we investigated the effect of temperature on the (**1**[Pt] + **2**) and (**1** + **2**) equimolar mixtures.

Both relative absorbance vs. temperature curves for (**1** + **2**) and (**1**[Pt] + **2**) (Figure 1a) present a sigmoidal shape, with respective melting temperatures of 55 and 28 °C at 2.3×10^{-5} and 8×10^{-6} M oligomer strand concentrations. (**1**[Pt] + **2**) shows less cooperativity than (**1** + **2**). That the observed melting profile of (**1**[Pt] + **2**) does not reflect the partial self-pairing of any of the two strands is ascertained by comparison with the curves of **1**[Pt] and **2** alone.[20]

The circular dichroism spectra of (**1** + **2**) and (**1**[Pt] + **2**) belong to the B DNA type,[21] the latter showing a larger differential absorption in the 270–290-nm region. The relative $\Delta\epsilon_{285}$ vs. temperature plots for (**1** + **2**) and (**1**[Pt] + **2**) (Figure 1b) show respective melting temperatures of 50 and 30 °C at 1.8×10^{-5} and 2×10^{-5} M oligomer strand concentrations. These T_m values are in agreement with those of the UV melting profiles. Here too, none of the $\Delta\epsilon_{285}$ vs. temperature curves for **1**[Pt] and **2** alone exhibit a sigmoidal profile.[22]

The NMR spectra of the exchangeable imino protons (G-N1H and T-N3H) of (**1** + **2**) and (**1**[Pt] + **2**) in water[23,24] are shown in Figure 2 at different temperatures. For (**1** + **2**) the integration gives eight imino protons. The lower field group (2 H) is assigned to the two A-T base pairs (2–15 and 3–14, see Figure 2 for the numbering) based on the nuclear Overhauser effects between these protons and the two A-H2. The two higher field groups of signals (4H and 2H) belong to the G-C base pairs.[26] All these signals are little affected by raising the temperature up to 40 °C. But at 44 °C, they experience a general broadening and disappear at 50 °C. For (**1**[Pt] + **2**) at low temperature, the signal pattern is completely different. It is noteworthy that there are still eight imino protons involved in hydrogen bonding.[26] Compared to (**1** + **2**), four G-C imino protons are moved: three are downfield shifted, two overlapping with the A-T's, and one is upfield shifted, overlapping with the two high field G-C's. Raising the temperature from 1 to 24 °C affects the three signals at 13.7, 13.6, and 13.30 ppm. At 30 °C all the signals have disappeared, and this agrees with the lower UV and CD T_m obtained for (**1**[Pt] + **2**) compared to (**1** + **2**). Three G-C imino protons of (**1**[Pt] + **2**) are involved in fraying of the duplex, which should first affect the (6–11), (7–10), and (8–9) base pairs of the platinated end if one takes into account the stabilization of the other end by the unpaired G(17) and C(18) bases of the decamer strand.[27,28] Therefore the three downfield shifted G-C imino protons should correspond to the G-platinated (6–11) and (7–10) pairs and to the distorted terminal (8–9) pair. The upfield shifted G-C imino proton could be assigned to the (5–12) pair because of the perturbation due to the adjacent platinum chelate. These assignments are tentative and are in agreement with preliminary results obtained by other workers.[29]

In conclusion, our preliminary results show that a d(GpG)-*cis*-Pt(NH_3)$_2$ chelate on a short oligonucleotide does not preclude duplex formation with a complementary strand. In our case, melting occurs at a temperature lower than 37 °C, but the duplex is quite short, and the platinated sequence is next to the helix end. This suggests that d(GpG)–platinum chelation should not induce a large distortion of the DNA duplex. This distortion might be quite similar to that of a kink[30] or of a region of systematically bent B DNA,[31] and this would raise the question of its detection by the repair enzymes.[32]

Acknowledgment. Support of this work by a grant from the "Association pour le développement de la Recherche sur le Cancer" (ARC) is gratefully acknowledged. We thank Dr. Toulmé, Laboratoire de Biophysique, Muséum d'Histoire Naturelle, Paris, and Dr. Gouyette, Institut Gustave Roussy, Villejuif, for the access to their UV and AAS facilities. We thank Engelhardt Industries, France, for a loan of platinum salt.

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[22] That of **1**[Pt] shows an immediate sharp increase with temperature up to 30 °C followed by a smaller one and no variation above 55 °C; that of **2** shows a nearly linear increase with temperature.

