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Synthesis and structural assignment of 2,4′-disubstituted benzylidenefluorenes and 4′-substituted benzylidene-1-azafluorenes

Rita Annunziata,* Valentina Molteni and Laura Raimondi

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Golgi 19, 20133 Milan, Italy

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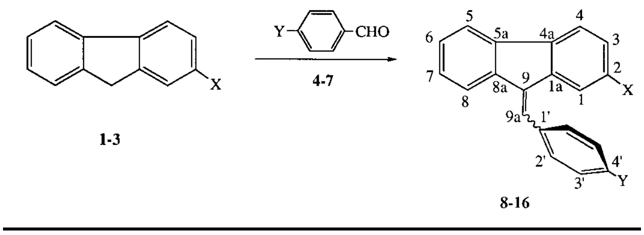
ABSTRACT: In the course of a study aimed at the investigation of edge-to-face arene–arene interactions, substituted benzylidenefluorenes **8–16** and benzylidene-1-azafluorenes **20–24** were synthesized as mixtures of *E–Z*-isomers. The full structural assignment of these compounds, performed by 2D NMR experiments, is described together with a study of their *E–Z* isomerization under equilibrating conditions. For compounds **8–16** no correlation was observed between the electron-donating or electron-withdrawing nature of the substituent groups and the *E*/*Z* equilibrium ratios. In the case of **20–24** the predominance of the *E*-isomers seems to depend exclusively on the N-lone pair–benzylidene ring electronic repulsion rather than on the nature of the *para* substituent on the aromatic ring. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; 2D NMR; ^{1}H NMR; ^{13}C NMR; arene–arene interaction; 2X,9-(4′Y)benzylidenefluorenes; 9-(4′Y)benzylidene-1-azafluorenes

INTRODUCTION

In the solid state, proximate benzenoid rings are often found in an edge-to-face orientation.[1,2] Moreover, recent molecular dynamic calculations suggest that benzene molecules prefer to associate in edge-to-face rather than parallel fashion in aqueous solution.[3] Attractive edge-to-face interactions between aromatic rings can play a significant role in protein folding, nucleoside base stacking, host–guest binding and drug–receptor interactions.[2] The energy of the interaction between two arene units divides roughly into a polar (electrostatic and induction) and a van der Waals term (dispersion).[4] The polar term depends on the relative charge distribution, which in benzene can be described as an electron-rich core surrounded by an electron-deficient periphery. The van der Waals term depends on the contact surface area, which in the case of two interacting benzenes is relatively small.

In the course of our program directed towards a better understanding of the arene–arene interactions, we have examined the behavior of stacked aryls in differently substituted 1,8-diarylnaphthalenes.[5] Currently, we are involved in developing a suitable model system for studying edge-to-face aromatic interactions in general, and how these are influenced by the electronic nature of the interacting aromatic rings in particular. The model system for this study should show a reduced conformational freedom and a short distance between the interacting aromatic rings in order to maximize an effect that can be very low in energy. On the basis of preliminary molecular mechanics calculations, that indicated a distance of 3.4 Å between the H-1 proton and the core of the *para*-substituted aryl ring in a benzylidenefluorene, we synthesized a series of 2X-9-(4′Y)benzylidenefluorenes (**8–16**) (Scheme 1) that were obtained as a pair of *E–Z*-diastereoisomers. These compounds feature substituents with different electronic availability, located at the C-2 and C-4′ positions with the ultimate goal of determining how their nature could influence the *E*/*Z* ratios of **8–16**, and of using this information to understand the nature and the extent of the edge-to-face interaction.



Fluorene	X	Aldehyde	Y	9-(Arylmethylidene) fluorene
1	NO_2	4	OMe	8
1	NO_2	5	Me	9
1	NO_2	6	Cl	10
1	NO_2	7	CF_3	11
2	NMe_2	5	Me	12
2	NMe_2	6	Cl	13
2	NMe_2	7	CF_3	14
3	Br	4	OMe	15
3	Br	7	CF_3	16

Scheme 1

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* *Correspondence to*: R. Annunziata, Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Golgi 19, 20133 Milan, Italy

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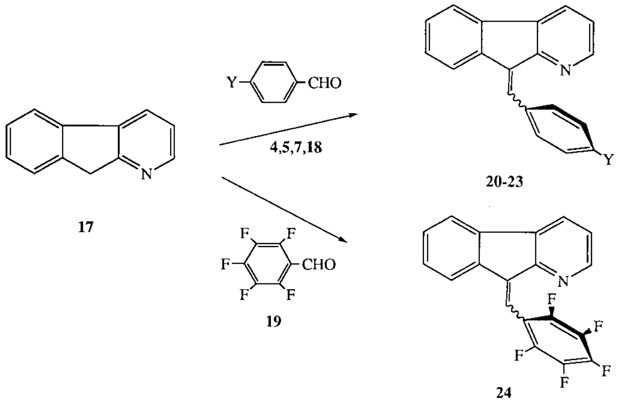


Aldehyde	Y	9-(Arylmethylidene) fluorine	Crude mixture: E/Z ratio[a]	Yield (%)
4	OMe	**20**	53:47	>99
5	Me	**21**	80:20	77
7	CF_3	**22**	74:26	62
18	H	**23**	80:20	93
19		**24**	80:20	20

[a] After purification by flash chromatography (see Experimental) the total E/Z ratio was unchanged

Scheme 2

We also synthesized a series of 9-(4′Y)-monosubstituted benzylidene-1-azafluorenes (**20**–**24**), also obtained as mixtures of *E*–*Z*-diasteroisomers (Scheme 2). In the 1-azafluorenes series, the presence of the pyridine nitrogen emphasizes the difference between the two edges of the fluorene structure with respect to the *para*-substituted aryl ring (C—H *vs.* N-lone pair).

The structural elucidation and the *E*–*Z* configurational assignment were completely performed by NMR spectroscopy. The small quantities of derivatives available make the inverse detection techniques the methods of choice to provide complete and unambigous ^{1}H and ^{13}C assignments.

