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Synthesis and Self-Assembly of Functionalized Donor−σ−Acceptor Molecules

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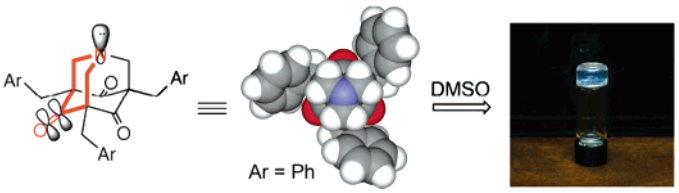
ABSTRACT



3,5,7-Tris(arylmethyl)-1-aza-adamantanetrione donor−σ−acceptor compounds have been synthesized in four steps. Computational and ^{1}H NMR analyses rationalize the solubility, gelation, and conformational properties of the C_3-symmetric molecules toward employing σ-coupled donor−acceptor interactions in molecular self-assembly.

Donor−σ(spacer)−acceptor molecules[1] are unique alternatives to traditional π-conjugated chromophores in applications ranging from nonlinear optics[2,3] to unimolecular electrical rectification;[4] a high transparency in the visible region and significantly dipolar excited state[5] underlie their function. While well-studied at the molecular level, only recently have these chromophores been considered as building blocks for advanced materials and polymers.[6,7] A common motif within the donor−σ−acceptor class features a nitrogen donor atom and carbonyl π-acceptor at opposite ends of a saturated three-carbon spacer;[8] the resulting through-bond interactions[1b] are apparent even in the ground state where they can influence the stereoselectivity of addition to the carbonyl group[9] and bias conformation at nitrogen.[10] We have initiated a research study that employs such donor−σ−acceptor chromophores in supramolecular

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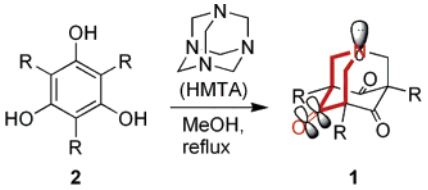
Scheme 1. Synthesis of Donor−σ−Acceptor 1-Aza-adamantanetriones from Substituted Phloroglucinol Derivatives[14]

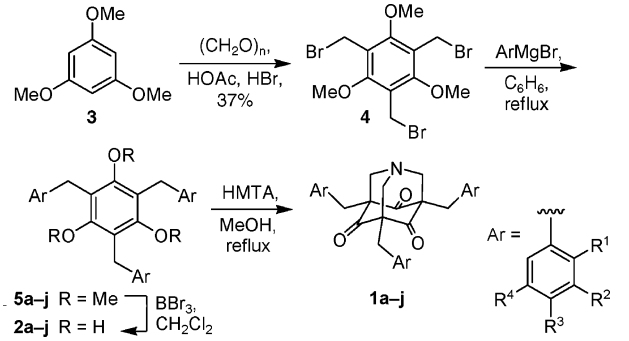


architectures; for example, reversible assemblies wherein the inherent dipole of the molecules should facilitate their one-dimensional organization in solution, an important morphology for gels,[11] liquid crystals,[12] and hydrogen-bonded assemblies[13] that display polar order.

The shape, symmetry, and rapid entry into 1-aza-adamantanetriones **1** made them an attractive scaffold to initiate our studies. Elegant work by Nicholas Risch and co-workers demonstrated the single-step conversion of 2,4,6-trialkylphloroglucinol derivatives **2** (where R = Me, Et, and *i*-Pr) to 3,5,7-trisubstituted 1-aza-adamantanetriones **1** via a Mannich-type reaction effected by hexamethylenetetramine (HMTA, Scheme 1).[14] Three carbonyl groups and three "R" groups converge on the concave underside of the adamantanoid platform; the constrained orientation of the bridgehead nitrogen lone pair with respect to the carbonyl π systems via an intervening three σ-bonds defines the donor−σ−acceptor framework. Enforced through-bond interactions are then evident in the ground state through greatly diminished nitrogen basicity[15] and nucleophilicity.[16] Reported here are the syntheses and solution-phase properties of the tris(arylmethyl) derivatives of the 1-aza-adamantantriones (**1a**−**j**, Table 1); once prepared and studied, we reasoned that a variety of structures could be derived from appropriate modifications to the aromatic periphery.

