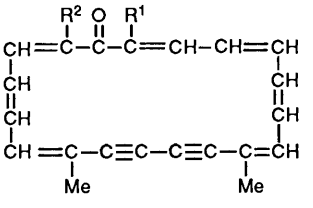
Configurational and Conformational Isomerism of 9,14-Dimethyl-, 2,9,14-Trimethyl- and 9,14,19-Trimethyl-10,11,12,13-tetradehydro[19]annulenones in Neutral and Acidic Solutions

Gaku Yamamoto,*[a] Hiroyuki Higuchi,[b] Hiroyuki Yamamoto[b] and Jūro Ojima*[b]
[a] *Department of Chemistry, Faculty of Science, The University of Tokyo, Bunkyo-ku, Tokyo 113, Japan*
[b] *Department of Chemistry, Faculty of Science, Toyama University, Gofuku, Toyama 930, Japan*

All of the title compounds (**1**–**3**) exist as single configurational isomers with 'all-*E*' geometry, when synthesized, and have been shown to be products formed under kinetic control which isomerize in trifluoroacetic acid to more stable isomers with '2-*Z*' and '4-*Z*' geometry. Most of these configurational isomers exist as a rapidly equilibrating mixture of two (or more) conformers. The results of ^{1}H NMR studies on the isomer equilibria and the isomerization rates in $CDCl_3$ and CF_3CO_2D–CD_2Cl_2 solutions including variable temperature experiments are reported. Complete isomer equilibria are not attained because some of the isomerization barriers are too high (> 27 kcal mol^{-1}).

A large number of annulenes have been synthesized and their properties related especially to tropicity have been extensively investigated.[1] Of these, several annulenes exist as a mixture of configurational and/or conformational isomers.[2] However, quantitative studies on geometries and energetics of mobile annulenes have been rather limited.

We report here configurational and conformational isomerization of the title compounds, *i.e.* 9,14-dimethyl- (**1**), 2,9,14-trimethyl- (**2**) and 9,14,19-trimethyl-cyclononadeca-2,4,6,8,14,16,18-pentaene-10,12-diynone (**3**), in neutral ($CDCl_3$) and acidic (CF_3CO_2D–CD_2Cl_2) solutions.[3]



1; $R^1 = R^2 = H$
2; $R^1 = Me$, $R^2 = H$
3; $R^1 = H$, $R^2 = Me$

We have previously reported syntheses and characterizations of these compounds.[4,5] Each of these compounds consisted of one configurational isomer, which existed in a single conformation, when synthesized, and showed no sign of isomerization during the spectroscopic experiments for the characterization, which at first resulted in us overlooking the isomerism in these compounds under neutral conditions. We have also measured ^{1}H NMR spectra of these compounds in trifluoroacetic acid (TFA) in order to study the tropic behaviour of the corresponding cationic species.[4,5] During the experiments we noticed that the ^{1}H NMR spectra of **1** and **2** changed with time owing to the formation of new species, but we could not identify these, mainly because of the use of a low-field CW NMR spectrometer. The recent availability of high-field pulse-FT NMR spectrometers prompted us to re-examine the behaviour of these compounds in TFA, which has revealed extensive isomerization of these compounds in this medium. Neutralization of the acidic solutions resulted in regeneration of **1**–**3** and they consisted of mixtures of isomers different from the ones obtained initially. We have made thorough spectroscopic characterizations of the isomers and estimations of the energy barriers to various isomerization processes in both neutral and acidic solutions, which are described here in detail.

In the present discussion the 19-membered macrocyclic ring is regarded as planar: even if the energy-minimum structures correspond to conformations where some of the atoms lie out of the average plane, interconversion among them can be assumed to be quite fast. Therefore in this article, the term 'configuration' refers to the *E*/*Z* geometry of double bonds and the term 'conformation' refers to the s-*cis*/s-*trans* geometry of single bonds flanked by two double bonds.

