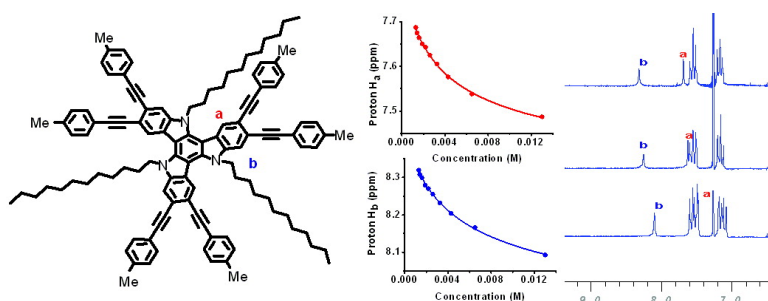


Synthesis and Self-Association Properties of Functionalized C-Symmetric Hexakis(*p*-substituted-phenylethynyl)triindoles

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Synthesis and Self-Association Properties of Functionalized C₃-Symmetric Hexakis(*p*-substituted-phenylethynyl)triindoles

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Abstract: A number of differently substituted phenylethynyl triindoles has been synthesized by 6-fold Sonogashira coupling in a key step. This new series of hexaalkynyl triindoles self-associate through arene–arene interactions in solution. The electronic communication of the external substituents with the central electron-rich triindole core has been demonstrated by means of cyclic voltammetry and optical absorption. A study of the effect of the electronic character of peripheral substituents on their self-association behavior is presented in an effort to shed light on the nature of the π -stacking interactions.

Introduction

One important purpose in supramolecular and materials chemistry is the preparation of molecules which organize into well-defined superstructures. To achieve this goal a better understanding and control of interactions among molecules is necessary.

π – π interactions have been the subject of numerous investigations both theoretically and experimentally due to their implication in important processes such as the stabilization of the double helical structure of DNA,¹ tertiary structures of proteins,² or host–guest chemistry.³ Recently interest on π – π interactions has been stimulated owing to their contribution in the arrangement of columnar discotic liquid crystals and other nanostructures.⁴ Additionally, the occurrence of π -stacking in solution has been proposed to facilitate the ordering of molecules when transferred to solid supports, essential for the development of molecular electronics.⁵

Despite their frequent occurrence the driving force of π – π interactions is not obvious, and its study is usually complicated by their weak nature.⁶ The influence of functional groups attached to the aromatic units on the aggregation behavior provides the opportunity to shed light into the nature of these interactions.