Upon designing the synthesis of **1a**−**j**, only *O*-protected tribenzyl precursor **5a** could be found in the literature,[17] the product of a five-step sequence beginning from phloroglucinol. Our alternative two-step sequence to this compound

Table 1. Synthesis of Tris(arylmethyl)-1-aza-adamantanetriones[a]



entry	R^1	R^2	R^3	R^4	% yield of **5**[b]	% yield of **1**[b,c]
a	H	H	H	H	90	65
b	CH_3	H	H	H	55	61
c	H	CH_3	H	H	42	62
d	H	H	CH_3	H	66	43
e	H	CH_3	H	CH_3	27	48
f	*i*-Pr	H	H	H	66	64
g	H	H	*t*-Bu	H	64	33
h	H	H	F	H	63	44
i	H	H	OR	H	63 (OMe)	58 (OH)
j	3-naphthalenyl				24	40

[a] See the Supporting Information for synthetic details. [b] Isolated yield. [c] Yield for two steps where the conversion of **5** to **2** is quantitative (HMTA = hexamethylenetetramine; Ar = aryl).

and various analogues (Table 1) begins with the bromomethylation[18] of commercially available 1,3,5-trimethoxybenzene **3** and subsequent 3-fold benzylic substitution with an appropriate, freshly prepared aryl Grignard reagent. The yields of **5a**−**j** are generally good, representing a minimum 80−90% average conversion at each of three benzylic sites. Some decrease in yield is observed as the size of the aryl group increases (e.g., **5e**, **5j**). Demethylation of **5a**−**j** is performed quantitatively by treatment with BBr_3 and condensation of the phloroglucinol products **2a**−**j** with HMTA in the manner described by Risch (methanol, reflux)[14] produces the tricyclic targets **1a**−**j**. While the yields of the desired 1-aza-adamantanetriones are modest, the products precipitate from methanol in each case and only filtration and washing are required for their isolation. Moreover, a variety of substituents can be accommodated in this final reaction, including fluorinated (**1h**) and bicyclic aromatics (**1j**) and phenols (**1i**).

The 1-aza-adamantanetrione cores have the expected spectroscopic signatures.[14] Using parent **1a** as an example, two intense carbonyl stretches (1735 and 1692 cm^{-1}) appear in the IR spectrum (Fermi resonance), and a weak UV transition is observed that is attributable to the σ-coupled transition (λ_{CT} = 284 nm (n → π^*), ϵ_{CT} = 2200 M^{-1} cm^{-1}, THF). The compounds show moderate solubility in haloge-

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(15) The pK_a values for the protonated 3,5,7-trimethyl-1-aza-adamantanetrione, -dione, and -one are 0.3 (3:1 water/dioxane), 3.5, and 7.14, respectively (ref 14f).
(16) For example, treatment of 3,5,7-tripropyl-1-aza-adamantanetrione **1l** (vide infra) with methyl iodide, hydrogen peroxide, or *m*-CPBA gives no reaction at the bridgehead nitrogen.
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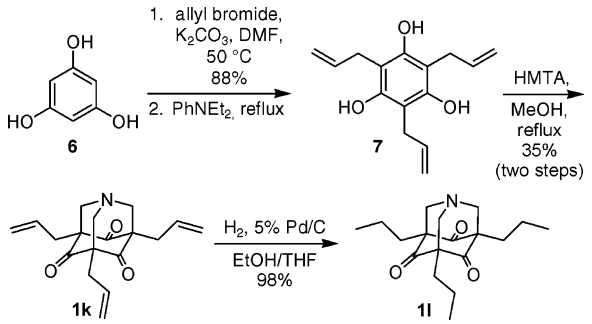
Table 2. Solvent-Dependent ^{1}H NMR Chemical Shifts[a] of the N-α-CH_2 Protons for Substituted 1-Aza-adamantantriones (300 MHz, 25 °C)[b]

compd	DMSO-d_6	pyridine-d_5	$CDCl_3$	C_6D_6
1a	3.15	3.37	3.11	2.63
1k	3.33	3.55	3.41	2.78
1l	3.47	3.62	3.38	2.74

