Liquid Crystals

Supramolecular Columnar Liquid Crystals with Tapered-Shape Simple Pyrazoles Obtained by Efficient Henry/Michael Reactions

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Abstract: A straightforward synthesis of mesogenic pyrazoles starting from benzaldehydes by a combination of efficient Henry and Michael reactions led to novel supramolecular liquid crystals. The mesogens are fluorescent 3,5-dimethyl-4-(di or trialkoxyphenyl)pyrazoles and, in spite of the tapered shape of these molecules and their structural simplicity (only one phenyl ring), columnar liquid-crystal phases

Introduction

Supramolecular liquid crystals are fascinating examples of soft matter in which the molecules give rise to ordered, yet fluid, arrangements through non-covalent interactions.^[1] There is increasing interest in finding novel supramolecular columnar liquid crystals, as they form architectures with control at the nanoscale, and have the potential to respond to different external stimuli such as temperature, pressure, pH, light, etc., which are beneficial attributes for efficient responsive materials.^[2]

Among other possibilities, molecules with hydrogen-bonding groups and appropriate shape anisotropy are able to form columnar mesophases. They can interact by intermolecular hydrogen bonds forming disc-like entities, which then self-assemble into columns or, in other cases, they provide dynamic hydrogen-bonded networks that self-assemble into columns without any intermediate stage of disc-like supramolecules. The latter approach allows a great variety of non-discoid mo-

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were formed that are stable at room temperature. The selfassembled structure was studied by XRD and the columnar cross section contains two molecules on average with an antiparallel arrangement of pyrazoles interacting through hydrogen bonds. In contrast, the single-crystal structure of a trimethoxy analog did not show hydrogen-bonded pyrazoles but chains of head-to-tail arranged molecules.

lecular shapes, such as tapered-shape ones, to yield columnar liquid crystals.^[3] In particular, the 1*H*-pyrazole heterocycle is able to form intermolecular NH···N interactions and this ability has been successfully exploited to yield columnar mesophases with luminescent properties with either disc-like supramolecular dimeric entities^[4] or aggregates formed by tapered molecules.^[5]

In terms of molecular structure, a common molecular design for columnar liquid crystals is to have aromatic rings substituted with two or three long alkoxy tails (C_6 or longer). To achieve this goal, it is necessary to adapt previously described synthetic routes for non-substituted analogs, or methoxy-substituted analogs, and this task is not always straightforward.^[6]

The work described here concerns novel supramolecular columnar liquid crystals made of structurally simple luminescent molecules. Moreover, these novel functional molecules have the desired property with a simple structural motif and are obtained with atom-economy and efficient synthetic methodologies.^[7] These compounds are 3,5-dimethyl-4-(di or trialkoxyphenyl)-1*H*-pyrazoles and were prepared by Henry and Michael reactions (Scheme 1). This synthesis is compatible with both methoxy-substituted compounds, and dialkoxy- or trialkoxyterminated (C₁₀ and C₁₄) molecules. In spite of the tapered shape of these molecules and their structural simplicity (only one phenyl ring), columnar liquid-crystal phases were formed that are stable at room temperature.

Results and Discussion

Synthesis

An efficient method frequently used in the synthesis of mesomorphic pyrazoles is the condensation reaction of a 1,3-diketone with hydrazine hydrate.^[8] The synthesis of the target 3,5dimethyl-4-aryl-1*H*-pyrazoles by this straightforward method



Scheme 1. Synthesis of the 3,5-dimethyl-4-polyalkoxyphenyl-1H-pyrazoles.

would require the preparation of the 3-aryl-2,4-pentanediones. For the synthesis of these substituted 1,3-diketone precursors, arylation of activated methylene compounds mediated by copper salts using iodoarenes is a well-established process^[9] and usually requires a stoichiometric^[9,10] or catalytic^[11] amount of copper salt. This approach was used to prepare 3-(4-benzyloxyphenyl)-2,4-pentanodione, a compound similar to our target, in moderate yield (54%).^[12] More recently, it has been reported that acetylacetone can be arylated with iodoarenes under milder conditions by treatment with a catalytic amount of copper(I) iodide and L-proline as a promoter.^[13] In this way, and after optimizing the reaction temperature and time in order to avoid the deacylation side reaction that leads to benzyl methyl ketones,^[14] the synthesis of 3-aryl-2,4-pentanodiones with one electron-withdrawing group (NO₂), or with one electron-donating group (OH or OCH₃) in the para-position was achieved with yields of 74% and 44%, respectively in our previous work.^[5]

This route could be applied to the required 1,3-diketones by using the commercially available 4-iodo-1,2-dimethoxybenzene and 5-iodo-1,2,3-trimethoxybenzene. In subsequent steps, the diketone would be demethylated and alkylated with the long chains, that is, a deprotection step would be necessary. However, all attempts to obtain the diketones gave only very low yields (less than 20%). This setback led us to explore other synthetic routes that were more compatible with the presence of two or three long alkoxy chains.