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Measurement of the Thermochromic Equilibrium Constant of a Nonthermochromic Compound: 1,1'-Dimethylbianthrone

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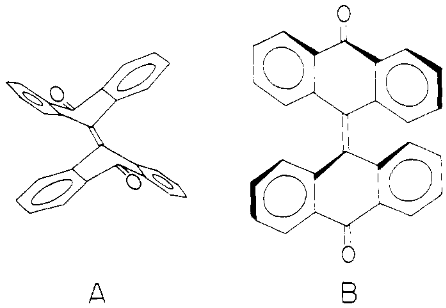
Bianthrone [Chemical Abstracts name: 10-(10-oxo-9-(10*H*)-anthracenylidene)-9(10*H*)-anthracenone (**1**)] is a thermochromic substance that exists at room temperature as a yellow A form. As solutions of **1** are heated, a significant fraction is converted to the green B form whose enthalpy is 3.0 kcal/mol greater than A.[1] Substituents larger than fluorine at the 1- and 1'-positions prevent thermochromicity.[2] It is likely that bulky substituents destabilize B more than A causing the energy difference to be too high to allow formation of detectable quantities of B at temperatures below decomposition.[3] Until now no means of measuring this energy difference has been available. We have developed an indirect electrochemical technique and have found $K_{AB} = [B]/[A] = 8 \times 10^{-6}$ at 373 K ($\Delta G_{A \to B}$ = 8.7 kcal/mol)



1

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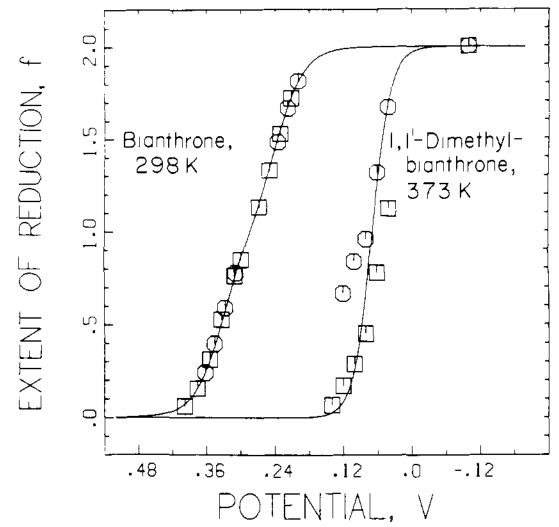
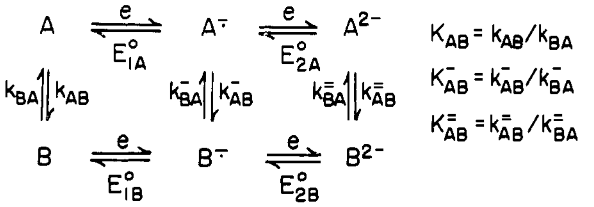
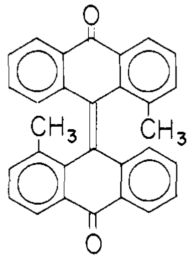


Figure 1. Extent of reduction as a function of potential as determined by thin-layer coulometry. 1.00 M tetraethylammonium perchlorate in *N,N*-dimethylformamide, 2.48 mM **1**, and 1.13 mM **2**. Squares, reduction steps; octagons, oxidation steps; curves, eq 1 for **1** and eq 2 for **2** using parameter values given in text.

Scheme I



for 1,1'-dimethylbianthrone [(*E*)-4-methyl-10-(1-methyl-10-oxo-9(10*H*)-anthracenylidene)-9(10*H*)-anthracenone (**2**)].



2

The reduction of **1**, **2**, and other substituted bianthrones is fully described by Scheme I.[4] A is reduced in an ECE sequence: A → $A^{-\cdot}$ → $B^{-\cdot}$ → B^{2-}. On the return scan of a cyclic voltammogram, sequential and reversible oxidation of B^{2-} to $B^{-\cdot}$ and then to B is seen at rapid scan rates.

It is important to realize that the above reaction sequence is kinetically controlled and is not the equilibrium thermodynamic pathway,[4e] which instead is $A \rightleftharpoons B \rightleftharpoons B^{-\cdot} \rightleftharpoons B^{2-}$. If the equilibrium potential, *E*, of an indicator electrode can be measured as a function of the extent of reduction of A, it will be possible to extract K_{AB} from the experimental data and values of $E_{1B}°$ and $E_{2B}°$ determined in independent cyclic voltammetric experiments. Typically[4a,d,h,i] $E_{1B}°$ and $E_{2B}°$ are separated by 0.2–0.3 V in which case the equilibrium potential will be given by eq 1 when $K_{AB} >$

