_3CCl_2C-	-Ph-	1.271, 1.275	1.397	126.7°	not reported	28
PhCH=CH-	$-CH_3$	1.300, 1.290	1.38	137°	not applicable	28b
p-HOPh-	$-CH_3$	1.278, 1.282	1.417	148°	13°, 20°	38
$R^1 = R^3$	$-CH_3$	1.274, 1.282	1.376	115°		
		1.296	1.379	180°	5.6°	39
Ph-	$-CH_2CH_3$	1.283	1.406	180°	5.9°	28
Ph-	$-CO_2Et$	1.277	1.418	180°	6.4°	this work
Ph-	$-CH_3$	1.278, 1.278	1.403	139°	0.4°, 19.7°	52
p-EtO_2CPh-	$-CH_3$	1.270, 1.288	1.41	180°	9°, 11°	41
p-FPh-	$-CH_3$	1.284, 1.285	1.396	138°	1.9°, 18.6°	52
p-ClPh-	$-CH_3$	1.282, 1.288	1.398	135°	29.3°, 30.5°	52
p-BrPh-	$-CH_3$	1.264, 1.269	1.383	125°	27.2°, 20.9°	52
o-O_2NPh	$-CH_3$	1.288	1.420	180°	31.1°	(*E,E*) 45
o-O_2NPh	$-CH_3$	1.278	1.418	166°	38.5°	(*E,Z*) 45
o-O_2NPh	-H	1.270	1.424	180°	37.0°	45
p-F_2CHOPh-	-H	1.276	1.413	180°	not reported	46
Ph	-H	1.275	1.418	180°	0°	47

[a] In Å and deg.

via substitution pattern variation. While it is understandable why the ester groups do not π-conjugate (*vide supra*), it is less clear what causes the variation in the Ph conformations. In the solid state structures of **3a** and **3b**, the Ph groups are almost in the plane of the molecule. In other closely related *trans* azines the Ph groups are twisted out of the best plane of the azine (Table II). These crystallographic results pose the question as to whether (i) the Ph conformations also are best for the free molecule, (ii) crystal packing prohibits the realization of the conformation most suitable for π-conjugation, or (iii) crystal packing forces the Ph groups into the observed conformations although there is no substantial conjugation. To address this question, we have carried out ab initio calculations for the *Z,Z*, *E,E*, and *E,Z* geometrical isomers of the parent diacid of **3** and of **3b**.

Ab Initio and Semiempirical N–N Rotational Profiles. The application of semiempirical theory seemed appealing because of size. The ab initio theoretical and experimental data for **4** can be used to examine the adequacy of the parameter sets for the larger azine **3**. This comparison is made for the N–N rotational energy profile in Figure 3. Both parameter sets overestimate the stability of *cis*-**4** and of the structures in the *gauche* region and predict *trans* **4** to be the transition state structure for enantiomerization of the C_2 minima. While AM1 exhibits a clear preference for the *gauche* minimum, PM3 performs better and predicts essentially the same energy and geometry for *trans* and *gauche* structures. Nevertheless, it appears that semiempirical theory does not reflect the N–N *s-trans* preference sufficiently while all the ab initio levels do, even when modest basis sets are employed. For **5–7** (*vide infra*) we found the same type of model dependency as discussed for **4**, and in addition, we found geometrical isomer preferences that differ qualitatively from the ab initio results. A critical comparison to the ab initio results will be published elsewhere.[53] The calculations reported by Ishida *et al.*[39] undoubtedly also suffer from these deficiencies.

Ab Initio Study of Geometrical Isomers of Benzoylformate Azine. The *Z,Z* and *E,E* isomers **5** and **6**,

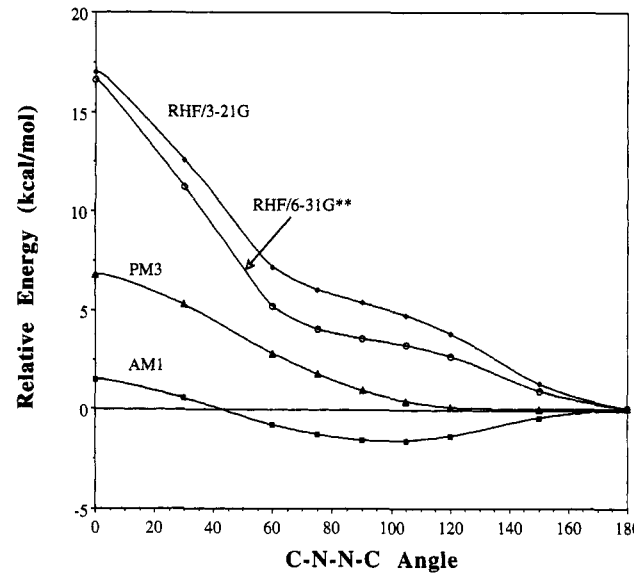


Figure 3. Relative energy of formaldazine as a function of the C–N–N–C dihedral angle τ. The PM3 (triangles) and AM1 (squares) rotational energy profiles are compared to the ab initio energy profile obtained at the RHF/3-21G level (diamonds) and at the RHF/6-31G** level (circles) reported by Oberhammer *et al.*