A successful route was identified and this involved the preparation of 3,5-dimethyl-4-aryl-1*H*-pyrazoles from 1,3-dinitroal-kanes,^[15] which can be obtained from readily accessible benzal-dehydes by efficient Henry/Michael reactions. This synthetic route, along with the chemical structures of the resulting pyrazoles **4a**–**f**, is depicted in Scheme 1. The di- and trialkoxy-substituted compounds were obtained in high yields.

The first step involved alkylation with 1-bromodecane or 1bromotetradecane of the commercially available 3,4-dihydroxyor 3,4,5-trihydroxybenzaldehyde under Williamson conditions.^[16] The alkylated products were obtained in high yields (about 90%) by using DMF at 120°C and 8 h for dialkylation or 15 h for trialkylation. This first step was not necessary for compound **4 f** as the 3,4,5-trimethoxybenzaldehyde is commercially available.

In the second and third steps, nitroethane was used both as the reagent and solvent. In the second step, the aldol condensation between nitroethane and polyalkoxybenzaldehyde^[17] (Henry reaction) gave the nitroalkene product in very high yield. In the third step, the Michael addition of nitroethane to the nitroalkene occurred at room temperature for the C₁₀ and at 50 $^{\circ}$ C for the C₁₄ derivatives owing to the low solubility of the latter in nitroethane. The 1,3-dinitroalkane product is not unique but a mixture of four stereoisomers^[18] owing to the formation of two stereogenic centers (a dl pair and two meso forms for **3a-d** and **3f**, and four diastereoisomers for **3e**), which appear on a thin layer chromatography (TLC) plate as three spots. These components could be isolated and characterized by ¹H NMR spectroscopy (Figure S1 in the Supporting Information). As in the next step all of the stereoisomers give the same pyrazole, the final isolated yield of this reaction is 70%.

The final step is the limiting one and it involves the reaction of the 1,3-dinitroalkanes with hydrazine hydrate to form the pyrazole ring.^[15] A side reaction related to that in which the 2aryl-1,3-dinitro compounds can be readily transformed under basic conditions into 2-isoxazoline-2-oxides or isoxazoles has been reported.^[18,19] In our case, the formation of the 3,5-dimethyl-4-arylisoxazole byproduct was also observed and this was minimized by adding acetic acid. The best reaction conditions provided the pyrazoles in 65% yield. In addition, the isoxazole byproduct could be isolated and transformed into the desired pyrazole in a further step (Figure S2 in the Supporting Information) by heating with hydrazine hydrate and Raney nickel.^[20] Pyrazoles were characterized by elemental analysis, NMR spectroscopy, and mass spectrometry and the data are consistent with the proposed chemical structures (see the Experimental Section).

UV/Vis absorption and fluorescence properties

The UV/Vis absorption spectra of the pyrazoles in tetrahydrofuran solution are different depending on the number of terminal alkoxy chains (Table 1). Two bands at 249 nm and 287 nm appear for the disubstituted compounds and only one band at 253 nm for the trisubstituted compounds, which is consistent with a less conjugated or less planar ground state for the latter

Table 1. UV/Vis and fluorescence data for the pyrazoles.					
Compound	λ_{abs} [nm]	$\varepsilon \times 10^{-4} [\text{Lmol}^{-1} \text{cm}^{-1}]$	$\lambda_{ m em}$ [nm]	QY [%] ^[a]	
4a	249, 287	1.14, 0.43	335	8.5	
4b	249, 287	1.36, 0.42	337	8.0	
4c	253	1.35	358	0.2	
4d	253	1.33	359	0.2	
4 f	253	1.27	364	0.1	
[a] Quantum yield (QY) relative to quinine sulfate. ^[22]					



(a non-planar structure is observed in the crystal structure of ${\bf 4\,f},$ see below).