[a] Reported in ppm versus TMS. [b] The shifts were concentration independent over the range permitted by solubility (2.5−50 mM).

nated solvents and DMSO, with excellent solubility in pyridine. A corresponding dependence of the N-α-CH_2 ^{1}H NMR chemical shift on solvent polarity/polarizability[19] is observed (Table 2) that roughly follows the expected dipolar properties of the core in solution. Namely, as the core dipole is stabilized (through-bond effects) in more polar solvents, the bridgehead nitrogen becomes more electron deficient; the consequence is a deshielding of the N-α-CH_2 protons.[20] That these effects are unique to the core and do not arise from chemical shift anisotropy (involving the aromatic substituents) is shown through model compounds. Threefold *O*-allylation of phloroglucinol **6** followed by a Claisen rearrangement offers new triallyl derivative **7** (Scheme 2).

Scheme 2. Synthesis of Model Compounds **1k** and **1l**



This material, although challenging to purify, was reacted with HMTA directly to provide triallyl 1-aza-adamantantrione **1k** in 35% yield (isolated yield for two steps). Similar chemical shift trends are observed for this compound and saturated tris(propyl) **1l** (Table 2), demonstrating that ground-state electronic stabilization of the core is responsible for the downfield shifts in more polar solvents.

Unexpected given the modest solubility of **1a**−**j** in most organic solvents, two derivatives, **1a** and **1i**, display gelation behavior.[21] Optically clear gels result from heating and cooling DMSO (Figure 1a) and $CHCl_3$ solutions of **1a** (~0.5 wt %). The gels take nearly 1 h to form and then exhibit a sol−gel transition (T_{gel}) at ~45 °C (determined by the inverted vial technique);[21] importantly, the process is reversible with no signs of decomposition or structural change to the monomer by ^{1}H NMR (DMSO-d_6).[22] Similarly, addition of water to DMSO solutions of **1i** results in gelation at the solvent interface.

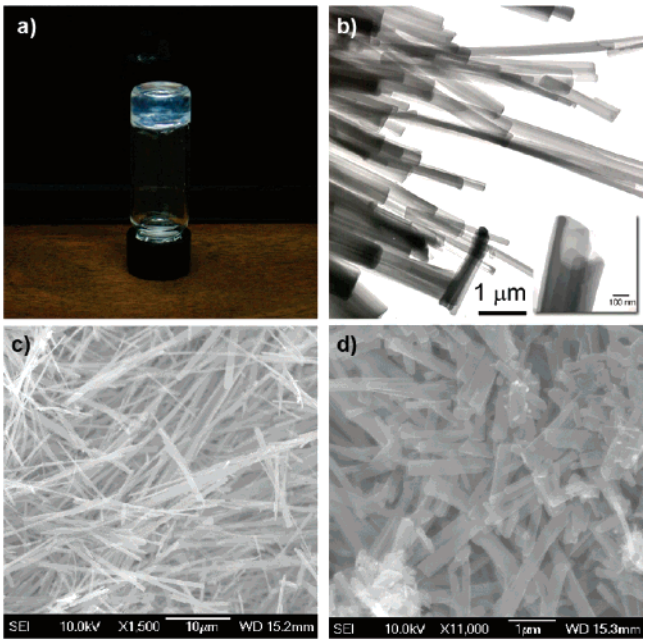


Figure 1. Organogels from tribenzyl-1-aza-adamantanetrione **1a**: (a) 0.5 wt % of **1a** in DMSO after heating and cooling; (b) TEM and (c) SEM images of a xerogel formed from critical point drying of an 0.5 wt % DMSO gel (inset: an ~0.5 μm fiber that appears as a tube); (d) SEM images of a xerogel formed from conventional freeze-drying of an 0.5 wt % DMSO gel.