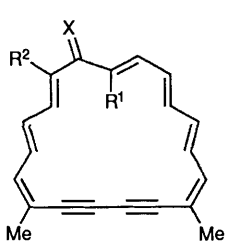
The ^{1}H NMR spectra obtained in both media were analysed as thoroughly as possible with the aid of careful homonuclear double resonance experiments. The geometries in neutral solutions were determined on the basis of the magnitudes of the vicinal coupling constants: 14–16 Hz for an *E* double bond, 9–12 Hz for a *Z* double bond, 10–12 Hz for an s-*trans* single bond between two double bonds and 5–7 Hz for an s-*cis* single bond.[6] In acidic solutions these criteria were occasionally violated because of the decrease of the bond alternation as shown later in this paper.

Results

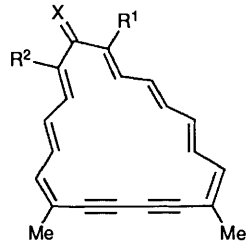
Isomerism in Compound **1**.—When synthesized according to the reported procedure[4] the ^{1}H NMR spectrum of compound **1** in $CDCl_3$ showed that it existed as a single configurational isomer in which all the CH=CH bonds are *E* (hereafter referred to as 'all-*E*'). From the magnitudes of the vicinal coupling constants, the geometry of **4A** was assigned [Fig. 1(*a*), Table 1 and Scheme 1]. No essential change in the ^{1}H NMR spectrum in the range of +60 to −60 °C suggested the conformational homogeneity, excluding the contribution of other conformers such as **4B**.[5] When the $CDCl_3$ solution of **4** was left standing at ambient temperature for a month, formation of only trace amounts of other configurational isomers were detected (see below) indicating that the energy barrier to isomerization of **4** is far higher than 27 kcal mol^{-1}.† Reflecting the diatropic nature of this compound, the alkenic protons located inside the macrocycle appear at a high field of δ 5.6–6.2 and the outside protons appear at a low field of δ 6.4–7.0.

Dissolution of **1**, which was composed solely of the 'all-*E*' isomer **4**, in CF_3CO_2D–CD_2Cl_2 (4:1) gave a dark green solution.[5] The ^{1}H NMR of the solution at 26 °C revealed that the initially formed cationic species **5** rapidly isomerized to a second species **7**, finally affording an equilibrium mixture of the

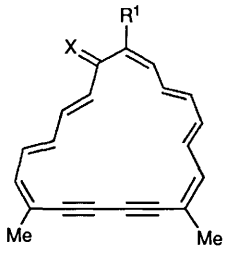
† 1 cal = 4.18 J.



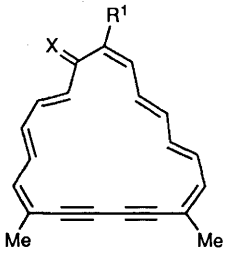
4A; $R^1 = R^2 = H$, X = O
5A; $R^1 = R^2 = H$, X = O$^+$D
10A; R^1 = Me, R^2 = H, X = O
11A; R^1 = Me, R^2 = H, X = O$^+$D
16A; R^1 = H, R^2 = Me, X = O
17A; R^1 = H, R^2 = Me, X = O$^+$D



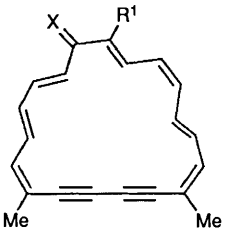
4B; $R^1 = R^2 = H$, X = O
5B; $R^1 = R^2 = H$, X = O$^+$D
10B; R^1 = Me, R^2 = H, X = O
11B; R^1 = Me, R^2 = H, X = O$^+$D
16B; R^1 = H, R^2 = Me, X = O
17B; R^1 = H, R^2 = Me, X = O$^+$D



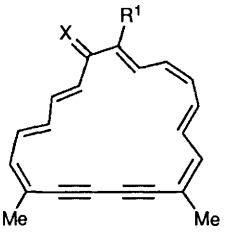
6A; R^1 = H, X = O
7A; R^1 = H, X = O$^+$D
12A; R^1 = Me, X = O
13A; R^1 = Me, X = O$^+$D