All these compounds showed one emission band in the near UV region. The emission wavelength is similar to that found for 3,5-bis(alkoxyphenyl)-substituted pyrazoles.^[4,21] The number of terminal chains also influences the fluorescence spectra. The trisubstituted compounds show a band at higher wavelengths with much lower quantum yields than the disubstituted compounds. This observation is consistent with these non-planar compounds having more effective pathways for non-radiative deactivation by torsional motions.

Liquid crystalline properties and self-organization model

Polarized optical microscopy (POM) and differential scanning calorimetry (DSC) studies were performed on the final pyrazole compounds **4a**–**e** to determine their mesomorphic properties. The thermal data are collected in Table 2. In addition, thermo-

Table 2. Thermal properties of the pyrazoles.			
Compound	Phase transitions, $T [^{\circ}C] (\Delta H [kJ mol^{-1}])^{[a]}$		
4a	Cr 71 (38.7) Iso ^(b) Iso 10 (18.0) Cr'		
4 b	Cr 50 ^[c] Cr' 85 ^[d] (56.6) Iso Iso 47 (48.4) Cr'		
4c	Col, 79 (12.7) Iso Iso 78 (13.1) Col,		
4 d	Cr 19 (21.0) Cr' 29 (15.7) Col _r 56 ^[d] (3.8) Iso Iso 49 (3.9) Col _r 25 (16.3) Cr' 13 (19.6) ^[e] Cr		
4e	Col, 76 (10.7) Iso Iso 74 (12.4) Col,		
[a] DSC data at 10° Cmin ⁻¹ of the first cooling and second heating cycle. Onset temperatures given. Abbreviations: Cr, Cr' = crystal phases, Col _r =			

rectangular columnar mesophase, lso = isotropic liquid. [b] First heating cycle. [c] Includes a cold recrystallization. [d] Peak temperature. [e] Combined enthalpy of several crystal-to-crystal transitions.

gravimetric analysis (see the Supporting Information) confirmed the stability of the compounds below 300°C, that is, well above the melting and clearing points.

The melting temperatures decrease upon increasing the number of alkoxy chains (**4a** vs. **4c** and **4b** vs. **4d**) and increase with the length of the alkoxy chain (**4a** vs. **4b** and **4c** vs. **4d**). The melting enthalpies are also higher for longer chains as a consequence of the increase in the London dispersion forces.

Although pyrazoles 4a-f do not have the classical shape of liquid crystals (i.e., rod-like or disc-like), the compounds with three long alkoxy chains, 4c, 4d, and 4e, display columnar liquid crystal phases (Figure 1).

Compound 4c is a viscous paste at room temperature and it shows birefringence by POM and a transition to the isotropic liquid at 79°C. On slow cooling, a texture growing as long





Figure 1. Microphotographs under crossed polarizers of the liquid-crystal textures observed on cooling from the isotropic liquid: a) **4c** at 64 °C (10× magnification), b) **4c** at 78 °C (20× magnification), c) **4d** at 45 °C (20× magnification), d) **4e** at 74 °C (10× magnification), e) sheared **4c** at 78 °C (20× magnification), f) sheared **4d** at 45 °C (20× magnification).

crossed needles appeared from the isotropic liquid (Figure 1 a) and this remained down to room temperature. A faster cooling of the sample gave rise to a texture with some pseudo focalconic defects more commonly observed for columnar mesophases (Figure 1 b). Similar behavior was observed for **4d**, albeit in a shorter temperature interval (Figure 1 c), and **4e** (Figure 1 d). Even though such needle-like growth is not conventional for liquid-crystal phases, the textures show shear flow, a typical property of a liquid-crystal phase (Figure 1 e, f).

The columnar-to-isotropic liquid transition of the DSC heating cycle is quite broad and showed some thermal hysteresis at a standard rate of 10° C min⁻¹ (6–12 °C considering the peak temperature maxima, but only 1–2 °C considering onset temperatures), which is a common behavior for viscous supramolecular liquid crystals. Moreover, by reducing the rate to 1 °C min⁻¹, the thermal hysteresis between peak maxima was reduced to 4–6 °C (see DSC thermograms in the Supporting Information).