EXPERIMENTAL

Synthesis of 2X-9-(4′Y)benzylidenefluorenes 8–16

General Procedure. The benzylidenefluorenes **8**–**16** were obtained[6] by condensation between the fluorenes **1**–**3** (1.0 mmol) and the aldehydes **4**–**7** (1.0 mmol), under phase-transfer catalysis conditions, in THF as solvent, and using 40% NaOH in the presence of triethylbutylammonium bromide (0.1 mmol). The experimental conditions (temperatures and reaction times) are given in Table 1. The mixtures were extracted with Et_2O and the combined organic phases were dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude residues were analyzed by ^{1}H NMR spectroscopy for *E*/*Z* ratio determination (see Table 1), before purification by flash chromatography (96:4 hexanes–Et_2O mixture as eluent). The benzylidenefluorenes **8**–**16** were recovered in yields ranging from 21 to 66%; the melting points and elemental analyses are given in Table 1.

Synthesis of 4-cyano-9-hydroxyfluorene (27), 4-cyano-9-chlorofluorene (28) and 9-(4-cyanofluorenyl)triphenylphosphonium chloride (29)

The 4-cyano-9-fluorenone **26**, obtained[7] from the commercially available diacid **25**, was dissolved in THF and an equimolecular quantity of $NaBH_4$ was added at room temperature. After stirring for 1.50 h the reaction was quenched with an aqueous solution of ammonium chloride. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over sodium sulfate, filtered and then evaporated *in vacuo*. The residue was purified by flash chromatography with a 60:40 hexanes–Et_2O mixture as eluent. Compound **27** (m.p. 131–132 °C) was obtained in 87% yield.

According to the literature procedures,[8] the 4-cyano-9-hydroxyfluorene **27** was converted into the corresponding 9-chlorofluorene **28** (m.p. 143–144 °C). Subsequently, reaction with PPh_3 in nitromethane as solvent provided the 9-(4-cyanofluorenyl)triphenylphosphonium chloride **29** (m.p. 233–235 °C) in 83% yield.[8]

Synthesis of 4-cyano-9-(4′-methoxyphenylmethylidene) and 9-[4-(trifluoromethyl)phenylmethylidene]fluorene (30 and 31, respectively)

General procedure. The 9-(4-cyanofluorenyl)triphenylphosphonium chloride **29** dissolved in CH_2Cl_2 was treated, in the presence of water (1 ml) and phenolphthalein (1% in EtOH), with 5% NaOH until pH 8.5. The aqueous phase was extracted with CH_2Cl_2 and the combined

Table 1. Reaction conditions, yields, *E*/*Z* ratios and physical characteristics of compounds 8–16

Reagents and conditions				Products						
								Elemental analysis		
Fluorene	Aldehyde	T(°C)	Reaction time (h)		Yield (%)	Crude mixture: E/Z ratio[a]	M.p.[b] (°C)	C(%)	H(%)	N(%)
1	**4**	r.t.	3.0	**8**	21	66:34	134–142	76.6	4.55	4.25
1	**5**	r.t.	3.0	**9**	25	58:42	138–142	80.5	4.8	4.5
1	**6**	−4	3.5	**10**	25	40:60	235–238	71.9	3.6	4.2
1	**7**	−4	3.5	**11**	47	52:48	164–166	68.7	3.3	3.8
2	**5**	0	16.0	**12**	66	50:50	(*E*)114–115; (*Z*)110–112	88.7	6.75	4.5
2	**6**	0	16.0	**13**	47	50:50	[c]	79.6	5.4	4.2
2	**7**	0	16.0	**14**	66	50:50	(*E*)127–128; (*Z*)147–149	75.6	4.9	3.8
3	**4**	r.t.	1.5	**15**	51	59:41	85–88	69.4	4.1	
3	**7**	r.t.	1.5	**16**	44	66:34	(*E*)88–89; (*Z*)95–96	62.8	3.0	

[a] After purification by flash chromatography (see Experimental) the total *E*/*Z* ratio was unchanged.
[b] Performed on the *E*–*Z* mixture or, where indicated, on the pure isomers recovered after chromatography.
[c] The *E*–*Z* mixture was obtained as an oil.

organic layers were dried over sodium sulfate, filtered and evaporated *in vacuo* to afford the corresponding ylide. To a solution of the ylide (1.0 mmol) in anhydrous tetrachloroethane, kept under nitrogen, aldehydes **5** and **7** (1.0 mmol) were added. After stirring at 100 °C for 2.50 h, the solvent was removed *in vacuo* and the crude mixture was purified by flash chromatography with a 90:10 hexane–Et_2O mixture as eluent. **30**: $E/Z = 35:65$; m.p. 126–128 °C; 64% yield; elemental analysis C 85.4, H 4.85, N 4.5%. (*E*)-**31**: m.p. 180–183 °C. (*Z*)-**31**: m.p. 191–192 °C; 86% yield; elemental analysis C 75.1, H 3.45, N 4.0%.

Synthesis of 9-(4′Y)benzylidene-1-azafluorenes 20–24

General procedure. To a solution of 1-azafluorene **17**[9] (1.0 mmol) in 30 ml of absolute ethanol, aldehydes **4**, **5**, **7** and **19** (1.0 mmol) and potassium *tert*-butylate (5.0 mmol) were added at room temperature under nitrogen.[10] After stirring at reflux for 2.0 h, the mixture was cooled to room temperature. The reaction mixture was stirred 12.0 h and quenched with water and ethanol and evaporated *in vacuo*. The aqueous phase was extracted with Et_2O and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residues were analyzed by ^1H NMR spectroscopy for the *E*/*Z* ratio determination, and then purified by flash chromatography with a 90:10 hexanes–Et_2O mixture as eluent to afford benzylideneazafluorenes **20**–**24** as mixtures of *Z*- and *E*-isomers. **20**: *E*/*Z* 53:47; m.p. 115–121 °C. (*E*) **22**: m.p. 66–69 °C. (*Z*) **22**: m.p. 105–107 °C. The *E*–*Z* mixtures of compounds **21**, **23** and **24** were recovered as oils. The yields of compounds **20**–**24** are shown in Scheme 2. The elemental analyses were as follows: **20**, C 84.5, H 4.9, N 4.9%; **21**, C 89.5, H 5.25, N 5.25%; **22**, C 74.5, H 3.4, N 4.3; **23**, C 89.8, H 4.7, N 5.5%; and **24**, C 66.1, H 2.3, N 4.05%.