respectively, of the diacid corresponding to **3** were optimized within C_i symmetry (method **A**) and again within C_i symmetry but with the additional constraint that the Ph rings be coplanar with the azine skeleton (method **B**). For (*E,Z*)-**7**, we optimized **7A** with τ(C–N–N–C) = 180°, and the resulting structure was then also optimized without constraints to obtain the asymmetric structure **7C**. All optimizations were carried out at the RHF/3-21G level. Selected structural parameters are shown in Figures 4–6 and complete structural data sets are available as supplemental material. Pertinent bond lengths of the solid-state structure of **3a** are included in Figure 4 for easy comparison; the agreement is excellent for bond lengths ($\Delta < 0.02$ Å) and angles ($\Delta < 2°$). In the crystal and in the gas phase, the azine prefers structures in which neither of the substituents is in full conjugation. The C–Ph and C–COOR torsional angles are affected significantly by

(53) Chen, G. S. PhD Dissertation, University of Missouri—Columbia, projected year of completion 1994.

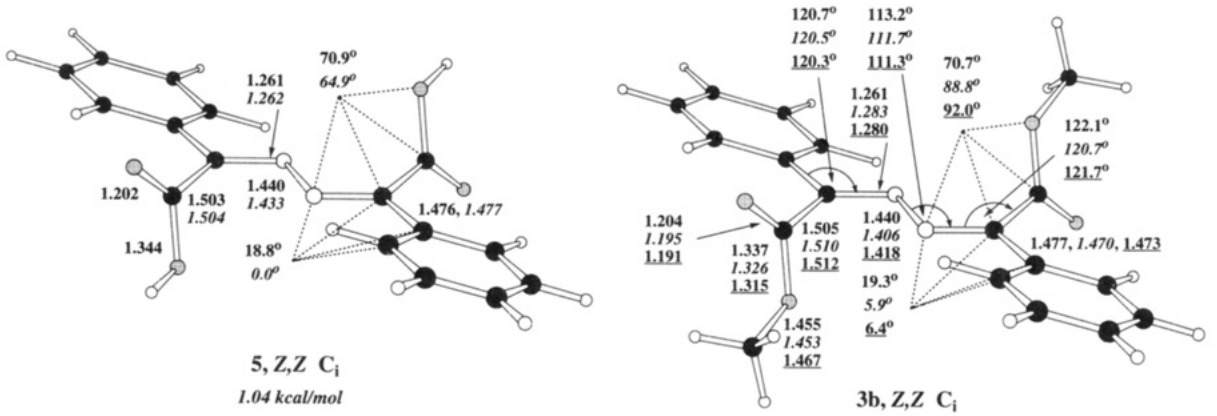


Figure 4. RHF/3–21G-optimized structures of (*Z,Z*)-**5A**. Numbers given in italics refer to the structure obtained with the Ph groups constrained to being coplanar with the azine fragment. The optimized diester **3b** is shown on the right together with the respective values for **3b** (italics) and **3a** (underlined) in the solid state.

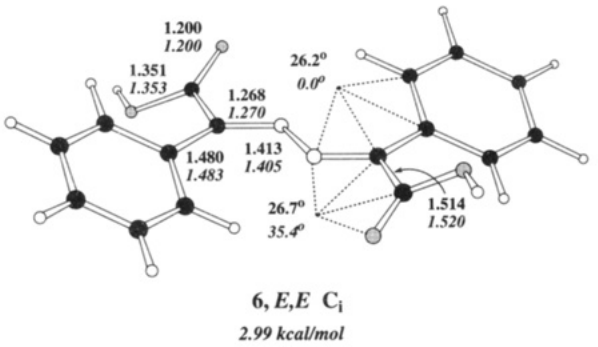


Figure 5. C_i-symmetric RHF/3–21G structures of (*E,E*)-**6A**. Numbers given in italics refer to the structure obtained with the Ph groups constrained to being coplanar with the azine fragment.

packing, which is understandable in light of the computed small energy requirement for these deformations (*vide infra*).

For **5A**, **6A**, and **7C** the Hessian matrices were calculated analytically to confirm the stationarity of the structures and to obtain vibrational frequencies together with zero-point energies. For the same structures we determined energies at the RHF/6–31G*//RHF/3–21G level to obtain better estimates of the isomer preference energies. Total energies and related energy data are summarized in Table III. The values of E_{conj} are the relative energies of the **B**-structures with respect to the **A**-structures, e.g., E_{conj}(**5**) = E(**5B**) − E(**5A**). These E_{conj} values serve as a measure of the steric effects opposing full Ph conjugation. The values of E_{gauche} are defined as the relative energy of the C_i symmetric **A**-structure compared to the asymmetric **C**-structure; that is, E_{gauche} estimates the *gauche* preference. The E_{rel} values are energies relative to **5A**, and they are our estimates for the geometrical isomer preferences.