6B; R^1 = H, X = O
7B; R^1 = H, X = O$^+$D
12B; R^1 = Me, X = O
13B; R^1 = Me, X = O$^+$D



8A; R^1 = H, X = O
9A; R^1 = H, X = O$^+$D
14A; R^1 = Me, X = O
15A; R^1 = Me, X = O$^+$D



8B; R^1 = H, X = O
9B; R^1 = H, X = O$^+$D
14B; R^1 = Me, X = O
15B; R^1 = Me, X = O$^+$D

two with the equilibrium constant K = [**7**]/[**5**] of 8.0 at 26 °C. The time dependence of the relative intensities of the methyl signals of the two isomers gave the rate constant for the **5** ⟶ **7** transformation at 26 °C of 1.4×10^{-3} s^{-1} based on the reversible first-order kinetics, which corresponded to a half-life of *ca.* 7 min and a free energy of activation $\Delta G^{\ddagger}$ of 21.4 kcal mol^{-1} at 26 °C.

In the following discussion, molecules **1**–**3** are assumed to be completely deuteriated under the present conditions. Although the survival of a small amount of non-deuteriated species might be possible, the equilibrium between deuteriated and non-deuteriated species would be very fast and would have a negligible effect.

The initially formed species **5** exhibited two sharp methyl singlets at δ 3.01 and 3.12 at 26 °C [Fig. 2(*a*)]. The alkenic protons gave poorly resolved four-proton multiplets at δ 1.0–1.5, well resolved six-proton multiplets at δ 8.5–8.8 together with very broad signals at δ 4.35 and 5.95 (one proton for each) [Table 1 and Fig. 2(*a*)]. While the signals of **5** rapidly disappeared at 26 °C because of fast isomerization, dissolution

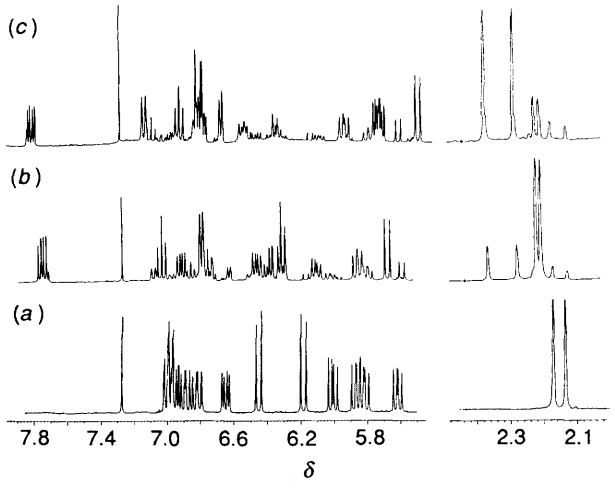


Fig. 1 ^{1}H NMR spectra of compound **1** in $CDCl_3$ at 26 °C: (*a*) isomer **4** obtained upon synthesis; (*b*) mixture of **4**, **6** and **8** obtained by neutralization of the TFA solution (isomer ratio **4**:**6**:**8** = 8:69:23, see the text); (*c*) the same sample as (*b*), 20 days later (isomer ratio **4**:**6**:**8** = 8:21:71, see text). The intensities of the methyl signals are reduced. The peak at δ 7.28 is due to $CHCl_3$.