The XRD studies confirmed unambiguously the liquid-crystal phase. An XRD study at 20 °C of **4c** gave a diffraction pattern that is compatible with a columnar mesophase (Figure 2a). In the high-angle region of the diffractogram a broad diffuse halo



Figure 2. a) X-ray diffractogram of 4c at 20 °C. b) Schematic drawing of a rectangular columnar mesophase with *p2gg* symmetry, indicating the parameters obtained for 4c.

that is characteristic of a liquid crystal was observed at a distance of 4.5 Å, which is typical of the conformational disorder of the hydrocarbon chains in a fluid phase. In addition, the diffractogram contained multiple diffraction maxima in the lowangle region and these can be assigned to a columnar mesophase with rectangular symmetry. Compound **4d** and **4e** gave similar diffractograms (see the Supporting Information).

It can be observed from the diffractograms for **4c**, **4d**, and **4e** that, for some reflections, the sum of the Miller indexes (h+k) is an odd number (Table 3). This suggests that the symmetry of the 2D packing of columns is p2gg and implies that in the mesophase the cross section of the columns is elliptical and the direction of the main axes of the ellipses is alternating (Figure 2b). The p2gg symmetry is consistent with the presence of two columns per unit cell in the rectangular columnar phase.

These data allow us to propose a model for the self-organization of the molecules of 4c in the mesophase. Although the molecular geometry of the molecule is tapered, it is known that molecules that do not have a discoid geometry can assemble through supramolecular interactions to give rise to a columnar organization.^[3]

An estimation of the number of molecules in the unit cell gives a value of four (see the Supporting Information). Taking into account that the proposed geometry of the rectangular cell includes two discs per cell unit, then each disc should be formed by two molecules on average. In addition, the IR spectrum of the mesophase indicates that the pyrazoles are associated by hydrogen bonding (3174 cm⁻¹ for the N–H stretching band). A model for the columnar mesophase can be proposed in which the columnar cross section is formed by a pair of mol-

Table 3.	XRD data	for the liquid	crystalline	phases.	
Comp- ound	Т [°С]	d _{obs} [Å]	hk	d _{calc} [Å]	Mesophase and lattice constants [Å]
4c	20	22.8	11	22.8	Col _r
		16.8	21	16.7	
		13.5	02	13.5	a=42.6
		12.2	31	12.6	b=27.0
		10.9 ^[a]	22, 40	11.4, 10.6	
		9.3 ^[a]	32, 13	9.8, 8.8	
		8.6	42	8.4	
		7.6	33	7.6	
		6.7	04	6.7	
		6.2	62	6.3	
		4.5 (br) ^[b]	-	-	
4d	35	25.9	20	25.85	Col _r
		14.5	31	14.5	
		12.0	22	12.0	a=51.7
		10.4	32	10.65	b=27.1
		10.0	51	9.7	
		7.3	43, 62	7.4, 7.3	
		4.5 (br) ^[b]	-	-	
4e	20	22.0	11	22.2	Col _r
		16.1	21	16.1	
		13.5	02	13.3	a=40.3
		12.3	31	12.0	b=26.6
		10.8	22	11.1	
		9.1 ^[a]	32, 13	9.5, 8.7	
		8.2	23, 42	8.1, 8.0	
		7.2	33	7.4	
		6.1	24, 62	6.3, 6.0	
		4.5 (br) ^[b]	-	-	
[a] This [b] br=b	peak pro road halo	bably corres	ponds to	two overlapp	ped reflections.

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ecules that interact by hydrogen bonds (Figure 3). The three alkoxy chains surround an inner polar region formed by hydrogen-bonded pyrazoles in a column, which is tilted in the rectangular columnar mesophase (Figure 2b).

Compounds **4d** and **4e** show the same features by POM and XRD, and the same model is applicable to these two compounds. The chiral terminal tails of compound **4e** do not impart any observable chiral features to the XRD diffractograms,^[4] although an increase in the lattice constant is observed for **4d**, as one would expect given the longer chains. On the other hand, **4e** has similar lattice constants (only slightly smaller) to **4c**. Although the chains are shorter for **4e** compared with **4c**, this is not relevant for the dimensions of the unit cell. Indeed, as a result of the high conformational disorder of the hydrocarbon chains in the columnar mesophase, for the same core, the lattice constants depend mainly on the total number of carbon atoms in the hydrocarbon chain (ten in both cases) and not on its length.

