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Steroid-Derived Naphthoquinoline Asphaltene Model Compounds: Hydriodic Acid Is the Active Catalyst in I_2-Promoted Multicomponent Cyclocondensation Reactions

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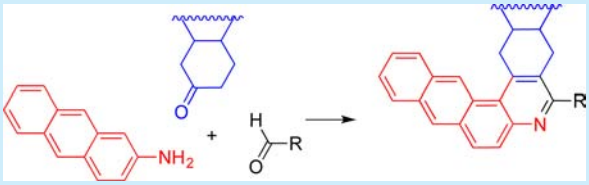
Supporting Information

ABSTRACT: A multicomponent cyclocondensation reaction between 2-aminoanthracene, aromatic aldehydes, and 5-α-cholestan-3-one has been used to synthesize model asphaltene compounds. The active catalyst for this reaction has been identified as hydriodic acid, which is formed *in situ* from the reaction of iodine with water, while iodine is not a catalyst under anhydrous conditions. The products, which contain a tetrahydro[4]helicene moiety, are optically active, and the stereochemical characteristics have been examined by VT-NMR and VT-CD spectroscopies, as well as X-ray crystallography.



With the increasing worldwide demand for energy, research has been directed toward developing renewable solutions.[1] At present, however, fossil fuels remain the most significant global energy source, and this is unlikely to change in the immediate future.[2] It is, thus, imperative to ensure that fossil fuel resources are used as efficiently as possible. This is especially true for "heavy oil" and bitumen, which continue to pose a technical and environmental challenge to utilization.[3,4] The asphaltenes are the highest molecular weight and structurally most complex constituents of "heavy oil" and consist of polycyclic aromatic and partially aromatic (naphthenic) hydrocarbons, heteroatoms (S, N, and, in some forms, O), terminal and bridging alkyl chains, and polar functional groups (e.g., carboxylic acids and nitrogen bases).[5,6]

Two models for the structure and topology of asphaltenes have been promoted, frequently labeled the "continental" and "archipelago" models.[5b,7] The continental model involves large, fused polycyclic ring systems, with the periphery substituted with alkyl chains.[7] In contrast, the archipelago model proposes smaller polycyclic "islands" substituted with short alkyl side chains and bridged by tethering alkyl chains.[5b] The continental model posits that π−π stacking interactions are the principal driving force for aggregation,[7] whereas the archipelago model invokes a variety of intermolecular interactions, including, e.g., acid−base interactions, hydrogen bonding, hydrophobic organization, etc., along with π−π stacking interactions.[5b] Both models may, of course, both be relevant to some extent.

"Biomarker" compounds, such as metalloporphyrins[8] and steroids,[9] were characterized early in the 20th century as components of petroleum. At the same time, the optical activity of some petroleum fractions was discovered,[9,10] and in 1912 Bushong suggested that optically active compounds should be extracted from petroleum and put to "industrial purposes".[11] Traditionally, the complexity of asphaltenes limited appreciation that steroid-derived materials were also constituents of the heaviest fractions of petroleum. More recently, however, larger hopane molecules incorporating fused heteroaromatic ring systems have been identified in heavy crude oils, including biomarker structures that feature benzoquinolines and naphthoquinolines (Figure 1).[12] Furthermore, it has been shown that steroid derivatives are tethered to other asphaltene segments (as suggested by the archipelago model),[13] and these are released from heavy oil fractions during processing.[14]

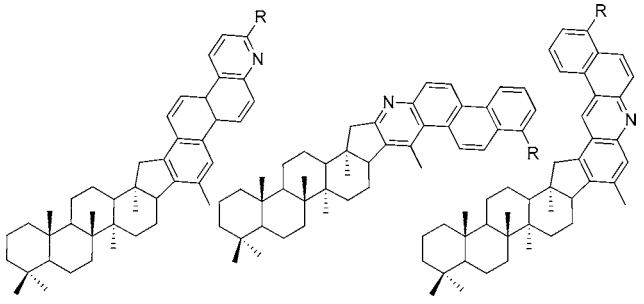


Figure 1. Suggested structures of biomarker molecules identified from petroleum samples; see ref 12.

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As it is often the case for asphaltenes, however, the specific configuration of these steroid derivatives could not been elucidated, leaving many questions regarding molecular structure and physical properties.