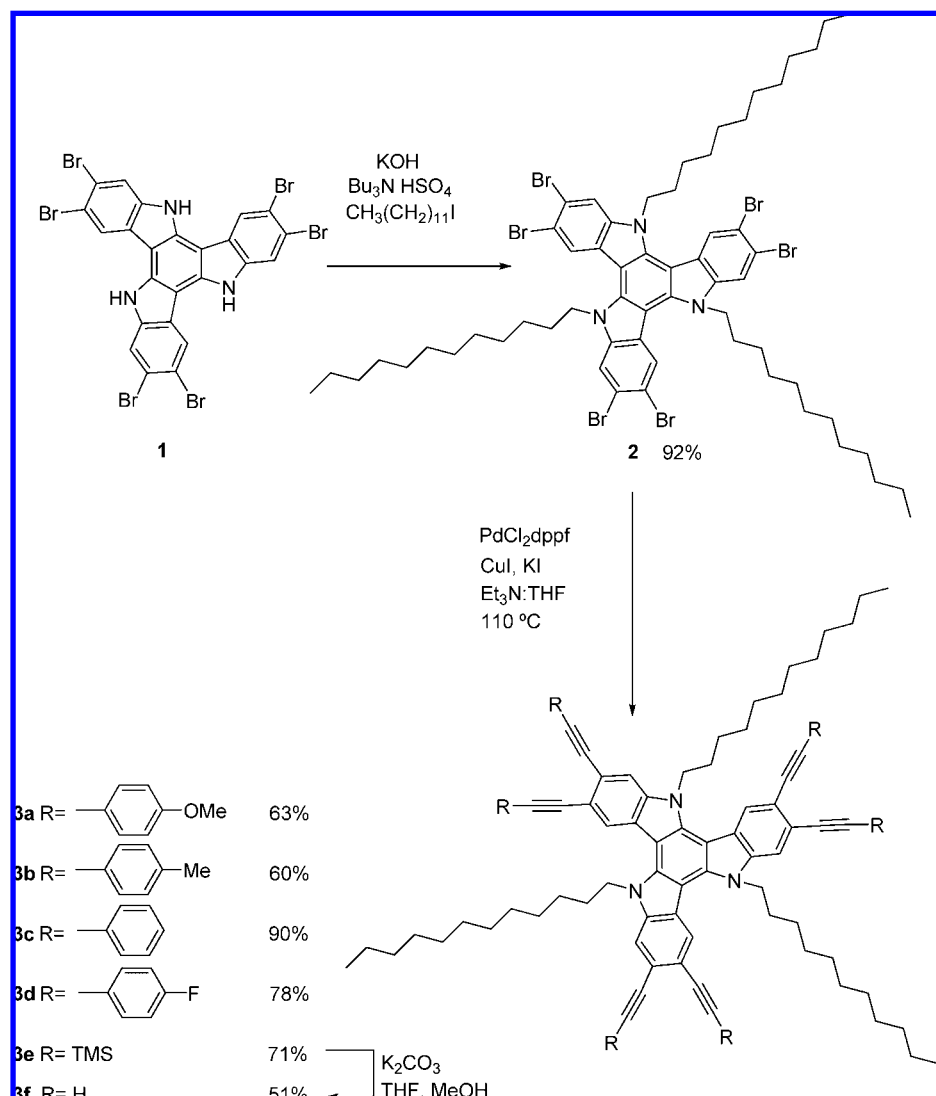
It has been commonly observed that the attachment of electron-withdrawing substituents tends to stabilize π -stacking complexes presumably by reducing electrostatic repulsion.⁷ Hunter and Sanders have originally proposed that π – π interactions derive from attractive electrostatic interactions between negatively charged π electrons and the positively charged σ framework (π – σ interactions). A diminution of the repulsion between two approaching π electron clouds would explain that introduction of electron-withdrawing substituents promotes self-aggregation.⁸ The electrostatic character of these interactions has been also highlighted by Cozzi and Siegel who propose that aromatic interactions are due to the polar character of aromatic rings (Polar/ π), again explaining a diminution of the Coulombic repulsive interaction between arenes as the electron density of the aromatic rings is reduced upon introduction of electron withdrawing substituents.⁹

Alternatively other studies claim a main contribution of dispersion effects on π -stacking.¹⁰ In that context, it has been predicted that any substituent (whether electron donating or electron withdrawing) will increase the strength of π – π interactions.^{10a} Finally, solvophobic effects have also been proposed to be an important factor in stabilizing arene–arene complexes.^{11,12}

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Scheme 1. Synthesis of Hexaalkynyl Triindoles 3a–f



The observation of such interactions in solution offers an excellent opportunity to make structure–relationships studies. Different aromatic systems, such as porphyrins,¹³ phthalocyanines,¹⁴ polycyclic aromatic hydrocarbons, or arylene ethylene macrocycles¹⁶ (AEMs) have shown to aggregate in solution through aromatic π -stacking.

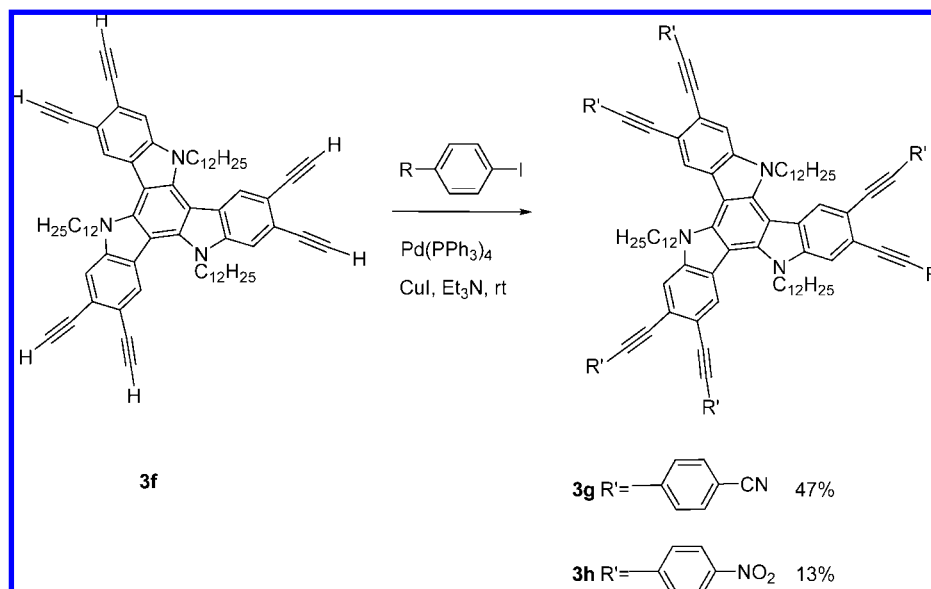
We have recently become interested in the electron-rich 10,15-dihydro-5*H*-diindolo[3,2-*a*;3',2'-*c*]carbazole (triindole) as a central core in the construction of discotic liquid crystals. In