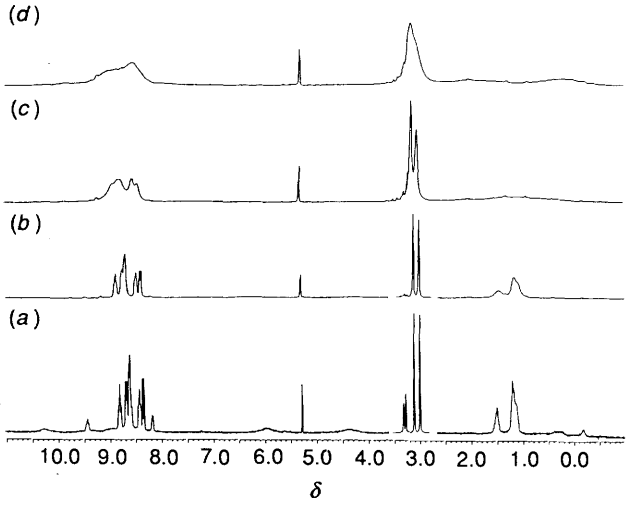


Fig. 2 ^{1}H NMR spectra of compound **1** in CF_3CO_2D–CD_2Cl_2 (4:1): (*a*) 26 °C, dissolved at ambient temperature and immediately measured —mainly isomer **5** but small signals due to **7** are seen; (*b*) 4 °C; (*c*) −20 °C; (*d*) −33 °C. For (*b*)–(*d*), **1** was dissolved below 0 °C. In (*a*) and (*b*) the intensities of the methyl signals are reduced. The sharp signal at δ 5.30 is due to $CHDCl_2$ and is used as the reference peak.

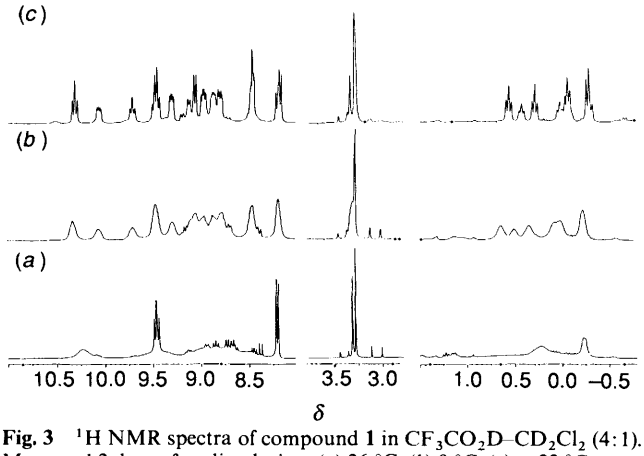


Fig. 3 ^{1}H NMR spectra of compound **1** in CF_3CO_2D–CD_2Cl_2 (4:1). Measured 2 days after dissolution: (*a*) 26 °C; (*b*) 0 °C; (*c*) −22 °C.

of **1** at a low temperature below 0 °C and NMR measurements at *ca.* 0 °C gave spectra of almost pure **5** [Fig. 2(*b*)].

Table 1 ^{1}H NMR spectral data of the isomers of **1** at 500 MHz[a]