E/*Z* Isomerization

General procedure. Benzylidenefluorenes, either as a pure distereoisomer or as a diastereoisomeric mixture, dissolved in $CHCl_3$, were stirred at reflux in the presence of a catalytic amount of thiophenol (10%) and azobisisobutyronitrile (1%) for 5.0 h (compounds **8**–**16**, **30** and **31**) or 24.0 h (compounds **20**–**23**). The mixture was then cooled to room temperature and the $CHCl_3$ evaporated. The residue was dissolved in Et_2O or THF and washed with 1 M NaOH solution and the organic layer was separated, dried over sodium sulfate, filtered and evaporated *in vacuo*. The reactions proceeded quantitatively, and no decomposition materials were observed.

NMR measurements

The ^1H and ^{13}C spectra were acquired on a Bruker AM 300 spectrometer (^1H at 300.133 MHz and ^{13}C at 75.47 MHz) in 5 mm sample tubes in $CDCl_3$ as the solvent. The $^{13}C\{^1H\}$ spectra were obtained using Waltz decoupling and were exponentially multiplied to give 0.8 Hz line broadening before Fourier transformation.

2D spectra. For all 2D NOESY NMR experiments the samples were prepared by dissolving 5–6 mg of the required fluorene derivative in 0.75 ml of $CDCl_3$. The solution was degassed to remove any dissolved oxygen. Pure absorption 2D spectra were recorded using the NOESY pulse sequence $90°–t_1–90°–\tau_m–90°–t_2$ and the method of phase cycling described by Marion and Wüthrich[11] with time-proportional phase incrementation (TPPI). The following parameter and procedures were generally employed: spectral width 2200 Hz, 1024 × 1024 data matrix, 256 time increments of 64 transient each; Fourier transformations were carried out with zero-filling only in f_1, and using the shifted sine-bell apodization function in both dimensions. A mixing time of 2.5 s and a relaxation delay of 7.5 s were used and the experiments were run at 28 °C.

The 2D COSY spectra were recorded with a 1024 × 1024 data matrix and 512 time increments of 16 scans each, in magnitude mode, and processed with zero-filling in f_1 and unshifted sine-bell apodization function.

The AM 300 spectrometer was equipped with a 5 mm inverse probe head to carry out the experiments described below. HOHAHA[12] was recorded in the phase-sensitive mode using TPPI technique 5 and MLEV-17 mixing sequence of 70 ms plus two trim pulses of 2.5 ms each (20 μs 90° ^1H pulse) and a relaxation delay of 1 s. The data size and processing were the same as described above for 2D COSY. For the $^1H–^{13}C$ one-bond (HMQC)[13] and $^1H–^{13}C$ long-range (HMBC)[14] heteronuclear chemical shift correlations the following acquisition parameters were applied: spectral widths in the f_1 and f_2 dimensions 13 000 and 2200 Hz, respectively, a 2048 × 1024 data matrix, 256 time increments of 256 transients each, relaxation delay 1.0 s, in both experiments $\Delta_1 = 3.5$ ms and the additional delay $\Delta_2 = 60$ ms for HMBC acquisition. Fourier transformations were performed with shifted and unshifted sine-bell apodization functions in the f_1 and f_2 dimensions, respectively.

AM1 calculations

Semi-empirical methods were applied to evaluate the energy differences between *E* and *Z* isomers of various fluorenes (see Results and Discussion). Ground-state structures (obtained from a preliminary MM2* optimization performed with MacroModel[15]) were first optimized with the AM1[16] hamiltonian by using MOPAC 6.0[17] with the options EF GNORM = 0.1. Thermodynamic calculations were performed on the ground states thus located for both isomers (FORCE THERMO ROT = 1) at 333.16 K (the isomerization temperature). The vibrational analyses ensured the nature of the stationary points.

RESULTS AND DISCUSSION

Structural assignment using 2D homo- and heteronuclear correlations

All 2-substituted-9-(4′Y)benzylidenefluorenes **8**–**16** and the 9-(4′Y)benzylidene-1-azafluorenes **20**–**24** were obtained as diastereoisomeric mixtures (see Scheme 1); owing to the difficulty in obtaining pure *E*- or *Z*-isomers, the NMR spectra were often very crowded in the aromatic region. Thus, together with the ^1H and ^{13}C 1D NMR spectra, a variety of 2D NMR experiments were performed to elucidate unambigously the structures of compounds prior to the *E*–*Z* configuration assignments. Homonuclear Hartmann–Hahn (HOHAHA),[12] COSY, ^1H-detected heteronuclear multiple-quantum coherence (HMQC)[13] and heteronuclear multiple-bond correlation (HMBC)[14] were used for this purpose. The assignment procedures followed for compounds **8–16** and **20–24** were analogous. First, in all derivatives the olefinic hydrogen H-9a was distinguished from the aromatic protons because it was the only singlet present in the proton spectrum; the negligible values, due to cancellation of positive (J^{σ}) and negative (J^{π}) contributions, observed for allylic coupling constants of H-9a ($^{4}J_{\mathrm{HH}} \approx 0$), were ascribed to the dependence on H-C(9a)—C(1′)—C(2′) angle and characteristic[18] for the found values of this angle: $300 \pm 2°$, as calculated for all model compounds (see below).