fact we have synthesized an electroactive hexadecyltriindole¹⁵¹⁷ that shows a stable hexagonal columnar mesophase over a wide range of temperatures.

We describe in this paper the synthesis of new *N*-alkyl-substituted hexaalkynyl triindoles which self-associate through aromatic π -stacking in CDCl₃ solution. Since alkyne linkages enable an efficient electronic communication between the peripheral substituents and the central core, the electronic properties of the triindole unit can be modulated modifying the character of the terminal arylethynyl substituents. The influence of the substituents on the self-aggregation has been studied

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Scheme 2. Synthesis of Hexaalkynyl Triindoles **3g–h**

revealing that increasing the electron-acceptor character of the terminal ethynylaryl substituents and therefore making the aromatic platforms more polar inhibit self-aggregation, contrary to what is usually observed. This fact, together with the enhancement of the degree of association with the polarity of the solvent, points to a solvophobic interaction as the predominant factor in the self-assembly in this particular case.

Results and Discussion

Synthesis of Triethynyltriindoles. The synthesis of the new hexasubstituted triindoles starts from known¹⁸ symmetrical hexabromotriindole **1** followed by a 6-fold Sonogashira coupling. Prior to the coupling, amino groups were N-alkylated by treatment of **1** with 1-iodododecane in the presence of KOH and Bu₄N HSO₄ that acts as a solid–liquid phase transfer catalyst. The presence of the long alkyl chains on the nitrogen functionalities confers to the molecule enhanced solubility and facilitates the Sonogashira reactions since the N-protected platform is unstable under the coupling reaction conditions (Scheme 1).

The coupling of hexabromotriindole with electron-rich phenyl alkynes proceeded efficiently in the presence of PdCl₂(dppf), CuI, and KI using a 1:1 mixture of Et₃N/THF as solvent. Under these conditions compounds **3a–e** were obtained in yields that ranged from 60 to 90%. In contrast, coupling phenyl alkynes substituted in para position with electron-withdrawing groups was cumbersome and in all cases led to incomplete coupling.¹⁹

In order to obtain compounds substituted with electron-withdrawing groups an alternative approach has been developed. Thus Sonogashira coupling with trimethylsilyl acetylene followed by standard TMS deprotection using an aqueous base in a methanol solution yielded a triindole with six free acetylenic functions, **3f**, in 51% yield (Scheme 1). Attachments of differently *p*-substituted iodobenzenes could be then accomplished to successfully yield compounds **3g** and **3h** (Scheme 2).

Electronic Properties. The electronic properties of this series of triindoles have been investigated by optical absorption spectroscopy. Comparison of the absorption properties of substituted triindoles **3a–3h** with the parent dodecyltriindole **2** reflects a clear bathochromic shift, as extending the conjugation upon functionalization. The influence of the peripheral groups on the electronic properties of the series of *p*-phenylethynyl triindoles is clearly reflected in their spectroscopic behavior. While **3a–d** absorption maxima do not show significant differences, **3g–h** show an important bathochromic effect upon increasing the electron-withdrawing capacity of terminal substituents reflecting a push–pull effect that is transmitted through the C–C skeleton of the ethynylphenylene subunit (Figure 1, Supporting Information). Due to the electron-rich character of the platform and its C₃ symmetry, attachment of peripheral electron-withdrawing substituents results in compounds with a polar (octupolar) character.