SEM and TEM techniques were used to explore the morphologies of xerogels formed from **1a** (Figure 1b−d). The solvent was removed from DMSO gels (e.g., Figure 1a) via both critical point drying and conventional freeze-drying.[23] TEM images reveal 0.5 μm fibers (Figure 1b) that do not show any discernible higher-ordered structure, although some do appear hollow (Figure 1b, inset). Extended fibrillar structures are also detected by SEM from each of the sample preparations; these show little entanglement, consistent with more crystalline gelators.[24,25] In all cases, the

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(20) The same effect is found upon introducing carbonyl groups to the 1-aza-adamantane core. For 1,3,5-trimethyl-1-aza-adamantane, ^{1}H NMR ($CDCl_3$) δ N-α-CH_2 = 2.60 ppm; this value increases through the monoketone (2.88−3.03), diketone (2.75−3.45), and triketone (3.41) indicative of enhanced through-bond effects (data taken from ref 14).

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(22) An important consideration as the tricyclic ring systems are not strain-free. The bond angle at the carbonyl is calculated as 114.5°, smaller than the optimum sp^2 bond angle of 120°.

(23) For a discussion of gel morphology dependence on drying technique see: Frey, M. W.; Cuculo, J. A.; Spontak, R. J. *J. Polym. Sci., Part B: Polym. Phys.* **1996**, *34*, 2049−2058.

(24) Wang, G. J.; Hamilton, A. D. *Chem. Eur. J.* **2002**, *8*, 1954−1961.

(25) DSC analysis of the monomer reveals a sharp endothermic transition upon first heating (297.1 °C) and sharp exotherm upon cooling (222.5 °C). Likewise, preliminary powder X-ray diffraction studies show a series of low angle diffraction peaks that are not readily indexed.

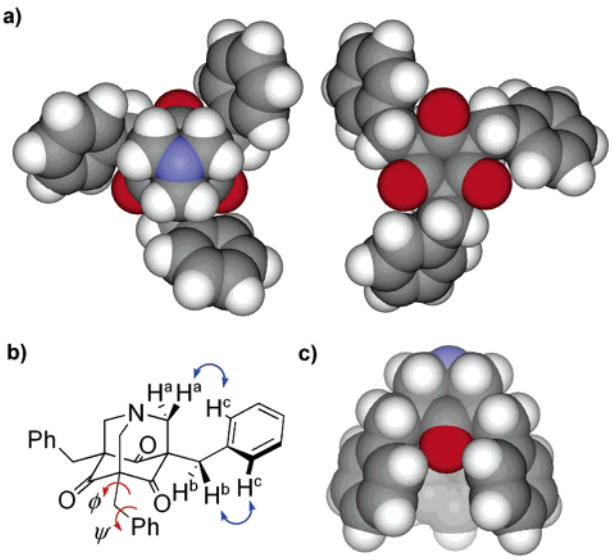

Figure 2. Low-energy conformations of **1a** identified from Monte Carlo conformational searching:[26] (a) energy-minimized lowest energy "all-arms-up" conformation (one enantiomer is shown); (b) NOE contacts identified by a NOESY experiment and labeling of critical dihedral angles, ϕ and ψ; (c) energy-minimized lowest energy "all-arms-down" conformation, approximately 5.8 kcal mol^{-1} higher in energy.

manifestation of fibers is consistent with other gelators, the assembly of which is generally understood to be one-dimensional organization of the monomers.[21]