The ^{1}H–^{1}H *J*-connectivities in the 2D COSY and HOHAHA spectra gave the related protons for each aryl ring. In fluorene derivatives **8–16** the proton assignments of the 2X-substituted aryl fluorene ring is made easy by the multiplicity of proton H-1, which is the only hydrogen to appear as a doublet with a small coupling constant ($^{4}J_{meta} = 1.5$ Hz). In the azafluorenes **20–24**, the low-field resonances of proton H-2 (see Table 2), characteristic for any pyridine proton, was used to establish the ^{1}H sequence of the pyridine ring. For both series of compounds the *para*-substituted phenyl rings protons (H-2′ and H-3′) were well recognizable, giving rise to an AB system; this assignment was confirmed by the following observations: (i) the H-3′ long-range coupling with the hydrogens or fluorine atoms of the *para*-substituent group (where Y = Me and CF_3, respectively); (ii) the peculiar H-3′ high-field resonances when the *para*-substituent was the methoxy group; (iii) the C–H longe range coupling of C-1′ with H-3′ and of C-4′ with H-2′ (see below).

For ^{1}H–^{13}C chemical shift correlation we performed the experiments with the inverse-detection mode. In addition to the HMQC spectra, producing direct attachment between protons and carbons, long-range chemical shift correlation HMBC experiments were performed, setting the optimum *J* value as 8.0 Hz, to assign the quaternary carbons and to examine the accuracy of the proton assignments. For both series of compounds **8–16** and **20–24**, the long-range quaternary carbon connectivities, which supported the structural assignment, were the following in all compounds: (i) C-1a with H-4 and H-9a; (ii) C-4a with H-3 (the correlation of this carbon with H-1 was present only for compounds **8–16**); (iii) C-5a with H-6, H-8 and H-4; (iv) C-8a with

Table 2. ^{1}H chemical shifts (ppm) of compounds **8–16**, **20–24**, **30** and **31** in $CDCl_3$ as solvent

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9a	H-2′	H-3′
8*E*	8.61		8.25	7.80	7.80	7.40	7.23	7.85	7.81	7.57	7.02
Z	8.64		8.20	7.79	7.79	7.46	7.79	7.79	7.82	7.57	7.02
9*E*	8.56		8.21	7.75	7.82	7.37	7.21	7.77	7.80	7.48	7.30
Z	8.53		8.16	7.74	7.82	7.45	7.45	7.77	7.83	7.48	7.30
10*E*	8.63		8.29	7.82	7.82	7.41	7.22	7.60	7.76	7.55	7.47
Z	8.46		8.23	7.81	7.81	7.47	7.47	7.85	7.77	7.54	7.49
11*E*	8.61		8.27	7.84	7.81	7.42	7.22	7.53	7.76	7.70[a]	7.75[a]
Z	8.28		8.20	7.82	7.86	7.47	7.47	7.86	7.79	7.70[a]	7.80[a]
12*E*	7.19		6.80	7.58	7.57	7.25	6.95	7.57	7.66	7.52	7.27
Z	7.11		6.73	7.57	7.59	7.33	7.22	7.73	7.64	7.56	7.28
13*E*	7.14		6.78	7.54	7.54	7.25	6.93	7.42	7.55	7.53	7.42
Z	6.90		6.71	7.52	7.54	7.31	7.18	7.67	7.51	7.55	7.415
14*E*	7.16		6.80	7.55	7.54	7.27	6.93	7.36	7.59	7.71[a]	7.71[a]
Z	6.71		6.69	7.52	7.55	7.35	7.22	7.69	7.54	7.70[a]	7.70[a]
15*E*	7.88		7.47	7.56	7.68	7.32	7.12	7.73	7.60	7.55	7.00
Z	7.88		7.42	7.54	7.68	7.35	7.35	7.76	7.67	7.55	7.00
16*E*	7.87		7.49	7.55	7.66	7.33	7.09	7.43	7.56	7.67[a]	7.72[a]
Z	7.55		7.45	7.56	7.67	7.41	7.36	7.76	7.65	7.67[a]	7.74[a]
20*E*		8.51	7.21	7.92	7.70	7.33	7.18	7.93	8.22	7.65	7.00
Z		8.60	7.21	7.97	7.71	7.37	7.37	7.82	7.65	8.60	7.02
21*E*		8.53	7.23	7.94	7.71	7.35	7.17	7.88	8.25	7.59	7.29
Z		8.55	7.23	7.99	7.72	7.38	7.38	7.84	7.69	8.39	7.29
22*E*		8.51	7.24	7.90	7.67	7.33	7.14	7.62	8.18	7.71	7.72
Z		8.50	7.24	7.96	7.70	7.40	7.40	7.81	7.62	8.50	7.70
23*E*		8.52	7.20	7.88	7.65	7.31	7.14	7.78	8.28	7.67	7.46
Z		8.54	7.23	7.97	7.70	7.37	7.37	7.84	7.70	8.47	7.49
24*E*		8.51	7.28	7.92	7.70	7.40	7.23	7.23	7.70		
Z		8.32	7.19	7.90	7.68	7.41	7.38	7.82	7.20		
30*E*	7.90	7.33	7.57		8.40	7.40	7.20	7.79	7.65	7.52	6.98
Z	7.88	7.11	7.53		8.40	7.43	7.43	7.79	7.73	7.47	6.98
31*E*	7.98	7.40	7.65		7.70	7.43	7.19	7.49	7.70	7.70[a]	7.73[a]
Z	7.58	7.13	7.57		7.76	7.48	7.48	7.84	7.76	7.65[a]	7.74[a]

[a] H-3′ and H-2′ give an AB system.

H-7, H-5 and H-9a; (v) C-9 with H-8 and H-9a. Moreover, we could specifically ascribe to compounds **8–16** the correlations of C-2 with H-1 and H-3 (the H-1 proton was easily recognizable for the above reported reason), and of C-9 with H-1, while the long-range coupling of C-1a with H-2 was peculiar to **20–24** derivatives. As for the *para*-substituted phenyl ring, the H-2′ and H-3′ hydrogens showed long-range correlations, in the HMBC map, with C-4′ and C-1′, respectively; it was possible to distinguish C-1′ from C-4′ because of its long-range coupling with H-9a.