N–N Conformational Preference. C_i (*Z,Z*)-**5A** is a minimum (Figure 4) and all vibrational frequencies are real, but there are several vibrational modes with frequencies below 100 cm^{-1} and a small deformation from τ = 180° requires little energy. Also shown in Figure 4 is the structure of the methyl diester **3b** of **5A**. The HO versus H_3CO replacement has but marginal structural consequences, and thus, the diacid does provide a good model for the analysis of **3**. We noted previously that the structures of **3a** and **3b** in the solid state also differ but marginally.

C_i (*E,E*)-**6A** was optimized (Figure 5), and the vibrational analysis shows one imaginary mode. The frequency *i*1.7 cm^{-1} of this a_u symmetric imaginary mode is exceedingly low and indicates that a *very* small deviation of τ would lead to the adjacent minimum. Since such a small structural change certainly will not affect the energy (*vide infra*) and since (*E,E*)-**6A** is significantly less stable than its *Z,Z* isomer, we did not further explore the potential energy surface in the vicinity of $\tau \approx 180°$.

We calculated (*E,Z*)-**7** first with the constraint τ = 180°, **7A**, and then reoptimized without constraints to obtain chiral **7C**. As can be seen from Figure 6, the deviation of τ from 180° is only 5°. Moreover, the vibrational frequency calculation of **7C** shows several frequencies below 100 cm^{-1},

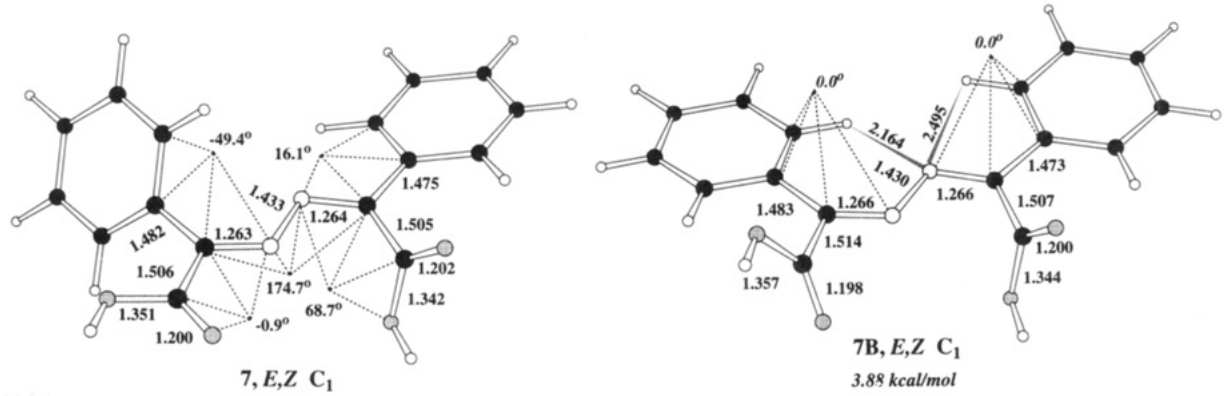


Figure 6. RHF/3–21G-optimized *E,Z* asymmetric structures of **7C**. The structure **7A** with τ = 180° is essenstially the same, and **7B** was obtained with the additional constraint τ(N=C–C–C_{ortho}) = 0° which forces conjugation of the Ph groups.

Table III. Total, Relative, and Vibrational Zero-Point Energies

molecule/parameter	energy[a] RHF/3-21G/ /RHF/3-21G	VZPE[b] RHF/3-21G	NIMAG[c]	energy[a] RHF/6-31G*/ /RHF/3-21G
3b, C_i	−1093.110 180			
5A: *Z,Z* azine, C_i	−1015.482 205	171.95	0	−1021.205 847
5B: and conj phenyl C_i	−1015.480 554			
E_{conj} (**5B** vs **5A**)	1.04			
6A: *E,E* azine, C_i	−1015.472 808	172.22	1	−1021.189 567
6B: and conj phenyl C_i	−1015.468 048			
E_{conj}(**6B** vs **6A**)	2.99			
E_{rel}(**6A** vs **5A**)	5.90			10.22
E_{rel}(**6B** vs **5B**)	7.85			
7A: *E,Z trans*, C_1	−1015.478 756			
7B: and conj phenyl C_1	−1015.472 577			
7C: *E,Z* azine, C_1	−1015.478 825	171.94	0	−1021.198 927
E_{conj}(**7B** vs **7A**)	3.88			
E_{gauche}(**7A** vs **7C**)	0.04			
E_{rel}(**7c** vs **5A**)	2.12			4.34

[a] Energies in atomic units, relative and vibrational zero-point energies in kcal/mol. [b] Vibrational zero-point energies. [c] Number of imaginary frequencies. [d] See text for definition of the energy parameters E_{rel}, E_{conj}, and E_{gauche}.

and the energetic preference of **7C** over **7A** is only E_{gauche} = 0.04 kcal/mol. Thus, the structure of (*E,Z*)-**7** is best described by a very fast equilibrium between the chiral and essentially N–N *s-trans* configured minima **7C**.