The driving force for the formation of the columnar mesophase is the nanosegregation between long alkoxy terminal chains (lipophilic part) and hydrogen-bonded pyrazoles (polar part). The change of the alkyl chain volume by decreasing the number of alkoxy tails from three to two resulted in the loss of mesomorphism. This behavior is different from that reported

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Figure 3. Proposed molecular organization in a column cross section with a pair of molecules interacting by hydrogen bonds.

for similar tapered amphiphiles such as 3,5-dihydroxycyclohexyl 3,4,5-trialkoxyphenylbenzoates^[23] or polyol-substituted 3,4,5trialkoxybenzamides,^[24] which usually display cubic or smectic phases on changing the lipophilic volume. In addition, the alkoxy substituents on the phenyl ring play a fundamental role in the formation of the NH···N hydrogen bonds between the pyrazoles as evident from the fact that in the single-crystal structure of the trimethoxy analog **4 f**, the hydrogen-bonded dimers do not form in the absence of long alkoxy chains (see next section).

The unexpected assembly capability found here is similar to analogous structures with hydrogen-bonding ability such as 3,4,5-trialkoxybenzamides.^[25] In contrast, 3,4,5-trialkoxybenzoic acids are not liquid crystals.^[26]

The supramolecular chemistry shown by these 3,5-dimethyl-4-(3,4,5-trialkoxyphenyl)pyrazoles can be used as a model or "generation-one"^[1c] of larger generation dendrons with a pyrazole at the apex. This possibility is currently being studied in our research group.

Crystal structure of the trimethoxy analog 4 f

The molecular structure of 4 f was solved by XRD crystallography on a suitable single crystal (Figure 4). The results show that the molecule is not flat and the pyrazole and the phenyl



Figure 4. ORTEP drawing of the molecular structure of 4 f.

rings are not co-planar but are twisted by 46.7°. This structure is consistent with reported single-crystal structures of 4-aryl-3,5-dimethylpyrazoles.^[5,27] The methyl groups of the methoxy substituent in the *meta*-position lie close to the plane of the phenyl ring (9.4° and 4°), whereas that in the *para*-position is almost perpendicular to the phenyl ring (78.4°).

As far as the packing structure is concerned, the molecules are arranged in antiparallel chains along the *c* axis, with each chain formed by a head-to-tail arrangement of molecules that interact by NH···OCH₃ hydrogen bonds between the NH of one pyrazole and the oxygen atoms of the next molecule (Figure 5, dashed lines). These distances (N1–O1' and N1–O2') are 2.94 Å and 3.29 Å, respectively, which are longer than typical hydrogen bonds. In addition, antiparallel chains establish N···H–CO short contacts in the *ac* plane, that is, between the pyridinic nitrogen of the pyrazole and the methoxy groups of adjacent chains (Figure 5, dashed lines).

Interestingly, the NH stretching band appears at 3353 cm⁻¹ in the IR spectrum of compound **4f** and this is a higher wavenumber than that for the NH···N associated pyrazoles found in **4a–d** and other pyrazoles (less than 3200 cm⁻¹). This finding is consistent with the absence of NH···N interactions in the single-crystal structure of **4f** but the presence of NH···OCH₃ interactions.

Conclusion

A combination of Henry and Michael reactions on polyalkoxybenzaldehydes provides novel fluorescent supramolecular



Figure 5. Detail of the packing of 4 f in chains along the c axis, with intrachain and interchain contacts (dashed lines).

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liquid crystals in an efficient way. The mesophases are stable at room temperature.

In the columnar liquid-crystal phase, the columns consist of the stacking of pairs of molecules on average formed by an outer region with a peripheral spread of the terminal chains and an inner region containing the rigid aromatic ring and the polar pyrazole rings. The comparison of the long-chained compounds with the trimethoxy parent compound shows that the substituents at the phenyl ring, which are the lipophilic part and determine the tapered shape, are an important driving force for the supramolecular organization. Moreover, hydrogen bonding and the tapered shape together, acting cooperatively, give rise to formation of the columnar aggregates.

Experimental Section

General synthetic procedures and characterization data for 4c and precursors are reported as an example. Full data for all products are collected in the Supporting Information.

General procedure for the synthesis of the aldehydes 1a-e

A solution of 3,4-dihydroxybenzaldehyde or 3,4,5-trihydroxybenzaldehyde (10 mmol) in DMF (100 mL) was mixed with anhydrous K_2CO_3 (70 or 100 mmol, respectively). 1-Bromodecane or 1-bromotetradecane (22 mmol for dialkylation or 32 mmol for trialkylation) was added dropwise. The reaction mixture was heated at 120 °C and stirred for 8 h (dialkylation) or 15 h (trialkylation). The mixture was cooled to room temperature and poured into distilled water (150 mL). The product was extracted with hexanes/ethyl acetate (9:1, 3×50 mL). The combined organic layers were dried (MgSO₄) and evaporated to dryness. The product was purified by flash column chromatography on silica gel.