Proton	Isomer						
	4A[b]	**6**[b]	**8**[b]	**5**[c]	**7A**[d]	**7B**[d]	**9A**[d]
2-H	6.175 d (15.8)	6.317 d (12.4)	6.767 d (15.7)	4.35 br*[1]	8.163 d (11.0)	8.187 d (11.5)	8.933 d (14.0)
3-H	6.949 dd (15.8, 6.4)	7.053 t (12.4)	5.730 dd (15.7, 11.8)	5.95 br*[1]	9.446 dd (13.0, 11.0)	9.470 dd (13.5, 11.5)	0.186 dd (14.0, 12.6)
4-H	6.643 dd (15.2, 6.4)	5.800 dd (14.8, 12.4)	6.771 t (11.8)	8.433 dd (14.4, 9.5)	0.280 dd (14.0, 13.0)	0.016 t (13.6)	8.962 dd (12.6, 10.2)
5-H	5.606 dd (15.2, 11.1)	6.931 dd (14.8, 8.8)	6.881 t (11.6)	*e*	9.292 dd (14.0, 7.2)	9.706 dd (13.9, 10.4)	9.499 dd (12.4, 10.2)
6-H	6.813 dd (14.7, 11.1)	6.442 dd (15.3, 8.8)	5.949 dd (15.4, 11.6)	8.64 t*[2] (12)	8.788 dd (14.6, 7.2)	0.418 dd (14.8, 10.4)	−0.035 dd (14.8, 12.4)
7-H	5.807 dd (14.7, 11.6)	6.075 dd (15.3, 9.5)	6.505 dd (15.4, 8.5)	*e*	−0.066 dd (14.6, 11.8)	8.868 dd (14.6, 7.2)	9.037 dd (14.8, 8.6)
8-H	7.000 d (11.6)	6.798 d (9.5)	6.638 d (8.5)	8.710 d*[3] (12.0)	9.050 d (11.8)	8.464 d (7.5)	8.496 d (8.6)
15-H	6.970 d (11.8)	6.798 d (9.5)	7.099 d (11.2)	8.650 d*[3] (11.7)	8.449 d (7.8)	9.112 d (11.1)	9.195 d (12.0)
16-H	5.856 dd (14.7, 11.8)	6.292 dd (15.5, 9.5)	5.751 dd (15.6, 11.2)	*e*	8.960 dd (14.8, 7.8)	−0.08[f]	−0.318 dd (14.0, 12.0)
17-H	6.883 dd (14.7, 11.1)	6.362 dd (15.5, 8.6)	6.748 dd (15.6, 6.6)	8.831 dd*[2] (13.2, 12.1)	0.553 dd (14.8, 12.0)	8.868 dd (14.6, 7.2)	8.904 dd (14.0, 7.0)
18-H	5.996 dd (16.2, 11.1)	7.775 dd (15.1, 8.6)	7.768 dd (15.4, 6.6)	*e*	10.308 dd (13.8, 12.0)	10.057 dd (14.6, 7.2)	10.088 dd (14.7, 7.0)
19-H	6.444 d (16.2)	5.617 d (15.1)	5.509 d (15.4)	8.352 d (14.7)	−0.280 d (13.8)	−0.311 d (14.6)	−0.671 d (14.7)
9-Me	2.127 s	2.200 s	2.378 s	3.005 s	3.298 s	3.298 s	3.475 s
14-Me	2.173 s	2.216 s	2.290 s	3.116 s	3.307 s	3.358 s	3.383 s

[a] Chemical shifts are in ppm; tetramethylsilane at δ 0.00 in $CDCl_3$ and $CHDCl_2$ at δ 5.30 in CF_3CO_2D–CD_2Cl_2 were used as the references. In parentheses are coupling constants in Hz, reliable to ±0.3 Hz. [b] Measured in $CDCl_3$ at 26 °C. [c] Measured in CF_3CO_2D–CD_2Cl_2 (4:1) at 26 °C. Assignments indicated by *1, *2 and *3 are mutually interchangeable. [d] Measured in CF_3CO_2D–CD_2Cl_2 (4:1) at −22 °C. [e] Appeared as a broad signal in the δ 1.0–1.5 region. [f] Coupling constants could not be read owing to signal overlap.

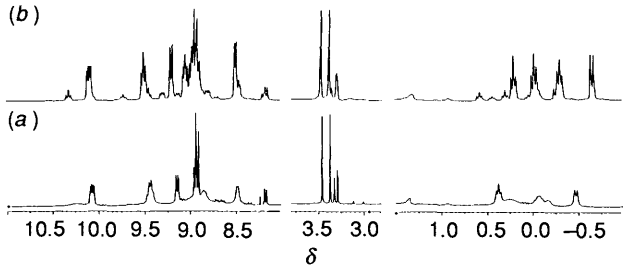


Fig. 4 ^{1}H NMR spectra in CF_3CO_2D–CD_2Cl_2 (4:1) of **1** containing **9** as the predominant isomer: (*a*) 26 °C; (*b*) −22 °C