The influence of the six peripheral groups, in communication with the central core on the electronic character of the triindole platform, has also been studied by cyclic voltammetry. The oxidizability of this molecule, associated to the easy generation

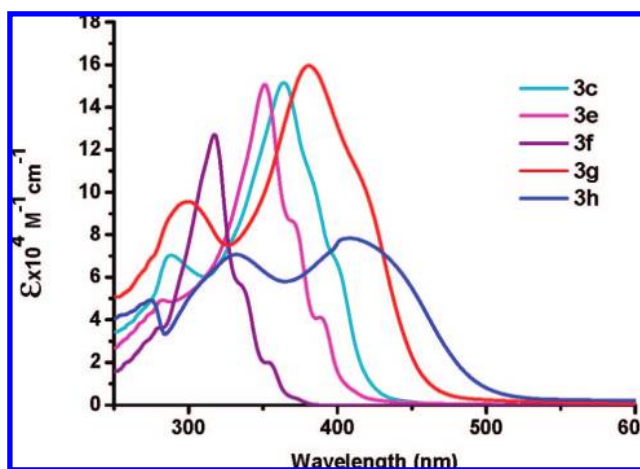


Figure 1. UV spectra of **3c**, **3e–h** in CH₂Cl₂.

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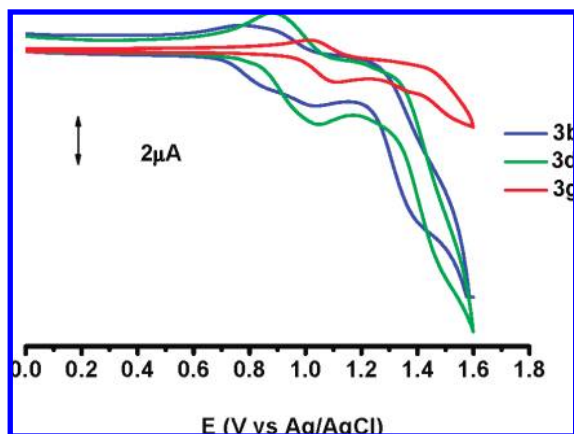


Figure 2. Cyclic voltammogram of **3b**, **3d**, and **3g** at $c = 10^{-3}$ in CH_2Cl_2 and 0.1 M tetra-*n*-butylammonium hexafluorophosphate (TBAPF₆) at a scan rate of 100 mV/s using a Pt working electrode.

of a cation radical in the electron-rich central platform,²⁰ varies in agreement with the nature of the peripheral substituents. Thus, compounds **3g–h** show a first reversible oxidation wave that shifts anodically with increasing electron-withdrawing character of the substituents. In contrast, upon attaching electron-donating (**3a** and **3b**) groups, this system tends to lose its electrochemical reversibility with a concomitant shift of the oxidation potential to lower values (Figure 2, Supporting Information).

Self-Assembly Behavior. The NMR spectra of **3a–h** are consistent with the C_3 symmetry of these molecules. The signals of the aromatic protons of central triindole core in compounds **3a–d** showed a remarkable dependence on concentration with chemical shifts moving upfield as the concentration increased on the order of 10^{-3} to 10^{-2} M. A less pronounced upfield effect was observed for the α -CH₂ proton signals of the *N*-dodecyl chains while proton signals of the periphery remained constant. No signal broadening has been observed upon increasing the concentration. In contrast **3g–h** showed no concentration dependent chemical shifting.

Chemical shift changes in nuclear magnetic resonance (NMR) spectroscopy have been well documented as a signature of aromatic stacking. When two or more aromatic units come into close vicinity of each other, the nuclei of one molecule are affected by the ring-current magnetic anisotropy of the other, resulting in resonance shifting. Additionally study of self-aggregation by NMR gives a lot of information on the association. In this particular case, the fact that only aromatic protons of triindoles are affected indicates that alkyne branches do not interact suggesting that the triindole platforms are not eclipsed but in an alternated arrangement.

The association constants (K_a) were quantitatively determined by least-squares curve fitting²¹ of the concentration dependent NMR chemical shifts for the hydrogens ortho (H_b) and meta (H_a) to the nitrogen functionalities on the central triindole cores (Figure 3, Supporting Information Tables S1–S4) considering

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(21) The least-square curve fitting to the theoretical equation $\delta = \delta_m + (\delta_a - \delta_m)[1 + (1 - \sqrt{8KC_t + 1})/4KC_t]$, where C_t is the total substrate concentration and δ is the observed ¹H NMR chemical shift, was carried out in order to determine the association constant K_a and the chemical shifts of the monomer δ_m and the dimer δ_d . See: Martin, R. B. *Chem. Rev.* **1996**, *96*, 3043–3064.