Phenyl Conjugation? In **5A** and **6A**, the Ph groups are twisted significantly out of the best plane of the azine, 18.8° for (*Z,Z*)-**5A**, and the twist of 26.2° for (*E,E*)-**6A** is larger. For these C_i structures, we estimated the energy associated with forcing the Ph groups to be coplanar with the azine skeleton. **5B** and **6B** differ from **5A** and **6A** marginally (italicized values in Figures 4 and 5), and in particular, there are no significant effects on any of the bond lengths in the π system. E_{conj}(**5**) = 1.04 kcal/mol is smaller than E_{conj}(**6**) = 2.99 kcal/mol, and steric repulsions between the *ortho*-H and one of the azine nitrogens provides a simple explanation for their difference. In the 5-membered ring in (*Z,Z*)-**5** the *ortho*-H remains far away (>2.5 Å) from the azine-N while the *ortho*-H in the 6-membered ring in (*E,E*)-**6** is too close to an azine-N (<2.2 Å). The repulsion in **6** is manifested in the angular distortions that accompany Ph coplanarity while such effects are less for **5**.

In (*E,Z*)-**7C**, the Ph groups also are twisted, and the twist is much larger for the (*E*)-C=N bond (49.4°) than for the (*Z*)-C=N bond (16.1°). **7B** was optimized with the additional constraint that the Ph groups be coplanar (Figure 6). The E_{conj} = 3.88 kcal/mol value for (*E,Z*)-**7** is higher than the average of the E_{conj} values of (*Z,Z*)-**5** and (*E,E*)-**6** (2.02 kcal/mol), although the distances between the *ortho*-Hs and the proximate N are slightly longer than in **5** and **6**.

The energy profile for Ph–C rotation was examined for the model azine **8** (Figure 7) to examine the energetic benefits of having the Ph groups in the best possible conformation for conjugation while avoiding repulsions of the type discussed. Structures of the N–N *s-trans* azine **8** were fully optimized at the RHF/3-21G level as a function of the $C_{(syn,ortho)}$–C_{ipso}–C=N dihedral angle, and energies were also determined at the RHF/6–31G*//RHF/3–21G level. The relative orientation of the carboxyl group was not affected to any significant extent by the variation in the Ph conformation. Figure 7 shows that the activation barrier to Ph rotation requires only about 4 kcal/mol at the RHF/6–31G*//RHF/3–21G level and demonstrates that conjugative interactions between the Ph substituent and the azine play only a minor role. The rotational energy

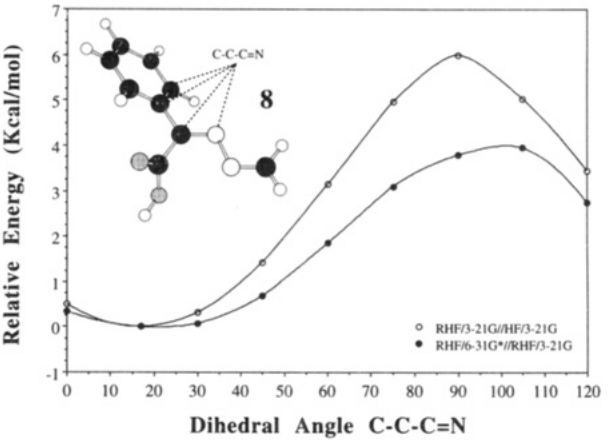


Figure 7. Rotational profiles for phenyl rotation in the model system HOOCCPh=NNCH$_2$, **8**, with τ = 180° as a function of the dihedral angle $C_{(syn,ortho)}$–C–C=N.

profile also illustrates that Ph rotations of as much as 50° require less than 1 kcal/mol, an energy so small that packing effects easily suffice to yield solid-state structures that differ from those of the free molecules. Conclusions as to the importance of phenyl conjugation in azines based on solid-state structures are not convincing.

Geometrical Isomer Preference. The RHF/3–21G energies indicate the ordering (*E,E*)-**6** < (*E,Z*)-**7** < (*Z,Z*)-**5** for the thermodynamic preferences where **5A** is preferred over **6A** by 5.90 kcal/mol and **5A** is preferred of **7C** by 2.12 kcal/mol. The vibrational zero-point energies computed for **5A**, **6A**, and **7C** are within 0.3 kcal/mol and thus have virtually no effect on the relative energies. At the RHF/6-31G*//RHF/3–21G level, we find the same ordering but the preferences are more pronounced: **5A** is preferred over **6A** by 10.22 kcal/mol and **5A** is preferred of **7C** by 4.34 kcal/mol. Each *E* configuration roughly destabilizes by 5 kcal/mol. The origin of the stabilization of the *Z* configuration is difficult to trace as many structural parameters vary from isomer to isomer. Nevertheless, it is worthwhile to point out that the isomer stability parallels the number of *cis* NN=CCO$_2$ arrangements. The carboxyl groups are in suitable conformations to allow for electrostatically favorable orientation of Nσ lone pair density toward the electron-deficient carboxyl-carbon (e.g., d(N---C) = 2.627 Å in **5**).