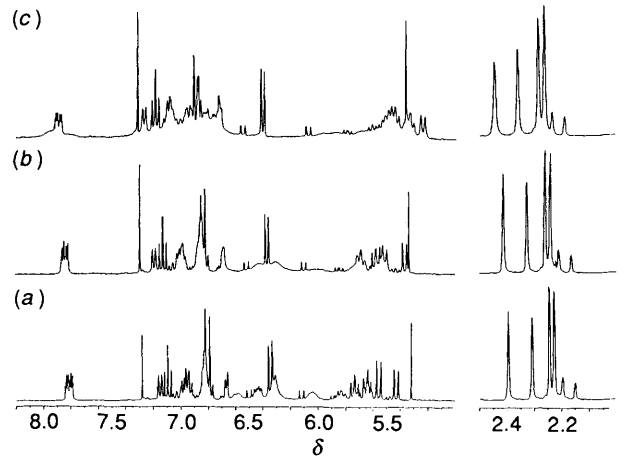


Fig. 5 ^{1}H NMR spectra of **1** in $CDCl_3$ composed of **4**, **6** and **8** in a ratio of *ca.* 1:4:4: (*a*) −5 °C; (*b*) −24 °C; (*c*) −55 °C. Peaks at δ 5.32 and 7.28 are due to CH_2Cl_2 and $CHCl_3$, respectively.

Lowering of the temperature caused all the signals to broaden and at −33 °C, the lowest temperature at which the NMR spectrum could be measured without freezing of the sample, only broad humps were observed at δ −0.5–4.0 and 8.0–9.5 [Fig. 2(*d*)]. This indicates that interconversion between two (or more) conformers takes place rapidly even at low temperatures. The free energy of activation for this process was estimated to be *ca.* 11 kcal mol^{-1}.

The protonated species show higher diatropicity than the corresponding unprotonated species because of the larger contribution from the dipolar canonical structure where the positive charge is delocalized in the macrocycle forming an 18 π-electron system, and thus the alkenic protons located outside the ring resonate at a very low field, δ >8 and those located inside the ring resonate at a high field, δ <2 when no conformational changes occur. If an alkenic proton changes its site from inside to outside the ring and *vice versa* by conformational change, the proton resonates at somewhere between the above extremes depending on the relative abundance of the conformers.

Appearance of the broad signals due to two protons in the intermediate region of δ 4–6.5 at 26 °C suggests that only one pair of protons exchange their sites between the inside and outside of the macrocyclic ring during the conformational change. Another spectral feature to be noted is that three rather sharp doublets are observed in the low field region (δ 8.3–8.8): two of them with $J \approx 12$ Hz are unambiguously assigned to 8-H and 15-H and the remaining one at δ 8.35 with J = 14.7 Hz is tentatively assigned to 19-H. Therefore, if the 'all-*E*' geometry in the precursor is assumed to be retained, the most reasonable candidates for the major conformers would be **5A** and **5B** which interconvert by rotation of the C(2)=C(3) moiety around the adjacent single bonds. Then the broad signals at δ 4.35 and 5.95 are assigned to 2-H and 3-H. If it is assumed that both 2-H and 3-H resonate at δ 1.0–1.5 when they are inside the ring and at δ 8.5–8.8 when outside, the population ratio of

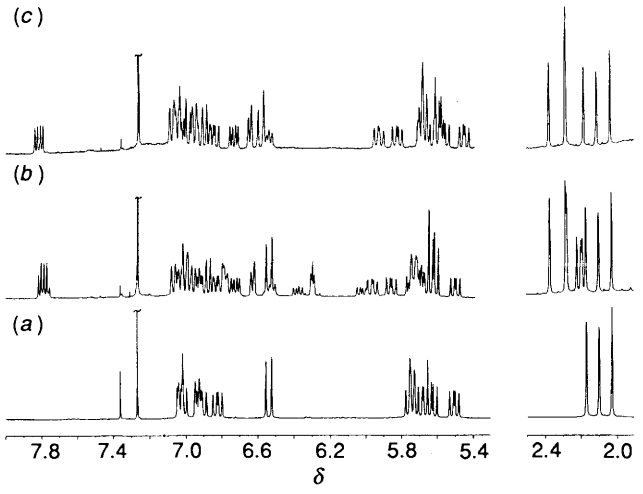


Fig. 6 ^{1}H NMR spectra of compound **2** in $CDCl_3$ at 26 °C: (*a*) isomer **10** obtained upon synthesis; (*b*) *ca.* 2:1:2 mixture of isomers **10**, **12** and **14**; (*c*) *ca.* 1:1 mixture of **10** and **14** [measured one day after (*b*)]. Signals at δ 7.2–7.4 are due to impurities.