The ^{1}H and ^{13}C NMR data are reported in Tables 2 and 3, respectively. It was possible to perform the ^{13}C assignments also when the chemical shift difference between two *E*–*Z* carbon atoms was *ca.* 0.1 ppm, because the HMQC and HMBC experiments were carried out on the pure isomers, when possible, or on highly enriched *E*–*Z* mixtures. All assignments satisfy the structural connectivity and are in the range of values reported in the literature for similar compounds.[19]

Configurational analysis

Spectral analyses rigorously assigned the H-1, H-9a, H-2′ and H-8 proton resonances as described above. On this basis we proceeded to perform nuclear Overhauser effect (NOE)[20] experiments to assign the *E*–*Z* configuration at the exocyclic C-9–C-9a double bond of the fluorene and azafluorene compounds. Indeed, in our case, the NOE to H-9a and/or to H-8, H-1 is adequate for an anambiguous *E*–*Z* configurational assignment. The 2D NOESY phase-sensitive pulse sequence[21] was used with a mixing time, τ_m, of the order of the T_1 of the hydrogens of interest (see Experimental). Compounds **9** and **10**, as 1:1 diastereoisomeric mixtures, and **12** and **13**, both as *Z*- and *E*-pure isomers, were chosen as model compounds to perform the NOE studies. All *E*-isomers showed correlations between H-1 and H-9a and between H-8 and H-2′, whereas the opposite behavior was observed for all *Z*-isomers where H-1 was correlated with H-2′ and H-8 with H-9a.

It was not necessary to carry out the 2D NOESY experiments with the other fluorenes, since all *Z*- and *E*-isomers showed diagnostic spectroscopic features. The substituent-induced chemical shifts (SCS) by an alkyl group in fluorenes[22] and by a phenyl group in benzylidenefluorene[23] derivatives have been examined previously. This analysis[23] showed that the perturbing *syn*-phenyl substituent at the C-9a of the exocyclic double bond caused a downfield ^{13}C shift but an upfield ^{1}H shift of the compressed atom (group).

Comparable behavior was found for compounds **8–16** and **20–24**. Indeed, an appreciable long-range effect (up to 5.1 ppm) was induced by the α-phenyl substituent at C-9a on the absorptions of *syn*- and *anti*-δ nuclei (C-1/C-8). The chemical shift values for the C-1 carbon of the *E*-isomers was 3.4–5.1 ppm lower than that of the corresponding *Z*-isomers (see Table 3). In the case of C-8 an opposite shift was observed, the shielding values of *E*-isomers being *ca.* 4.0 ppm higher than those of the corresponding *Z*-isomers. The C-4a and C-5a carbons (*syn*/*anti*-ε nuclei) revealed the same trend, but with a lower chemical shift difference, with $\Delta\delta = 2.2$–1.7 and 2.75–1.7 ppm, respectively. For these carbons an upfield shift and a downfield shift for the *E*- and the *Z*-isomers were observed for C-4a and C-5a, respectively. The ^{1}H NMR spectra also revealed a trend relative to the H-1 of compounds **8–16**, but with opposite behavior to that shown previously by C-1 in ^{13}C NMR: in the *E*-isomers H-1 were more upfield than in the *Z*-isomers. The methoxy-substituted compounds **8**, **15** and **20** were an exception to this trend (see Table 2).

As suggested by one of referees, the *E*–*Z* shift differences [$\Delta\delta_{E-Z}$] for the mutually analogous protons H-1 and H-8, within the series of differently substituted derivatives, showed a peculiar trend: $\Delta\delta_{E-Z}$ (H-1) was in the range from $+0.03$ to $+0.45$ ppm and $\Delta\delta_{E-Z}$ (H-8) from 0.00 to -0.33 ppm for compounds **9–14** and **16**, and in the case of the 4′-OCH_3 derivatives **8** and **15** $\Delta\delta_{E-Z}$ (H-1) was -0.03 ppm and $\Delta\delta_{E-Z}$ (H-8) from 0.00 to $+0.06$ ppm. The positions of H-3 and H-6, however, which, from a mesomeric point of view, are electronically identical with those of H-1 and H-8, respectively, showed identical *E*–*Z* shifts for all compounds: $+0.05$ to $+0.07$ ppm for H-3 and -0.06 to -0.08 for H-6. These data suggested that the π-electron cloud dipole of the orthogonally oriented 9a-aryl ring influenced the respective π-electron distribution within the fluorene C-1–C-1a and C-8a–C-8 bonds. Moreover, the corresponding ^{13}C resonances (C-1 and C-8) only showed the effect of the difference in steric congestion between the *E*- and *Z*-isomers, while the quaternary carbons of the fluorene five-membered ring (see Table 3) showed a strange behavior: the C-1a resonances were 0.6–0.8 ppm downfield for the *Z*-relative to the *E*-isomer of the 2-nitro derivatives **8–11** but this trend was reversed for all other compounds; the structurally corresponding C-8a carbons revealed a trend that was the mirror image of that observed for C-1a. In apparent contrast, C-4a and C-5a showed, for all compounds, the same behavior as C-1 and C-8, respectively (see above). All these effects seem to indicate a distorsion of the π-electron density of the fluorene moiety by the orthogonally oriented π-electron dipole of the 9a-aryl group. As reported by Katritzky and Topson,[24] a π-inductive effect can be invoked to justify change in the π-electron system densities (fluorene moiety) arising from repulsive interaction with π-electron dipole (in our case the 9a-aryl ring differently polarized by the 4′-substituent); however, the electron density change may not always be easily predicted. The fairly severe distortion of the fluorene π-cloud, suggested by the ^{13}C shifts of the quaternary carbons, was reflected in the different Mulliken electronic distributions in the AM1 calculated structures (see below).