As ascertaining molecular ordering and conformation from the gel phase remains an interminable challenge,[21] both solution-phase NMR experiments and computation were undertaken to preliminarily probe the conformational preferences of **1a**. Monte Carlo conformational searching[26] identifies the chiral (but racemic) C_3-symmetric "all-arms-up" arrangement as the lowest energy conformation (Figure 2a) with values of $\phi \sim 45°$ and $\psi \sim 90°$ (Figure 2b) for the two relevant dihedral angles.[27] Although appealing from a molecular recognition standpoint, the "all-arms-down" conformations (Figure 2c) are predicted to be significantly higher in energy. The lowest energy of these is shown ($\Delta\Delta E_{rel}$ = 5.75 kcal mol^{-1}, HF/3-21G*)[26] and reveals eclipsed interactions between the N-α-CH_2 hydrogens (H^a) and benzylic hydrogens (H^b); additionally, the *o*-phenyl hydrogens are poorly aligned to participate in favorable C−H···O interactions[28] with the core carbonyl oxygens, and in fact, these electrostatic interactions are likely repulsive.

Evidence for the lowest energy conformation in solution comes through a NOESY experiment where NOEs are observed between hydrogens H^c on the aromatic ring and H^a on the core (Figure 2b; d = 2.7 Å in the minimized structure of **1a**), a result only possible if the "all-arms-up" conformer is present in solution. In any case, compounds **1a**−**j** exist as equilibrium mixtures of conformers in solution,[29] as indicated by the relatively large temperature dependence of their chemical shifts. The temperature dependence coefficient is 0.2 ppb/K for H^a and 1.1 ppb/K for H^b in **1a**; these coefficients increase in **1b** to −2.6 and 2.3 ppb/K, respectively. The *o*-CH_3 protons of **1b** also display a large temperature dependence (0.6 ppb/K) as does the *o*-proton of the aromatic ring (4.1 ppb/K). The barriers to conformational exchange become even higher for **1e**; at −80 °C, H^a and H^b display a pattern of at least eight lines which coalesce into two at 20 °C.

A survey of the literature reveals that while low molecular weight organogelators of diverse structure have been identified,[21] few possess the structural and functional attributes of **1a**,**i**. While our studies have offered a glimpse of the monomer structure and behavior of **1a** in solution, our current efforts seek to understand why this molecule is a gelator at all. Certainly an appreciable ground-state dipole moment for **1a** (∼4 D) is predicted by computation, and the dipole-driven stacking of molecules is conceivable in solution[12] where other factors—complementary monomer shape, aryl substitution (i.e., $\pi-\pi$ interactions), weak intermolecular contacts (e.g., dispersion and C−H···O), and solvation—also play a role.[30] Further studies are now conceivable to show how through-bond interactions might both facilitate the organization of donor−σ−acceptor molecules such as **1a** in solution and impart their assemblies with unique electronic properties.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**7**, DSC data, computational details, and relevant NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) MacroModel *v*. 8.6 (Schrödinger, LLC), Amber* force field, $CHCl_3$ GB/SA solvation model. The structures were further minimized at the ab initio (HF/3-21G*) level using Gaussian 98 (Revision A.7, Gaussian, Inc.: Wallingford, CT, 2004). Details and references are provided in the Supporting Information.

(27) Close in energy are the C_s-symmetric "all-arms-up" conformers bearing one disparate arm with $\phi \sim -45°$ and $\psi \sim -90°$.

(28) Castellano, R. K. *Curr. Org. Chem.* **2004**, *8*, 845−865.

(29) Solid-state ^{13}C CPMAS NMR (10 kHz) of a powdered sample of **1a** reveals multiple resonances in the C═O, N-α-CH_2, and CH_2Ar regions.

(30) For comprehensive studies of dipolar aggregation phenomena in solution see: Yao, S.; Beginn, U.; Gress, T.; Lysetska, M.; Würthner, F. *J. Am. Chem. Soc.* **2004**, *126*, 8336−8348 and references therein.