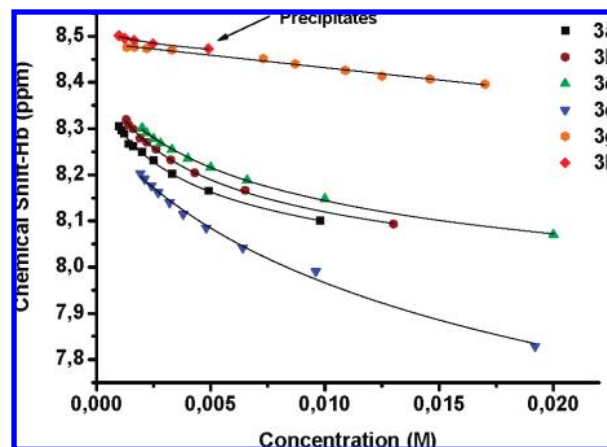


Figure 3. Concentration dependence of ¹H NMR chemical shifts for the aromatic ortho protons with respect to the nitrogen (H_b) of **3a–d**, **3g**, and **3h**.

Table 1. Association Constants and Chemical Shifts for Self-Aggregation of **3a–d**

compd	H_b			H_a		
	K_a (M^{-1}) ^a	δ_d^b	δ_m^c	K_a (M^{-1}) ^a	δ_d^b	δ_m^c
3a	129 ± 32	7.84	8.40	173 ± 45	7.27	7.77
3b	117 ± 17	7.84	8.43	150 ± 25	7.26	7.80
3c	63 ± 9	7.79	8.40	78 ± 8	7.22	7.78
3d	25 ± 6	7.07	8.30	33 ± 9	6.70	7.67

^a Determined in CDCl_3 at ambient temperature determined on the basis of the dimerization model by the NMR method. ^b Calculated chemical shifts for the aromatic protons of the dimer. ^c Calculated chemical shifts for the aromatic protons of the monomer.

that the predominant aggregation phenomenon is a monomer–dimer equilibrium.²²

Association constants K_a were found to range from 33 to 173 M^{-1} when using data of NMR shifts for H_a and from 25 to 129 M^{-1} when using data for H_b . As can be observed (Table 1), the association constants calculated from chemical shifts of H_a are slightly larger than the ones calculated from chemical shifts of H_b . However both set of data show the same trend: the association constant increases with the donor character of the peripheral substituents.

The increase of the stacking tendency upon attaching electron-donating groups, and therefore as the central triindole core becomes more electron-rich and its inhibition upon attaching electron-withdrawing groups, contrasts with the commonly accepted models that qualitatively predict substituents effects on the basis of predominant electrostatic interactions. The unusual effect exerted by the substituents in the stacking tendency in this series of compounds can be better explained considering that the dominant factor in stacking is a solvent-driven effect. Increasing the polarity of the stacking surfaces would diminish their mutual repulsion from the surrounding solvent and therefore their stacking propensity. The thermodynamic parameters of the self-association behavior of **3c** were obtained from determination of the average association constants

(22) Vapor pressure osmometry (VPO) measurements in dry CHCl_3 at 40 °C were undertaken on compounds **3b** to determine the average molecular weight of the aggregate at a concentration range of 0.01–0.02 M. An average molecular weight of 2436, close to that expected for a dimer, was found, indicating that although the presence of higher oligomers cannot be ruled out, a dimeric complex predominates under these conditions.

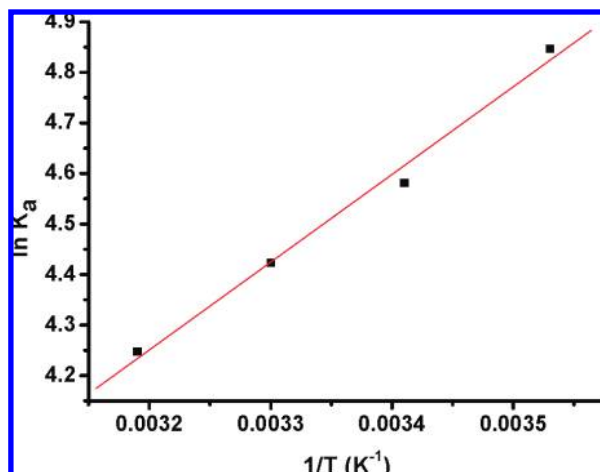


Figure 4. van't Hoff plot of self-association constants for **3c** in CDCl_3 .