$$E = E_{1B}° + (RT/F) \ln K_{AB} + (RT/F) \ln [(1 - f)/f] \qquad 0 < f < 1.0 \tag{1}$$

$$E = E_{2B}° + (RT/F) \ln [(2 - f)/(f - 1)] \qquad 1.0 < f < 2.0 \tag{1'}$$

$$E = (E_{1B}° + E_{2B}°)/2 + (RT/(2F)) \ln K_{AB} + (RT/(2F)) \ln [(2 - f)/f] \qquad 0 < f < 2 \tag{2}$$

$$f = 2Q/Q_t \tag{3}$$

10^{-3} (as with **1**) and by eq 2 when $K_{AB} \lesssim 10^{-4}$ (as with **2**) where *f* is the extent of reduction, *Q* is the number of coulombs required to reach the equilibrium composition at potential *E*, and Q_t is the number of coulombs required for complete reduction to B^{2-}.

The measurement of *E* as a function of *f* was achieved by thin-layer coulometry[5] in which a solution of A was reduced or a solution of B^{2-} (formed by initial reduction of A) was oxidized and the total charge required to reach equlibrium at each potential was measured. Results for **1** at 298 K are shown in Figure 1 where good agreement is found between the data and eq 1 using $K_{AB} = 1.9 \times 10^{-3}$, $E_{1B}° = 0.493$ V, $E_{2B}° = 0.237$ V (determined by cyclic voltammetry). Spectrophotometric determination[11,12] of K_{AB} in DMF at 298 K gives $K_{AB} = 2.1 \times 10^{-3}$.

Assuming K_{AB} is very small for **2**, we must expect very slow electrolysis because k_{AB} will also be very small. In fact, at 298 K negligible current is obtained and it is only at temperatures above 350 K that a steady charge is obtained in a reasonable time period. The data for **2** shown in Figure 1 were obtained at 373 K. For initial reduction steps, a significant charge is first observed near +0.15 V; for oxidation steps (obtained after initially reducing all A to B^{2-} (−0.20 V) then stepping to a more positive potential) the charge begins to build up near +0.10 V. The true equilibrium response must lie between these two extremes. A theoretical curve based on eq 2 with $K_{AB} = 8 \times 10^{-6}$, $E_{1B}° = 0.355$, and $E_{2B}° = 0.160$ V is shown in Figure 1. Though some deviation occurs for large charges on either the reduction or oxidation curves, $K_{AB} = 8 \times 10^{-6}$ appears to be a sound estimate of the equilibrium constant.

The above value of K_{AB} is supported by rate measurements. For a CEE scheme, the initial current obtained after a potential step to values negative of $E_{2B}°$ (+0.10 − 0.00 V) will be[13]

$$i = 2FAD_A^{1/2}C_A^{*}K_{AB}k_{BA}^{1/2} \tag{4}$$

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(5) Our cell was similar to that of Heineman et al.[6] but included getter electrodes[7] above and below the working electrode and was sealed with Tefzel.[8] The cell was set up in a small drybox that was purged with nitrogen gas, and the temperature was controlled by pumping water from a water bath through the cell jacket. The reference electrode was a saturated $CdCl_2$, Cd amalgam, DMF electrode[9] whose potential was −0.693 V vs. aqueous SCE at 298 K. Potentials were controlled by a Princeton Applied Research (PAR) Model 173 potentiostat, and charge was measured with a PAR 179 digital coulometer. The charge–potential curves were generated by allowing equilibrium to be achieved at each potential and measuring the charge passed for the reduction of A or oxidation of B^{2-}. For compound **1** the getter current existing at the time of the measurement of charge created an *IR* drop in solution which caused a small hysteresis (5–10 mV) between the *E*–*f* curve for reduction steps and that for oxidation steps. This *IR* was apportioned according to the magnitude of the getter currents at a given charge, and small corrections were applied giving the curve shown in Figure 1. Values of $E_{1B}°$ and $E_{2B}°$ were obtained by cyclic voltammetry[4a,d,h] by using the instrumentation and techniques described earlier.[10] For **2**, *E*° values were measured from 293 to 333 K, and values at 373 K were obtained by extrapolation of linear *E*° vs. 1/*T* plots.

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where A is the area of the electrode in the thin-layer cell, D_A is the diffusion coefficient, and $C_A{}^*$ is the concentration of A. D_A for **2** at 373 K was estimated from the known[4a] diffusion coefficient of **1** at 294 K and the viscosity of DMF using the Stokes–Einstein relation. The value of k_{BA} at 373 K was estimated from its measured value[4d] at 294 K and the assumption that the entropy of activation was negligible. The observed initial current for reduction of **2** gave $K_{AB} = 2 \times 10^{-5}$ when calculated by eq 4.