To unravel some of the ambiguities associated with the molecular structure of the asphaltenes, model compounds have been designed, synthesized, and investigated.[15] As part of our synthetic effort in this area, we envisioned a library of functionalized model compounds that could be efficiently constructed in one step through the use of multicomponent reactions (MCRs).[16] In particular, Lin et al. reported[17] the development of an MCR to form quinolines based on a Kozlov-type cyclocondensation.[18] Subsequently, the preparation of benzo- and naphthoquinoline derivatives by this MCR has been detailed by Wang et al.,[19] using catalytic iodine in THF to condense an aromatic amine, an aromatic aldehyde, and a ketone. Some time ago, we attempted the synthesis of steroid-containing benzoquinolines via the Wang MCR protocol using 2-aminonaphthalene (**1a**, Figure 2),[20] but we were not

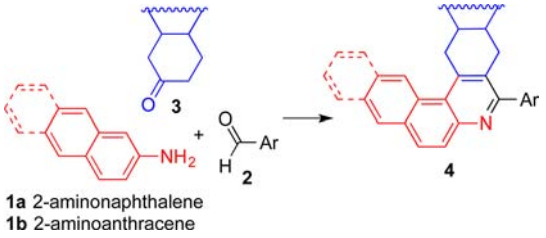


Figure 2. Schematic formation of benzo/naphthoquinolines via a multicomponent reaction.

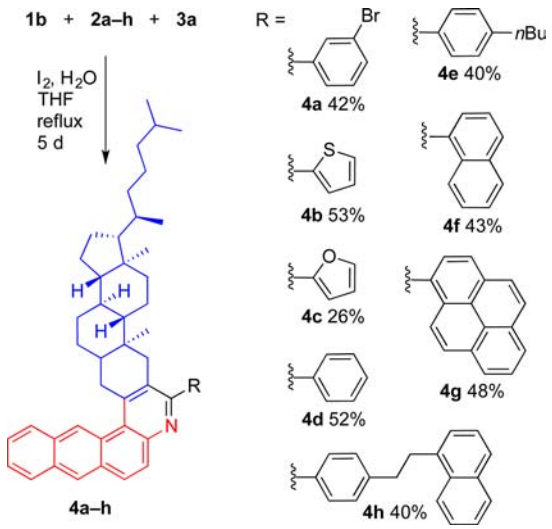
successful in reproducing a clean, high-yielding transformation.[19] We thus turned to a stepwise procedure,[18] using imine intermediates as precursors.[21] At the same time, we hypothesized that we could extend this general protocol to naphthoquinolines through the use of 2-aminoanthracene (**1b**). This route was particularly attractive because 2-aminoanthracene is more readily available than 2-aminonaphthalene.

In this paper, we explore the use of iodine-promoted MCRs to incorporate a natural biomarker into a naphthoquinoline core, providing a unique new class of eight optically active asphaltene model compounds that mimic structural features with known components of heavy oil. The ring system constitutes a chiral tetrahydro[4]helicene, and this feature has been studied by X-ray crystallography and CD spectroscopy. Additionally, we describe the identification of the active MCR catalyst and the reoptimization of the Wang protocol for the synthesis of naphtho[2,3-*f*]quinolines.[19]

The general synthetic approach is presented in Scheme 1 based on Wang's MCR protocol. As the source of THF and the water content for Wang's iodine catalyzed MCRs had not been reported,[19] we initially used rigorously dry anhydrous THF and added a catalytic amount of water in the reaction of 2-aminoanthracene (**1b**), 3-bromobenzaldehyde (**2a**), and 5-α-cholestan-3-one (**3a**). The reaction gave naphthoquinoline **4a** in an unoptimized 42% isolated yield as a spectroscopically pure solid by Soxhlet extraction (see Supporting Information (SI) for synthetic details).

As asphaltenes consists of a broad range of aromatic components,[5b,22] our immediate goal was to apply this convenient MCR for the direct preparation of a library of steroid-derived compounds. Thus, the MCR was extended to

Scheme 1. Multicomponent Reactions toward Naphthoquinolines 4a–h



aldehydes **2b–h** under analogous conditions to give steroidal naphthoquinolines **4b–h** (Scheme 1). While the yields from these MCRs were moderate, purification for some derivatives could be achieved readily by Soxhlet extraction (**4a**, **4d**), recrystallization (**4b**), or conversion of the product to the corresponding hydrochloride salt and precipitation (**4e**). In this way, chromatography could be avoided and the reactions easily scaled.[20]

It is noteworthy that the reactions are highly regioselective for ketone enolization parallel to the A/B ring fusion, as anticipated.[23] The regioselectivity was confirmed by NMR spectroscopic analysis, as well as X-ray crystallographic analysis for thienyl and phenyl derivatives, **4b** and **4d**, respectively (Figure 3). The structural solution for naphthoquinoline **4b**