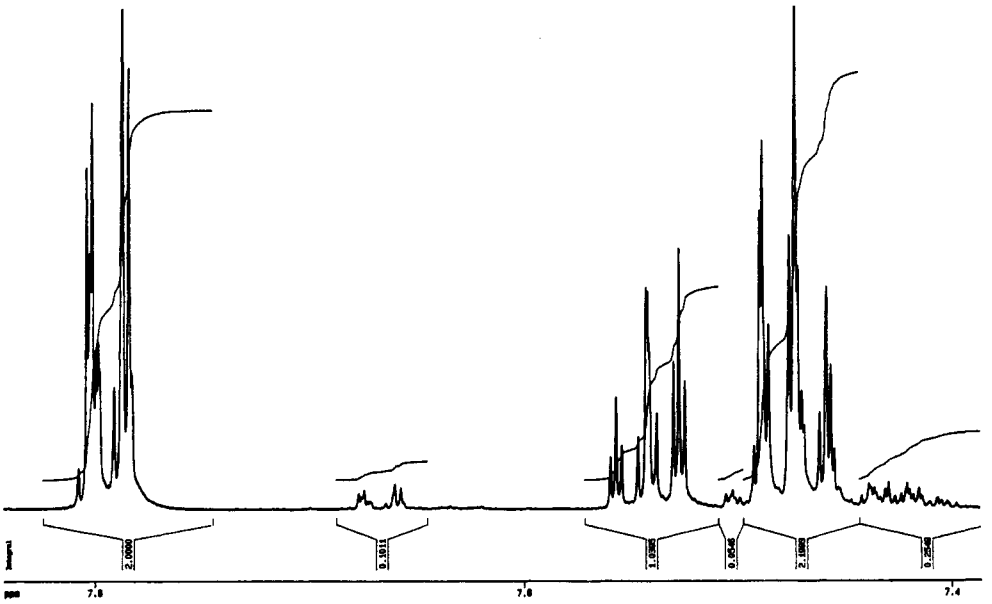


Figure 8. Phenyl region in the 500-MHz ^{1}H-NMR spectrum of **3a**. The spectrum is not first-order, and $^3J_{om}$ and $^3J_{mp}$ cannot be determined directly. Peak separation of the Ph signals varies between 7.09 and 7.69 Hz.

^{1}H-, ^{13}C- and ^{15}N-NMR Spectroscopy. At room temperature, the 500 MHz ^{1}H-NMR spectrum of **3a** shows one CH_3 (δ = 1.43 ppm, t) and one CH_2 signal (δ = 4.50 ppm, q). The Ph signals occur between 7.41 and 7.81 ppm (Figure 8). The aromatic protons are deshielded with respect to benzene (δ = 7.3 ppm) indicative of the overall electron-withdrawing ability of the azine substituent. The *para* proton gives rise to the signal at δ = 7.52 ppm. Since the shielding is determined by the M-effect,[54] we can assign the signals at δ = 7.79 ppm and δ = 7.47 ppm to the *ortho* and *meta* protons, respectively. We examined the ^{1}H-NMR signals of **3a** for 25 °C > T > −53 °C, and the T-independence found indicates that only one isomer is present. These measurements suggest further that the small peaks on the high-field side of the major signals are not due to an isomer.[55]

The proton-decoupled 300 MHz ^{13}C-NMR spectrum of the **3a** shows eight peaks. There are only single peaks for the CH_3 (δ = 14.6 ppm) and CH_2 (δ = 62.2 ppm) carbons. The low-field peaks at δ = 162.7 and 165.4 ppm correspond to unique imine and carboxy carbons, and the four peaks between 128.2–132.5 ppm are the signals of a unique phenyl group.

The proton-decoupled 500 MHz natural abundance ^{15}N-NMR spectrum shows a single peak with a chemical shift of 39.6 ppm relative to neat CH_3NO_2. For azines RHC=NN=CHR (R = Me, n-Pr, i-Pr, Ph, Bz) chemical shifts of 14.5–21.4 ppm were reported with δ = 19.4 ppm for R = Ph.[56,57] Thus, we find that the azine N in **3a** is *more shielded* compared to the aldazines *despite* the withdrawing carboxyl group. For the nuclear shielding σ both the diamagnetic term σ_{loc}^d and the paramagnetic terms σ_{loc}^p and σ_{nonloc}^p need to be considered.[56c] The diamagnetic term depends on the charge density at N, but the charge dependence is very modest and σ_{loc}^d is nearly constant (202 ± 15 ppm). The term σ_{loc}^p is positive, about 1 order of magnitude greater than σ_{nonloc}^p, and it is this term that is responsible for the *higher* shielding in **3a**.

On the basis of the computed structures, one might expect an NOE in the ^{15}N NMR spectrum upon irradiation of the *ortho* H which could be useful for the stereochemical assignment. We have carried out this experiment for **3a** but no significant NOE was observed.