1 c:^[16b] Eluent for purification (hexane/CH₂Cl₂ 3:2). Yield: 85%, white solid. *R*_f: 0.71 (hexane/CH₂Cl₂ 1:9); m.p.: 35°C; ¹H NMR (400 MHz, CDCl₃, 20°C, TMS): δ = 9.83 (s, 1 H), 7.08 (s, 2 H), 4.07–4.02 (m, 6 H), 1.86–1.71 (m, 6 H), 1.51–1.44 (m, 6 H), 1.40–1.20 (m, 36 H), 0.88 ppm (t, *J*=6.9 Hz, 9 H); ¹³C NMR (100 MHz, CDCl₃, 20°C, TMS): δ = 191.3, 153.5, 143.9, 131.4, 107.9, 73.6, 69.2, 31.94, 31.92, 30.3, 29.73, 29.67, 29.63, 29.59, 29.55, 29.38, 29.35, 29.3, 26.1, 26.0, 22.7, 14.1 ppm; IR (KBr): ν = 2955, 2918, 2871, 2849, 1699, 1693, 1587,1501, 1256, 1239, 1226, 1145, 1118 cm⁻¹; elemental analysis calcd (%) for C₃₇H₆₆O₄: C 77.30, H 11.57; found: C 77.23, H 11.01.

General procedure for the synthesis of the nitroalkenes 2 a–f

A mixture of the appropriate benzaldehyde (10 mmol), NH₄OAc (10 mmol), and nitroethane (20–70 mL) was heated at reflux for 10 h. The mixture was cooled to room temperature and poured into distilled water (100 mL). The product was extracted with hexane/ethyl acetate (9:1, 3×50 mL). The combined organic layers were dried (MgSO₄) and evaporated to dryness. The product was purified by flash column chromatography on silica gel or by recrystallization.

2 c: Eluent for purification (hexane/CH₂Cl₂ 4:1). Yield: 95%, yellow solid. $R_{\rm f}$: 0.85 (hexane/CH₂Cl₂ 1:9); m.p.: 34 °C; ¹H NMR (400 MHz, CDCl₃, 20 °C, TMS): δ = 8.01 (s, 1H), 6.63 (s, 2H), 4.03–3.96 (m, 6H), 2.47 (d, J=0.9 Hz, 3H), 1.85–1.71 (m, 6H), 1.53–1.42 (m, 6H), 1.40–1.19 (m, 36H), 0.88 ppm (t, J=6.9 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃, 20 °C, TMS): δ = 153.3, 146.6, 140.2, 134.2, 127.2, 109.1, 73.7,

69.4, 32.0, 31.9, 30.3, 29.74, 29.68, 29.64, 29.59, 29.4, 29.35, 26.1, 22.7, 14.2, 14.1 ppm; IR (KBr): $\nu = 3068$, 2954, 2919, 2870, 2847, 1649, 1577, 1516, 1495, 1385, 1361, 1252, 1171, 1120 cm⁻¹; elemental analysis calcd (%) for C₃₉H₆₉NO₅: C 74.12, H 11.00, N 2.22; found: C 74.26, H 10.77, N 2.52.

General procedure for the synthesis of the dinitroalkanes 3 a–f

A mixture of the nitroalkene (10 mmol), nitroethane (50–100 mL), and anhydrous K_2CO_3 (8 mmol) was stirred at room temperature (at 50 °C for tetradecyloxy chains) for 10 h. The reaction mixture was filtered, evaporated to dryness, and purified by column chromatography on silica gel or by recrystallization.