Bis Heteroannulation. 7. Total Syntheses of (±)-Gnididione and (±)-Isognididione

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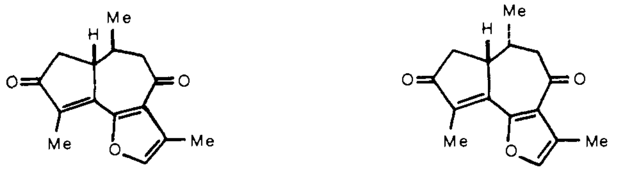
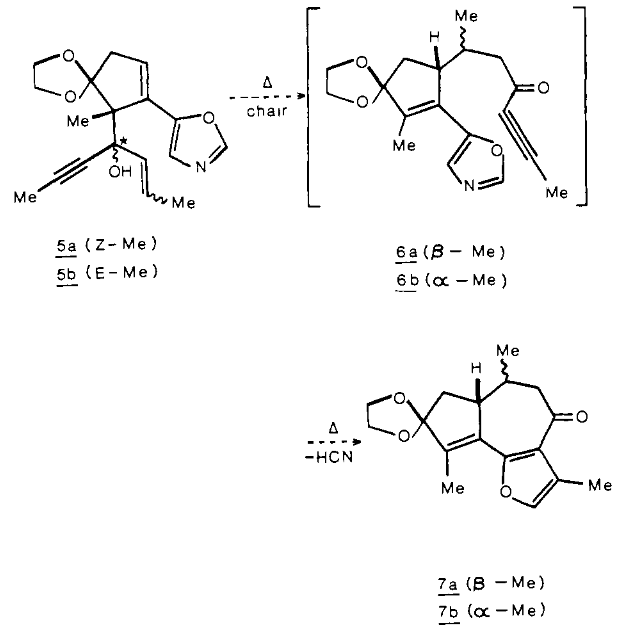
During the course of a search for plant-based tumor inhibitors Kupchan et al. isolated the furanosesquiterpene gnididione from the antileukemic fractions of *Gnidia latifolia* and proposed the structure **1** for this material on the basis of chemical and spectroscopic evidence (Figure 1).[1] This compound has a number of structural features that make it an attractive synthetic target, not the least of these being the furan ring, the first example of this functionality occurring in a guaiane sesquiterpene, and the cis relationship between H-1 and Me-10. This last substitution pattern is quite rare among members of this class[2] and has led to the suggestion that the alternative structure **2** might better fit the experimental data.[3] In addition, the guaiane skeleton itself represents a distinct synthetic challenge. These materials have attracted considerably less attention than the biogenetically related pseudoguaianes[4] and there have been only scattered reports describing the total synthesis of naturally occurring members of this class.[5] In this paper we report on an unequivocal synthesis of both **1** and **2** which firmly establishes the structure of gnididione as **1**.



Gnididione (1) Isognididione (2)

Figure 1.

Scheme I



For some time now we have been developing a general synthetic approach to the furanosesquiterpenes and this strategy appeared to be particularly well suited for the synthesis of **1** and **2** ("bis heteroannulation").[6] Thus, we envisioned that acetylenic oxazoles **6a** and **6b** should be directly convertable to the annulated derivatives **7a** and **7b**, which upon mild acid hydrolysis would provide the desired target compounds (Scheme I). As one advantage of this approach *regio*chemical control is assured by the geometrical constraints of the intramolecular Diels–Alder reaction,[6] and, furthermore, it occurred to us that *stereo*chemical control in the preparation of **6a** and **6b** might be established through the use of an oxy-Cope reaction[7] if certain criteria could be met. It was our hope, in particular, the *chemo*selectivity in the conversin of **5a,b** to **6a,b** might be effectively controlled by conformational factors relating to the relative configuration at C-8 (*), thereby overriding the usual tendency of such reactions to proceed at a faster rate with acetylenic π-bond participation (Scheme II).[8] Thus, of the four possible diastereomers of general structure **5** models clearly indicate that **8** and **9** should be strongly biased in favor of conformations **8a** and **9a**, while **10** and **11** should react preferentially through conformations **10b** and **11b**. In the event, these predictions were readily tested by experiment.

The key intermediate for our synthesis of **8–11** was the oxazole aldehyde **18**, which was readily prepared as indicated and further elaborated as follows (Scheme III).[9] Thus, **18** was first treated with *cis*-lithiopropene[12] to give an 86% yield of the allylic alcohol **19a** which was directly oxidized with Swern's reagent[13] to the corresponding enone **20a** (82%). This material, upon condensation

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