The ^{1}H-, ^{13}C-, and ^{15}N-NMR spectra are consistent with (a) a single geometrical C_i isomer with *Z,Z* or *E,E* configuration or (b) a fast equilibrium between enantiomers of one geometrical C_1 isomer with *Z,Z* or *E,E* configuration. In principle, these spectra also are consistent with a fast equilibrium between the enantiomers of the chiral *E,Z* geometrical isomer and concomitant fast rotation–inversion isomerization *E,Z* ⇔ *Z,E*. The relative isomer stabilities predicted by the ab initio calculations suggest that option a is realized.

Infrared and Raman Spectroscopy. For **5A**, **6A**, and **7C** the vibrational frequencies and their IR and Raman intensities were calculated, and the IR spectrum of **3a** was measured. The high number of 96 vibrations makes the analysis of the displacement vectors tedious, and listings of the results would be exceedingly space demanding. To overcome these obstacles, we analyzed the important modes visually with Vibrate,[58] and we present the calculated spectra graphically (Figure 9). As computed vibrational frequencies are overestimated rather consistently, appropriate scaling (factor 0.9) was applied.

Infrared Spectra. Three strong bands occur in the IR fingerprint region around 1755, 1680, and 1110 cm^{-1}.

(54) (a) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH Verlagsgesellschaft: New York, 1991; p 50 ff. (b) Zanger, M. *Organ. Magn. Reson.* **1972**, *4*, 1–25.

(55) (a) They also are not due to starting material; the respective signals of the diazo compound occur at higher field. (b) The minor component was still present after recrystallization.

(56) Witanowski, M.; Stefaniak, L.; Webb, G. A. Nitrogen NMR Spectroscopy. In *Annual Reports on NMR Spectroscopy*; Academic Press: New York, 1981; Vol. 11B. (a) For chemical shifts, see p 219 ff. (b) Positive chemical shifts are assigned to nuclei with increased magnetic shielding relative to the external standard neat nitromethane. The chemical shifts reported are the "nitrogen shieldings" proposed by Witanowski *et al.* (p 16). Note that this is opposite to the convention in ^{1}H and ^{13}C NMR chemical shift assignments. (c) For discussion of nuclear shielding, see p 4 ff.

(57) (a) Witanowski, M.; Webb, G. A. *Nitrogen NMR*; Plenum Press: New York, 1973. (b) Witanowski, M.; Stefaniak, L.; Webb, G. A. Nitrogen NMR Spectroscopy. In *Annual Reports on NMR Spectroscopy*; Webb, G. A., Ed.; Academic Press: New York, 1986; Vol. 18.

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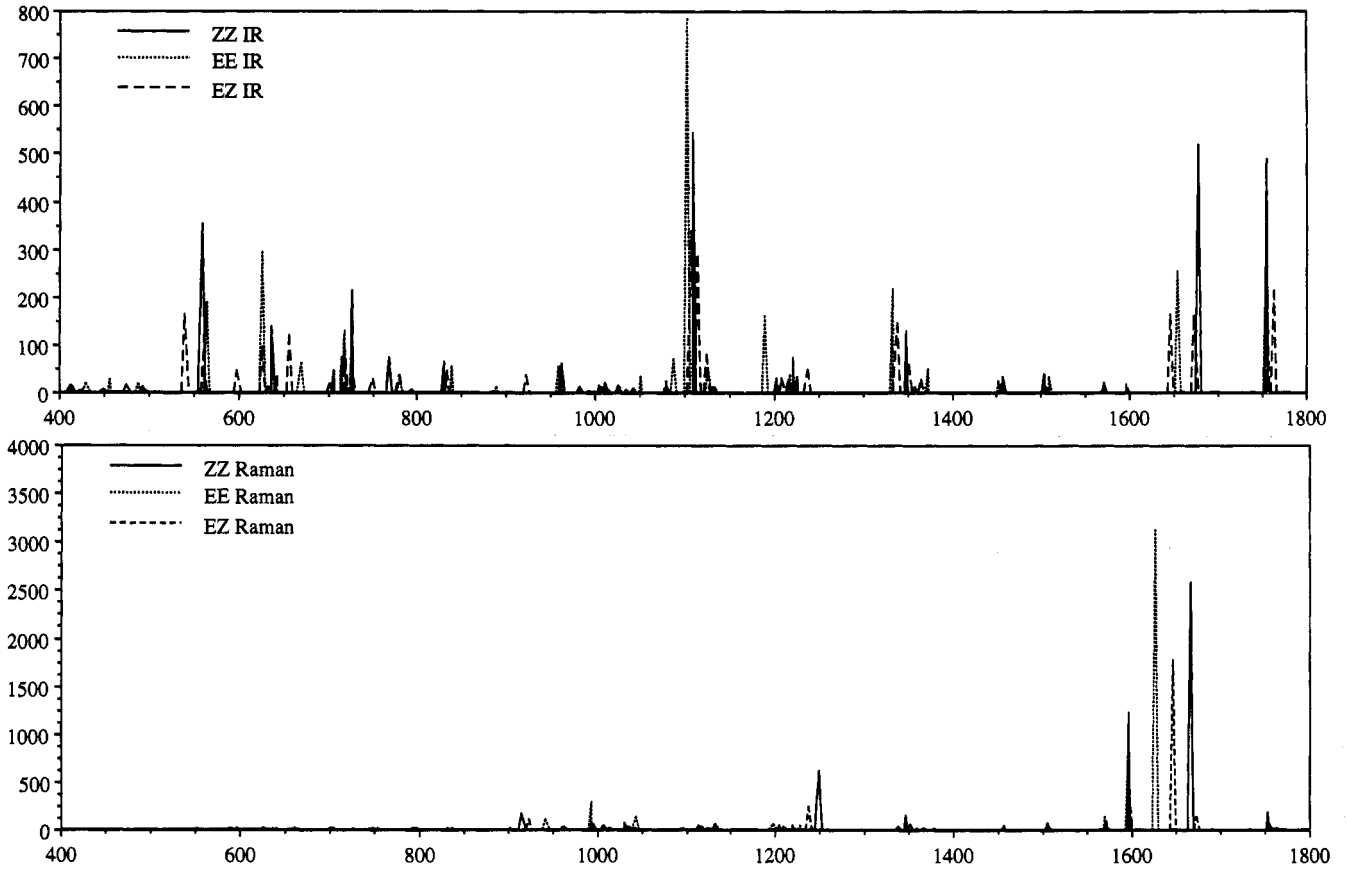