Analysis of the ^{1}H and ^{13}C NMR spectra of the benzylidenefluorenes **8–16** and the benzylidene-1-azafluorenes **20–24** confirmed that the α-phenyl substituent

Table 3. ^{13}C chemical shifts (ppm) of compounds **8**–**16**, **20**–**24**, **30** and **31** in $CDCl_3$ as solvent

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1a	C-4a	C-5a	C-8a	C-9a	C-1′	C-2′	C-3′	C-4′
8*E*	115.6	147.0	123.2	119.5	121.05	128.8	128.6	124.3	133.4	140.1	144.0	138.8	138.1	130.5	127.7	131.1	114.1	160.2
Z	119.5	146.5	123.6	119.5	120.85	128.8	128.3	120.35	133.4	141.0	146.35	136.8	136.6	130.65	128.3	131.1	114.3	160.4
9*E*	115.7	147.1	123.35	119.5	121.0	128.9	128.6	124.5	134.2	140.3	144.3	138.85	138.1	130.65	132.8	129.5	129.3	138.95
Z	119.7	146.5	123.7	119.5	120.85	128.9	128.3	120.5	134.2	141.1	146.5	136.8	136.9	130.8	132.5	129.5	129.3	139.3
10*E*	115.9	147.1	123.85	119.75	121.2	129.3	128.75	124.5	135.2	139.9	144.5	139.0	137.6	128.75	134.2	130.6	129.0	134.6
Z	119.3	146.7	124.2	119.75	121.0	129.1	128.9	120.6	135.1	140.65	146.7	136.5	136.9	128.85	133.8	130.6	129.0	135.0
11*E*	115.9	147.3	124.1	119.8	121.3	129.6	128.9	124.55	136.2	139.9	144.7	139.25	137.5	127.95	139.6	129.5	125.7[a]	130.5[b]
Z	119.65	146.8	124.5	119.8	121.1	129.3	129.1	120.8	136.2	140.5	146.7	136.5	137.2	128.1	139.3	129.5	125.8[a]	131.0[b]
12*E*	104.3	150.55	113.2	120.2	118.35	128.4	124.7	124.2	136.7	141.1	129.0	142.1	136.3	126.4	134.1	129.2	129.15	137.7
Z	109.4	150.0	113.1	120.2	118.3	128.1	125.1	119.9	137.0	138.15	130.8	140.1	139.2	126.5	134.3	119.1	119.15	137.7
13*E*	104.3	150.6	113.4	120.3	118.5	128.8	124.8	124.1	137.8	140.75	129.0	142.4	136.0	124.5	135.6	130.7	128.7	133.6
Z	109.1	150.0	113.3	120.4	118.4	128.5	125.2	120.05	137.8	138.0	130.8	140.3	138.8	124.6	135.8	130.6	128.6	133.6
14*E*	104.4	150.65	113.6	120.4	118.55	129.1	124.9	124.1	138.7	140.6	129.1	142.55	135.8	123.9	141.0	129.6	125.4[a]	129.8[b]
Z	109.1	150.0	113.4	120.45	118.4	128.8	125.25	120.2	138.95	137.7	130.8	140.5	138.5	124.0	141.4	129.5	125.4[a]	129.8[b]
15*E*	123.4	120.1	130.6	120.8	119.8	128.5	127.0	124.0	134.3	141.6	137.7	140.1	136.4	128.7	128.35	130.9	114.0	159.9
Z	127.2	120.3	130.9	120.8	119.55	128.0	127.0	120.1	134.3	137.9	139.9	138.4	139.2	128.8	128.4	130.9	114.1	159.8
16*E*	123.75	121.0	131.4	121.0	120.0	129.2	126.2	124.3	137.0	140.6	138.1	140.6	135.8	127.2	140.1	129.5	125.55[a]	129.8[b]
Z	127.3	120.45	131.8	121.1	119.7	128.9	126.3	120.45	136.9	137.8	140.3	138.4	138.8	127.3	139.9	129.5	125.6[a]	130.2[b]
20*E*		147.65	122.2	126.6	120.5	128.4	127.5	123.9	134.5	158.5	132.2	137.8	136.0	131.2	128.6	131.2	114.0	160.0
Z		147.1	121.8	126.5	120.1	127.5	127.4	119.7	134.5	156.7	134.5	135.3	139.6	132.0	128.4	135.3	113.7	160.7
21*E*		147.7	122.4	126.7	120.5	128.6	127.5	124.15	134.2	158.3	132.4	137.9	135.2	131.25	133.4	129.5	129.3	138.6
Z		147.3	122.0	126.5	120.1	127.7	127.6	119.9	134.0	157.0	134.6	135.8	139.65	132.0	133.0	132.35	128.8	139.65
22*E*		147.9	122.9	126.8	120.7	129.2	127.7	124.0	136.3	157.85	132.8	138.3	134.7	128.6	140.2	129.6	125.5	130.0
Z		147.4	122.8	126.7	120.3	128.6	127.9	120.3	136.0	156.3	135.3	136.2	138.7	129.45	138.7	132.2	124.8	130.0
23*E*		147.7	122.5	126.7	120.5	128.7	127.5	124.15	134.8	158.2	132.5	138.0	135.2	130.9	136.4	129.4	128.5	128.5
Z		147.3	122.2	126.5	120.2	127.7	127.55	120.0	133.9	156.7	134.8	135.8	139.2	131.7	135.4	132.3	128.0	129.25
24*E*		148.2	123.6	126.9	120.8	130.0	128.2	123.9	141.0	157.1	133.4	138.6	134.4	110.9	111.0[c]	145.2[d]	137.7[d]	141.1[d]
30*E*	124.1	126.6	132.0	103.9	122.2	128.7	128.4	124.1	133.4	140.8	139.7	138.1	137.0	129.7	128.1	131.1	114.2	160.05
Z	128.0	126.4	132.3	104.15	122.2	128.5	128.5	120.2	133.3	137.7	142.1	136.0	140.1	129.85	128.2	131.1	114.2	160.05
31*E*	124.3	126.85	132.8	104.4	122.3	129.7	128.6	124.3	136.0	140.1	140.4	138.5	136.5	127.1	139.8	129.5	125.7[a]	130.0[b]
Z	128.1	126.6	132.9	104.5	122.2	129.35	128.9	120.4	136.0	137.2	142.6	136.5	139.35	127.2	139.9	129.5	125.7[a]	130.0[b]

[a] This carbon atom shows a coupling constant with the CF_3 group: $^3J_{C,F} = 5$ Hz.
[b] This carbon atom shows a coupling constant with the CF_3 group, $^2J_{C,F} = 15$ Hz.
[c] $^2J_{C,F} = 20$ Hz.
[d] $^1J_{C,F} = 250$ Hz

could not be coplanar with the C-9–C-9a(C-α) double bond and with the fluorene moiety for its reduced rotational freedom. As expected from the magnetic anisotropy of the phenyl substituent, an upfield shift for the *syn* H-1 was observed.