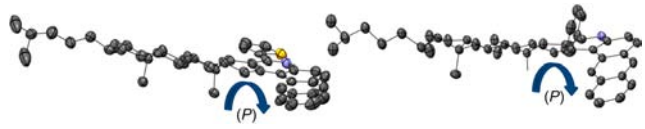


Figure 3. X-ray structures of naphthoquinolines **4b** (left) and **4d** (right) showing a (*P*)-helical structure (thermal ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity).[24]

features an almost planar arrangement between the thienyl and pyridine units (torsion angle ~8°), while the structure of **4d** shows that the phenyl ring lies at an angle of 63° with respect to the aromatic core. Both **4b** and **4d** exhibit a (*P*)-configured helical framework in the solid state.[24]

The possibility of a helical conformation in the solution phase was investigated by electronic circular dichroism (CD). Spectra were recorded in CH_2Cl_2 solutions for **4b**, **4d**, and **4g** (Figure 4). Each shows an intense CD absorption at ca. 280 nm and a significant negative absorption at lower energy, which is in agreement with the UV–vis absorptions (Figure 4).

VT CD measurements on **4d** and **4g** (see SI) in 1,1,2,2-tetrachloroethane over the range 20–110 °C reveal that the CD signals maintain the same overall signs and absorption profiles over the entire temperature range, with only a slight decrease in intensity for each sample. From these observations, we conclude that the naphthoquinolines adopt and maintain their helical conformation in solution.[25]

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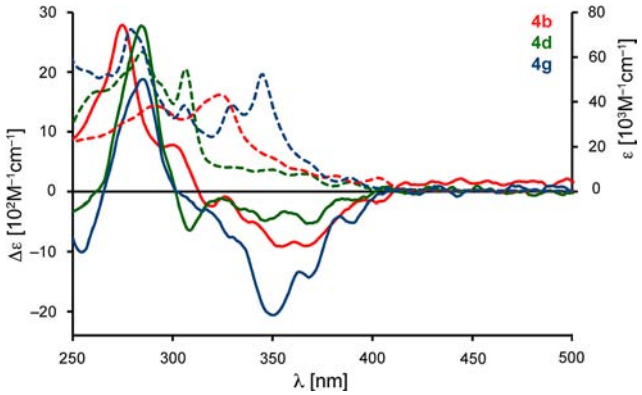
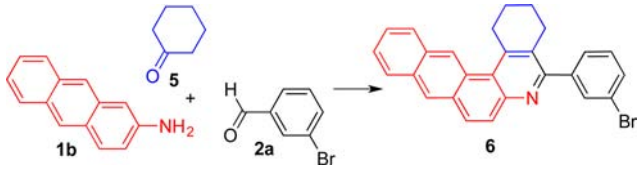


Figure 4. CD (solid) and UV–vis (dotted) spectra of **4b**, **4d**, and **4g** in CH_2Cl_2 solutions ($c = 1 \times 10^{-5}$ M).

As described above, only moderate yields for naphthoquinolines **4a–h** were achievable using catalytic amounts of iodine. As our studies progressed, however, we suspected that the actual catalyst was more complex than the "mild Lewis acidity" proposed for the role of molecular iodine.[17,19,26] We sought to identify the active catalyst for reoptimization of the Wang MCR procedure. As a starting point, the Kozlov–Wang MCR was repeated using substrates and conditions previously reported by Wang and co-workers,[18,19] namely, 2-aminoanthracene (**1b**), 3-bromobenzaldehyde (**2a**), and cyclohexanone (**5**) combined in THF in the presence of catalytic iodine (Scheme 2). In our hands, the yields of the desired

Scheme 2. General Representation of Multicomponent Reactions toward Naphthoquinoline 6[a]



[a]See text and Tables 1–2 for reagents and conditions.

cyclization product, naphthoquinoline **6**, was strongly dependent on the source of the THF and the scale/concentration of the run. Furthermore, a strong correlation was observed between catalytic turnover and the concentration of water present in the reaction medium. For example, little conversion was observed using I_2 in rigorously anhydrous THF (distilled under nitrogen from Na/benzophenone ketyl), while the use of "nominally anhydrous" THF (i.e., HPLC grade) under an inert atmosphere gave wildly varying yields of cycloadduct **6** (from 7 to 65%), depending on scale. "Wet" THF, i.e., off the shelf and not distilled, afforded a slightly better outcome, although isolated yields remained stubbornly variable.