Figure 9. Fingerprint regions of the calculated infrared and Raman spectra (RHF/3-21G, scaled, factor 0.9) are shown for (*Z,Z*)-**5A**, (*E,E*)-**6A**, and (*E,Z*)-**7C**.

The highest intensity band around 1100 cm^{-1} is predicted to occur at a slightly higher frequency for (*Z,Z*)-**5A** (1110 cm^{-1}) than for (*E,E*)-**6A** (1103 cm^{-1}), and it is split for (*E,Z*)-**7C** (1108 and 1115 cm^{-1}). The same is true for the band around 1755 cm^{-1}; our computations predict one peak at 1755 ± 2 cm^{-1} for each isomer, and the (*E,Z*) isomer exhibits an additional shoulder at 1764 cm^{-1}. The bands at 1755 and 1110 cm^{-1} are associated with carboxyl group motions which are diagnostic for these azines. The peaks around 1650 cm^{-1} are the best stereochemical indicators: This band occurs at 1678 cm^{-1} for (*Z,Z*)-**5A**, is significantly lower (1655 cm^{-1}) for (*E,E*)-**6A**, and is split (1646 and 1674 cm^{-1}) for (*E,Z*)-**7C**. The bands around 1680 cm^{-1} correspond to the a_u symmetric C=N stretching modes (←)C=N(→)N(→)=C(←) for **5A** and **6A**. The associated C=N a_g vibration occurs in the Raman spectra only for the C_i isomers, but both modes are active for the (*E,Z*) isomer.

Raman Spectra. The calculated Raman spectra are characterized by strong signals slightly below 1700 cm^{-1} corresponding to the a_g symmetric C=N stretching mode in the sense (←)C=N(→)N(←)=C(→) for **5A** and **6A**. The frequency of this band is significantly higher for (*Z,Z*)-**5A** (1666 cm^{-1}) than for (*E,E*)-**6A** (1626 cm^{-1}), and the respective band for (*E,Z*)-**7C** occurs in between at 1646 cm^{-1} together with a low intensity band at 1674 cm^{-1}.

IR Spectrum of 3a. The two strong peaks in the measured IR spectrum of **3a** at 1733 and 1209 cm^{-1} may be assigned to the C=O and CO stretching modes of the ester groups. The agreement with theory is quite good considering that we calculated the spectra of the diacid. The C=N stretching mode corresponds to the strong signal at 1609 cm^{-1}; it is at the lower end of the typical range,[59a] and it also is ~50–80 cm^{-1} lower than predicted by theory. The peak at 1575 cm^{-1} is typical for aromatic CC bonds.[59b] Thus, the IR spectrum shows only one peak in the C=N stretching region allowing us to rule out the presence of the *E,Z* isomer. The comparison of the fingerprint regions of the measured and calculated spectra points up that RHF level theory underestimates the intensities of skeletal vibrations.

Conclusion

In the solid state, **3a** and **3b** assume N–N s-*trans* (*Z,Z*) C_i structures, and the computational analysis suggests this preference to be intrinsic. The configurational preference is consistent with the steric demand of the phenyl and carboxyl substituents. The carboxyl groups assume conformations that impede π backdonation[60] but allow for favorable electrostatic interactions between the electron-deficient carboxyl carbon and the proximate N_σ lone pair thereby favoring the *Z*-configuration (Scheme III). The phenyl groups are in conformations that would allow for conjugation in the solid state structure. Our theoretical results indicate, however, that the Ph groups prefer to be twisted in the gas phase and suggest attenuated conjugation and that the phenyl conformation in the crystal is a consequence of packing that requires only modest energy

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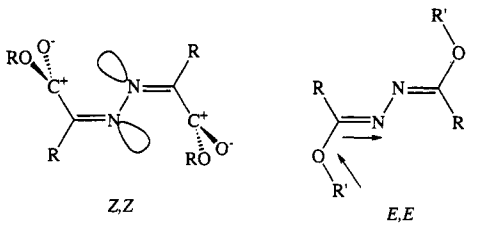
(60) Hyperconjugative stabilization of the azine C atom by the carboxyl CO bonds could occur but is not manifested in the structural parameters of the carboxyl groups.