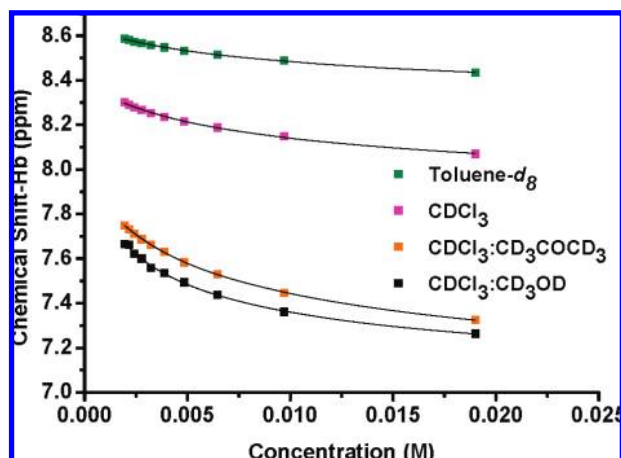


Figure 5. Concentration dependence of ^1H NMR chemical shifts for the aromatic ortho protons with respect to the nitrogen (H_b) of **3c** in different solvents.

at different temperatures. A van't Hoff analysis of **3c** (Figure 4, Table S5) led to $\Delta H = -14.17 \pm 0.15 \text{ kJ mol}^{-1}$, $\Delta S = -14.96 \pm 0.5 \text{ J mol}^{-1} \text{ K}^{-1}$, $\Delta G_{293\text{K}} = -9.79 \pm 0.52 \text{ kJ mol}^{-1}$ which indicates that the association is an enthalpy driven process.

In order to determine the effect of solvents in the self-association behavior of these derivatives, we have analyzed the self-assembly of **3c** in different solvents. Since **3c** was not soluble in neat CD_3COD and CD_3COOD , at the NMR concentration level, the NMR experiments were carried out in mixed solvent systems (Figure 5). It has been observed that self-association is sensitive to the polarity of the solvents, exhibiting an increasing tendency to self-associate with increasing the polarity of the solvent mixture (Table 2, Tables S6–S8). This result demonstrates the important contribution of solvophobic interactions in this particular case.

The effect of aromatic solvents on the association of **3c** has also been studied. It has been observed that chemical shifts are not concentration dependent in toluene (Figure 5) indicating that

Table 2. Association Constants and Chemical Shifts for Self-Aggregation for H_b of **3c** in Different Solvents at Ambient Temperature

	NMR solvent	$K_a \text{ (M}^{-1}\text{)}^a$	δ_d^b	δ_m^c
3c	toluene- d_8	46 ± 7	8.21	8.64
	CDCl_3	63 ± 9	7.79	8.40
	$\text{CDCl}_3/\text{CD}_3\text{COCD}_3 = 7/3$	73 ± 6	6.86	8.0
	$\text{CDCl}_3/\text{CD}_3\text{OD} = 7/3$	218 ± 60	6.94	8.11

^a Determined in CDCl_3 at ambient temperature determined on the basis of the dimerization model by the NMR method. ^b Calculated chemical shifts for the aromatic protons of the dimer. ^c Calculated chemical shifts for the aromatic protons of the monomer.

in this solvent π -interaction between the solute and the solvent prevails over those between solute molecules.

Conclusion

In conclusion, we have described the synthesis of a series of differently substituted hexaphenylethynyl triindoles, a new class of materials that self-associate in solution through arene–arene interactions. A study of the electronic character of the peripheral substituents on their self-association behavior indicates that, contrary to what is commonly observed, increasing the electron-donating character of the terminal *p*-phenyl substituents facilitates self-association while electron-withdrawing groups inhibit aggregation. A study of the self-assembly process at different solvent compositions indicates that upon increasing the polarity of the solvent the stacking tendency increases. The increase of the stacking tendency as the central triindole core becomes more electron-rich and its inhibition when the molecules gain a polar character suggest that in this particular case electrostatic interactions do not have an appreciable contribution to the aggregate stability. This trend, together with the influence of the polarity of the solvents in the stacking process, is however in agreement with a solvophobic-driven self-assembly.

While π – π stacking is an important noncovalent interaction the nature of this interaction remains under debate. The results presented here can contribute to clarifying the intrinsic nature of the π – π interactions. Additionally, these results suggest the possibility of tuning the intermolecular interactions between triindole units through control of the electronic character of the peripheral substituents, as well as through the choice of the solvent which holds great promise for obtaining well-defined arrangements, relevant for their electronic applications.

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Supporting Information Available: Experimental procedures and synthesis, characterization, and copies of ^1H NMR and ^{13}C NMR spectra of all new compounds. UV–vis spectra of **3a–h** and CV traces for **3a–d** and **3g–h**. Copies of ^1H NMR spectra of **3b** at varied concentrations. Tabulated ^1H NMR data, calculated association constants, and chemical shifts for the monomer and dimer of **3c** at different temperatures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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