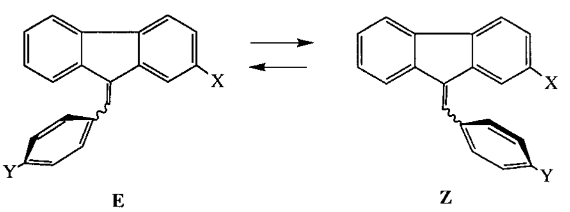
Isomerization process

The NMR analysis revealed the *E*–*Z* composition of the crude reaction mixtures of fluorenes **8**–**16** and **20**–**24**. The data reported in Scheme 2 show that the *E*-isomer is always the diastereoisomer predominantly produced in the synthesis of 9-arylidenazafluorenes **20**–**24**. In the case of 9-arylidenfluorenes **8**–**16**, the *E*/*Z* ratio mainly depends on the nature of the X substituent at the C-2 position (see Table 1); in fact, with the NMe_2 group the ratio is 50:50 and with NO_2 and Br groups the *E*-diastereoisomer prevails, with the exception of compound **10**.

However, as reported above, we became interested in building a molecular model suitable for studying the edge-to-face interaction of aromatic rings. In the present case, we hoped to observe a correlation between the electronic nature of the substituents at C-2, C-4′ and the *E*–*Z* composition at equilibrium. Therefore, in order to assess the thermodynamic preference in the equilibrium, we subjected our compounds to isomerization. This reaction was performed on mixtures of different diastereoisomeric composition (as recovered after flash chromatography) at reflux in $CHCl_3$, until equilibrium was reached (see Experimental).

The results of the isomerization of 9-arylidene derivatives **8**–**16** (reported in Table 4) showed that independently of the *E*–*Z* composition of starting mixtures the equilibration process led to an *E*/*Z* ratio very close to 50:50, with the exception of compound **11**. Depending on the nature of the C-2 substituent, the main difference was observed on comparing the series **12**–**14** with the other two series of compounds **8**–**11** and **15**–**16**. The *Z*-isomer prevailed slightly in the 2-NMe_2-substituted series, whereas the *E*-isomer became predominant for 2-nitro- and 2-bromofluorenes. This set of data clearly showed that in the molecular system under examination the edge-to-face interactions, if present, only weakly affected the *E*/*Z* ratios.

These conclusions were supported by AM1 calculations (for details on the method, see Experimental). The energy differences, evaluated for each *E*–*Z* pair at the isomerization temperature (336.16 K), are reported in Scheme 3 (for the experimentally observed values, see Table 4). Although the energy differences amounted to a few hundred cal mol^{-1}, the results did reveal a trend. Thus, for nitrofluorene derivatives the *Z*-isomer is



9-(Arylmethylidene) fluorene	X[b]	Y	ΔΔ*E* (cal mol^{-1})	Calculated *E*/*Z* ratio
—[a]	NO_2	H	0	41:59
9	NO_2	Me	−239	50:50
—[a]	NO_2	NO_2	+107	37:63
10	NO_2	Cl	−15	41:59
11	NO_2	CF_3	+135	36:64
8	NO_2	OMe	−347	54:46
—[a]	NH_2	H	0	54:46
12	NH_2	Me	−6	54:46
13	NH_2	Cl	+49	56:44
16	NH_2	CF_3	+71	57:43
—[a]	NH_2	NO_2	+7	54:46

[a] This compound was not synthesized, it is theoretical.

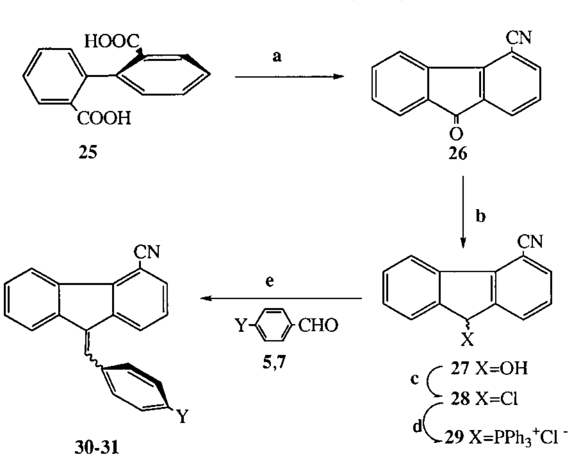
[b] The NH_2 group was used in the calculation, instead of the NMe_2 group.

Scheme 3. ΔΔ*E* values calculated for the isomerization reaction of some 2X,9-(4′Y)benzylidenfluorenes (AM1, 333.16 K0.

Table 4. *E*/*Z* ratios after equilibration for compounds **8**–**16** and **30**–**31**.

9-(Arylmethylidene) derivative	X	Y	Starting mixture[a]: *E*/*Z* ratio	Equilibrium mixture: *E*/*Z* ratio
8	NO_2	OMe	66:34	55:45
9	NO_2	Me	69:31	55:45
10	NO_2	Cl	27:73	53:47
11	NO_2	CF_3	>98:2	68:32
12	NMe_2	Me	>98:2	47:53
12	NMe_2	Me	<2:98	47:53
13	NMe_2	Cl	>98:2	49:51
13	NMe_2	Cl	<2:98	45:55
14	NMe_2	CF_3	>98:2	45:55
14	NMe_2	CF_3	<2:98	45:55
15	Br	OMe	59:41	55:45
16	Br	CF_3	67:33	57:43
30	CN	OMe	30:70	57:43
31	CN	CF_3	15:85	56:44

[a] Differently enriched after flash chromatography.



a, H_2SO_4, 140 °C; $SOCl_2$, 25 °C; $NH_2SO_2NH_2$, 120 °C; b, $NaBH_4$, THF, 25 °C; c, $SOCl_2$, 25 °C; d, PPh_3, CH_3NO_2, 25 °C; e, 5% NaOH, then **5** or **7**.