Scheme III



Z,Z E,E

(E_{conj}). The rotational profile of 8 provides further evidence that Ph conjugation is of minor importance only. We conclude that the structures of **3a** in the solid and in gas phases are essentially the same. The spectroscopic analyses suggest that the same stereochemistry also is realized in solution.

This situation in carboxy-substituted azines thus differs markedly from the one observed in azines of esters which show a preference for the *E*-configuration even if the R group is larger than the alkoxy group. Kreus and Warketin explained the preference for the *E*-configuration with favorable dipole alignments and steric hindrance in the *Z*-configuration.[61]

Experimental and Computational Details

X-ray Structure of 3a. Ethyl benzoylformate azine, $C_{20}H_{20}N_2O_4$, M_r = 352.38 monoclinic, space group $P2_1/n$, a = 8.9370(6) Å, b = 11.4419(5) Å, c = 9.631(1) Å, and β = 97.8884(3), V = 975.5(1) Å^3, Z = 4, D_x = 1.200 g cm^{-3}, λ(Cu Kα) = 1.540 56 Å, linear absorption coefficient μ = 7.2 cm^{-1}, $F(000)$ = 399.92. The data were collected at a temperature of 298 K on an Enraf-Nonius CAD4 diffractometer. The crystals were pale yellow, 0.20 × 0.33 × 0.35 mm; density not measured; 25 reflections with $20 \le \theta \le 25°$, Cu Kα, used to refine cell dimensions; systematic absences, $k = 0$, $h + l \neq 2n$; $0k0$, $k \neq 2n$, and successful refinement; no absorption correction applied; $2\theta_{max} = 139.6°$; $-10 \le h \le 10$, $0 \le k \le 13$, and $0 \le l \le 11$; three standard reflections measured after every 3600 s of X-ray exposure indicated less than 1% decay; 1951 total reflections 1841 unique, R_i = 0.019, 1613 observed [$I > 2.0\sigma(I)$]; structure solved by direct methods; refinement on F, function minimized during refinement was $\Sigma\omega(F_o - F_c)^2$, with $\omega = 1/[\sigma^2(F) + 0.0008(F^2)]$; H atoms located in difference map and refined with fixed isotropic thermal parameters; non-H atoms refined with anisotropic thermal parameters: R = 0.058, R_w = 0.101, S = 2.79; $(\Delta/\sigma)_{max}$ = 5.1%, final difference map max = 0.49, min = −0.27 e Å^{-3}. Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography*;[62] structure solution and all calculations performed with the program NRCVAX.[63]

NMR Experiments were performed on Bruker 300- and 500-MHz spectrometers. The assignment of the *syn* and *anti* isomers of ethyl phenylglyoxylate hydrazone was made assuming that the chemical shift of the amino-H signal of the *syn* isomer is larger than in the *anti* isomer. H signals were then assigned based on intensity. *Syn*-isomer: ^{1}H-NMR (CD_2Cl_2) δ 1.30 (t, 3 H), 4.29 (q, 2 H), 7.26–7.51 (m, 5 H), 8.40 (broad, 2 H). *Anti*-isomer: ^{1}H-NMR (CD_2Cl_2) δ 1.29 (t, 3 H), 4.23 (q, 2 H), 6.20 (broad, 2 H), 7.26–7.51 (m, 5 H). Ethyl benzoylformate azine, **3a**: ^{1}H-NMR (CD_2Cl_2) δ 1.43 (t, 6 H), 4.5 (q, 4H), 7.41-7.81 (m, 10 H). ^{13}C-NMR (CD_2Cl_2) δ in ppm 14.6, 62.2, 128.2, 129.2, 131.5, 132.5, 162.7, and 165.4. ^{15}N-NMR (CD_2Cl_2) δ +39.6 ppm relative to external standard nitromethane.

Ab initio calculations were carried out with Gaussian92[64] on an IBM 3090E 170J mainframe and RISC RS-6000 workstations Models 560 and 580 using direct methods. Visual analysis of vibrational properties were performed with the program Vibrate[57] on Silicon Graphics Personal Iris workstations.

Semiempirical calculations were carried out with Dewar's MNDO method (using Mopac[65a] on Vax Systems) with the Austin Model 1 (AM1)[65b] and with Stewart's parametric model 3 (PM3)[65c] parameters. An extensive review of these parameter sets is available.[65d] Optimizations were performed with tight convergence criteria (key word precise).

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Supplementary Material Available: ^{13}C- and ^{15}N-NMR and IR spectra of **3a** and the ab initio structures **3b** and **5–7** and details of the vibrational analysis are available from the authors. Atomic coordinates, structure factors, positional parameters, and anisotropic thermal parameters for **3a** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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