3c: Eluent for purification (hexane/ethyl acetate 9:1). Yield: 73%, white solid. R_f: 0.83 (meso 1); 0.72 (dl pair); 0.55 (meso 2) (hexane/ ethyl acetate 8:2); m.p.: 33 °C (mixture of stereoisomers); ¹H NMR (400 MHz, CDCl₃, 20 °C, TMS): $\delta = \text{meso 1}$ (2*R*,3*S*,4*S*): 6.21 (s, 2H), 4.77 (q, J=6.5 Hz, 2H), 3.99 (t, J=7.7 Hz, 1H), 3.95-3.86 (m, 6H), 1.81–1.69 (m, 6H), 1.46 (d, J=6.5 Hz, 6H), 1.48–1.42 (m, 6H), 1.38– 1.18 (m, 36 H), 0.87 (t, J = 6.9 Hz, 9 H); dI pair (2R,4R) + (2S,4S): 6.19 (s, 2 H), 5.21 (dq, J=6.7, 10.2 Hz, 1 H), 4.77 (dq, J=4.8, 6.6 Hz, 1 H), 3.95-3.86 (m, 6H), 3.48 (dd, J=10.2, 4.8 Hz, 1H), 1.81-1.69 (m, 6H), 1.48–1.42 (m, 6H), 1.46 (d, J=6.6 Hz, 3H), 1.37 (d, J=6.7 Hz, 3H), 1.38–1.18 (m, 36 H), 0.87 (t, J=6.9 Hz, 9 H); meso 2 (2R,3R,4S): 6.19 (s, 2H), 5.12 (q, J=6.4 Hz, 2H), 3.95–3.86 (m, 6H), 3.39 (t, J=6.8 Hz, 1 H), 1.81–1.69 (m, 6 H), 1.65 (d, J=6.4 Hz, 6 H), 1.48–1.42 (m, 6 H), 1.38–1.18 (m, 36H), 0.87 ppm (t, J=6.9 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃, 20 °C, TMS): (mixture of stereoisomers) $\delta = 153.5$, 153.1, 138.83, 138.76, 127.1, 126.9, 126.5, 107.8, 107.32, 107.27, 83.53, 83.47, 83.0, 82.2, 73.34, 73.32, 73.2, 69.4, 69.3, 69.2, 53.9, 53.7, 52.6, 31.88, 31.86, 30.3, 29.7, 29.61, 29.57, 29.5, 29.4, 29.34, 29.32, 29.30, 26.0, 22.64, 22.63, 19.3, 17.6, 17.0, 16.1, 14.0 ppm; IR (KBr): ν = 1589, 1557, 1389, 1356, 1338, 1244, 1167, 1114 cm⁻¹; elemental analysis calcd (%) for C₄₁H₇₄N₂O₇: C 69.65, H 10.55, N 3.96; found: C 70.05, H 10.23, N 4.01.

General procedure for the synthesis of the pyrazoles 4a-f

A solution of hydrazine hydrate (20 mmol) and acetic acid (20 mmol) in ethanol (10 mL) was added to a solution of dinitroalkane (10 mmol) in ethanol (100 mL) at 50 °C. The mixture was heated at reflux for 10 h. The solvent was evaporated and the residue was extracted with ethyl acetate (3×75 mL). The combined organic layers were dried (MgSO₄) and evaporated to dryness. The product was purified by column chromatography on silica gel or by recrystallization.

4 c: Eluent for purification (hexane/ethyl acetate 8:2). Yield: 65%, ivory solid. *R*_f: 0.17 (hexane/ethyl acetate 7:3); m.p.: see Table 2; ¹H NMR (400 MHz, CD₂Cl₂, 20°C, TMS): δ = 6.43 (s, 2 H), 4.01–3.91 (m, 6H), 2.26 (s, 6H), 1.84–1.69 (m, 6H), 1.52–1.42 (m, 6H), 1.42–1.20 (m, 36H), 0.88 ppm (t, *J* = 6.9 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃, 20°C, TMS): δ = 153.0, 141.8, 137.1, 128.7, 118.8, 108.3, 73.5, 69.3, 31.96, 31.92, 30.4, 29.8, 29.7, 29.66, 29.60, 29.5, 29.41, 29.36, 29.55, 2924, 2854, 1601, 1585, 1526, 1504, 1242, 1210, 1118 cm⁻¹; elemental analysis calcd (%) for C₄₁H₇₂N₂O₃: C 76.82, H 11.32, N 4.37; found: C 77.15, H 10.98, N 4.54; MS (MALDI⁺, dithranol): *m*/z: 641.6 [*M*+H]⁺.

Crystal data for 4 f

Colorless crystals suitable for crystallographic analysis were obtained by slow diffusion of hexane into a solution of the com-

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pound in dichloromethane at 5 °C. The crystals were filtered off, washed with ethanol and dried. CCDC 1051504 contains the supplementary crystallographic data for this paper (excluding structure factors). These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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