9-(Arylmethylidene) fluorene	Y	Yield	Crude mixture: *E*/*Z* ratio
30	OMe	64	33:65
31	CF_3	86	34:66

Scheme 4

favored (or less disfavored) for C-4′ methyl and methoxy derivatives **8** and **9**; in fact, in these cases the aryl π-system is electron-rich and thus the edge-to-face interaction with H-1 more favorable. The opposite situation is observed with electron-deficient aryls; the electron-withdrawing effect of the C-4′ substituent favors an edge-to-face interaction of the π-system with the less positive H-8. However, the differences between the two extremes (**8** and **11**) amounted to 0.5 kcal mol^{-1}; in the aminofluorene series even lower energy differences were calculated. The AM1 method, in other words, seemed to suggest a small effect favorable to an edge-to-face interaction, but the energy involved was so small that nothing can be argued in favor of this hypothesis.

Although the diastereisomeric ratio was not too unbalanced, it was possible to conclude that the C-2 electron-withdrawing substituents promoted the formation of the *E*-isomer **8**–**11**, **15** and **16** and the electron-donating substituents the *Z*-isomers **12**–**14**. To verify that these results were not exclusively ascribable to the C-2 substitution effect, we decided to synthesize the derivatives **30** and **31** substituted at the C-4 position by a cyano group, following the synthetic procedure reported in Scheme 4. The crude mixtures of 4-cyano-9-(4′Y)benzylidenefluorenes **30** and **31** showed an *E*/*Z* ratio close to 34:66, as determined by ^{1}H NMR. Their spectroscopic data, reported in Tables 2 and 3, were in agreement and followed the same behavior as compounds **8**–**16**. The structural and configurational analyses were performed as described previously for **8**–**16**. Compounds **30** and **31** were isomerized starting from *E*–*Z* mixtures (30:70 and 15:85, respectively) and the results are reported in Table 4. The *E*-isomer was always slightly prevalent, thus confirming the trend seen previously for the 9-arylidenfluorenes substituted at C-2 by an electron-withdrawing group.

Table 5. *E*/*Z* ratios after equilibration for compounds **20**, **22** and **23**

1-Aza-9-arylidene derivative	Y	Starting mixture[a]: *E*/*Z* ratio	Equilibrium mixture: *E*/*Z* ratio
20	OMe	81:19	68:32
20	OMe	20:80	70:30
22	CF_3	>98:2	75:25
22	CF_3	<2:98	76:24
23	H	>98:2	83:17

[a] Differently enriched after flash chromatography.

Our system allowed us to observe the interaction of a C_{aryl}—H bond with the π-surface of an aromatic ring with different electronic availability. The small effect observed should be ascribed to a difficulty of the aromatic ring substituents to alter the polarity of the $C^{\delta-}_{aryl}$—$H^{\delta+}$ σ-bond. In other words, the substituents on an aromatic ring mainly affect the π-electron system, which is easier to polarize that the σ-bond framework. The small energy differences evaluated did not allow us to speculate further on the *E*/*Z* ratios. However, the results of Poliwal *et al.*[25] led us to question severely our choice of the molecular system, which was not well suited for evidencing edge-to-face interactions.

Before abandoning any further work on substituted fluorenes, we tried to increase the structural and electronic difference between the two edges of the fluorene aromatic rings, in order to maximize the effects of their possible interaction with the phenyl substituent at C-9a. The presence of the nitrogen atom made the benzylidene-1-azafluorene derivatives **20**–**24** particularly attractive for our purpose. The isomerization reactions of these compounds were performed, as usual, on mixtures of different isomeric composition. The data reported in Table 5 showed that the thermodynamically favored *E*-diastereoisomer always prevailed over the *Z*-isomer, confirming that the nitrogen substitution really differentiates the two edges of the fluorenyl structure. Edge-to-face interaction is now possible only for the *E*-isomers, while the *Z*-compounds should experience an unfavorable lone-pair–π-system interaction.

Therefore, the observed configurational preference of azafluorenes **20**–**24** for the *E*-isomer, bearing the phenyl substituent on the side opposite to the pyridine moiety, can be easily rationalized. Nevertheless, the *E*/*Z* ratios were not strongly affected by the nature of the 4′Y *para*-substituent on the aromatic ring. Further, the influence exerted by the Y substituent was inconsistent with the model of the polar interactions, a higher *E*/*Z* ratio in favor of the *E*-isomer being observed with the unsubstituted derivative **23**.

CONCLUSION

We have synthesised two new series of *E*- and *Z*-isomers of benzylidenefluorene derivatives, **8**–**16** and

20–24, featuring arene rings which are spatially close and thus have a reduced conformational freedom, as model systems for studying the edge-to-face interactions between aromatic rings. An exhaustive spectroscopic analysis allowed us to perform the structural and configurational assignment of all *E*- and *Z*-diastereoisomers. In the isomerization process, the *E*-isomer was, to a different extent, thermodynamically favored with the exception of the compounds with an NMe_2 group as substituent at the C-2 position (compounds **12–14**). In order to recognize an edge-to-face interaction we should have found the *E*/*Z* ratios to be controlled by the nature of the 4′-aryl substituent within each series with different substitution at C-2. In contrast, in the benzylidenefluorenes **8–16**, the observed diastereoisomeric excesses were too small to allow any speculation. The AM1 calculations performed on two series of compounds with nitro and amino groups as substituents at C-2 revealed a trend, inside each series, depending on the 4′-aryl substituent but, according to the experimental results, the calculated energy differences (ΔE) were again to small to allow any speculation (see Scheme 3). To maximize these effects, we synthesized the series of the azafluorene derivatives **20–24** which showed that the *E*-isomer was thermodynamically favored. Anyway, also in this case, the *E*/*Z* ratio was randomly depending on the substitution at C-4′, hence substituted benzylidene fluorenes were not suitable for modeling and measuring edge-to-face interactions.

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