Thus, the reaction was carefully optimized for the molar amount of water present in the medium. Using 5 mol % I_2 catalyst loading and reaction conditions as otherwise described by Wang et al.,[19] the amount of water was varied in the cyclocondensation reaction of **1b**, **2a**, and **5** in initially anhydrous THF (Table 1).

The results reveal a sensitive relationship between the success of the reaction (product yield) and the quantity of water present. The highest isolated yield for naphthoquinoline **6**, at 88%, was observed at a water content of 150 mol %,

Table 1. Water-Content Screening for the Synthesis of Naphthoquinoline 6[a]

entry	H_2O [mol %]	yield
1	10%	40%
2	27%	44%
3	75%	55%
4	150%	88%
5	200%	85%

[a]Reactions of **1b**, **2a**, and **5** carried out in dry THF for 12 h under a N_2-atmosphere, followed by an additional 24 h under ambient conditions at reflux with the given amount of H_2O and I_2 (5 mol %).

whereas lower concentrations of water led to a dramatic decrease in yield. The dependence of the reaction yield on the concentration of water strongly suggests that iodine functions not as a mild Lewis acid catalyst, but instead as a precatalyst, reacting with water to form the Brønsted acid HI and hypoiodous acid, a known reaction.[27] In this reaction mixture, the protic acid is presumably buffered, initially by the starting aniline and subsequently by the more strongly basic naphthoquinoline cycloadduct. It is reasonable, then, to conclude that buffered HI is the active catalyst in many previously reported reactions nominally catalyzed by iodine, but conducted in wet solvent(s).[17,19,26a,c]

Surprisingly, the role of the iodide counterion in the catalytic process is equally essential (Table 2).[28] It is striking that the

Table 2. Catalyst Screening for the Synthesis of Naphthoquinoline 6[a]

entry	catalyst [mol %]	H_2O [mol %]	yield
1	I_2, 5%	27%	44%
2	HI, 5%	27%	43%
3	HCl, 5%	27%	10%
4	H_2SO_4, 2.5%	27%	traces

[a]All reactions were carried out for 12 h under a N_2-atmosphere and for another 24 h under ambient conditions at reflux in dry THF.[28]

isolated yields of the HI- and I_2-catalyzed MCRs are identical within experimental error provided the water content is equivalent (entries 1, 2). But replacing molecular iodine with Brønsted acid catalysts other than HI under equivalently wet conditions leads to greatly attenuated yields (entries 3, 4). The mechanistic role of the iodide cocatalyst in this reaction remains under investigation.

After identification of the actual catalyst, we returned to the synthesis of the steroidal derivative **4a** using the reoptimized reaction conditions. As suspected, the MCR between **1b**, **2a**, and **3a** using 5 mol % I_2 and 150 mol % H_2O as an additive led to an increase in isolated yield, albeit only from 42% to 60%. While we have not repeated the synthesis of the remaining derivatives **4b–4h**, we presume that those yields will also improve, although in some cases the purification process also plays a significant role in determining isolated yields.

In summary, complex naphthoquinoline/steroid conjugates have been synthesized in one step via a "modified" Kozlov–Wang multicomponent reaction.[18,19] The combination of 2-aminoanthracene, an aromatic aldehyde, and a steroidal ketone in the presence of water and a catalytic amount of iodine produces optically active steroidal naphthoquinolines in acceptable yields. The naphthenic naphthoquinolines represent both small continental model asphaltenes (**4a–g**) and simple

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"two-island" archipelago constructs (**4h**). Two structurally characterized compounds, **4b** and **4d**, adopt (*P*)-helical conformations in the solid state, which are maintained in solution, as analyzed by CD spectroscopy. Applications of these new compounds to the investigation of supramolecular interactions and multifunctional aggregation in model and natural asphaltenes remain in progress. Finally, our investigations have established that the active catalyst for such iodine-promoted cyclocondensations is hydrated HI, formed from the reaction of iodine and water,[27] rather than iodine itself as generally assumed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03193.

Experimental details, physical properties and spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(24) The Flack parameter for **4d** was ambiguous after refinement, and assignment of an absolute configuration was not possible. Assigment of (*P*)-helicity is thus based on comparison with **4b**, and the results in ref 20.
(25) ^{1}H NMR analysis shows no evidence for the formation of other diastereoisomers regardless of reaction time or temperature. Atropisomers of **4f** and **4g** are clearly present because of restricted rotation about the bond to the naphthyl and pyrenyl groups, respectively (for VT ^{1}H NMR analysis, see SI).
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(28) Water content was standardized to that of concentrated HI (57%, Fisher Scientific).

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