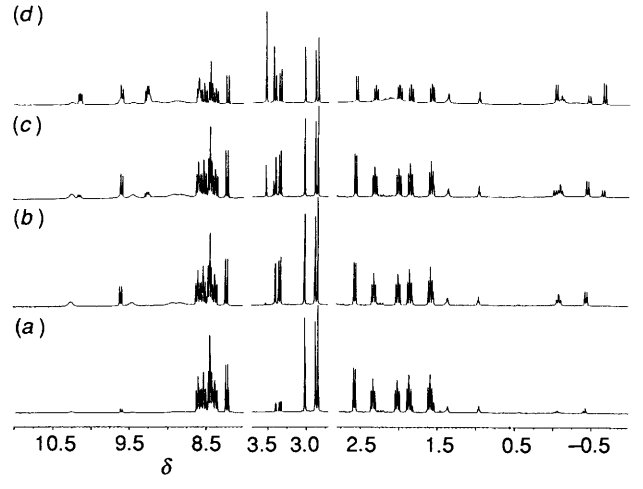


Fig. 7 ^{1}H NMR spectra of **2** in CF_3CO_2D–CD_2Cl_2 (3:1) at 26 °C: (*a*) immediately after dissolution; (*b*) after 1.5 h; (*c*) after 24 h; (*d*) after 2 weeks—Signals at δ 0.95, 1.35 and 2.25 are due to impurities. The broad peak around δ 2.0 in (*d*) is due to decomposition/polymerization products.

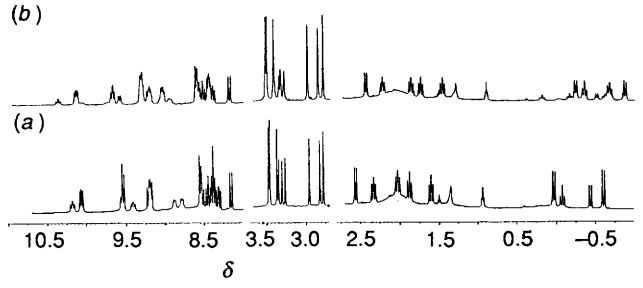


Fig. 8 ^{1}H NMR spectra of **2** in CF_3CO_2D–CD_2Cl_2 (3:1) composed of **11**, **13** and **15** in a ratio of *ca.* 2:1:2: (*a*) 47 °C; (*b*) −35 °C—Signals at δ 0.95 and 1.35 are due to impurities. The broad peak around δ 2.0 is due to decomposition/polymerization products.

the conformers is estimated to be *ca.* 3:2, although which conformer of the two is more populated cannot be determined.

The second species **7** gave broadened signals at 26 °C [Fig. 3(*a*)]: two slightly broad methyl singlets at δ 3.28 and 3.32, a series of broad humps at δ −0.3–0.6 by four protons and at δ 8.3–10.5 by six protons together with a doublet at δ 8.21 and an apparent triplet at δ 9.46. The broad signals sharpened upon lowering the temperature and two sets of signals due to two conformers in a ratio of 3:2 were observed at −22 °C [Fig. 3(*c*)]. Detailed analysis of the ^{1}H NMR spectra at −22 °C (Table 1) established the geometries of the two conformers: *i.e.* **7A** for the major conformer and **7B** for the minor one. The C(2)=C(3) double bond has *Z* configuration in either conformer indicating that **7** is the '2-*Z*' isomer. The interconversion between **7A** and **7B** may occur with simultaneous or consecutive rotation of the C(6)=C(7) and C(16)=C(17) moieties around their adjacent single bonds and the free energy of activation is estimated to be *ca.* 13.7 kcal mol^{-1} by the conventional coalescence method.

The presence of a small amount (*ca.* 4%) of a third species was detected as revealed by small peaks at δ 3.35 and 3.45 [*e.g.* Fig. 3(*a*)]. The geometrical assignment could not be made at this point but later it was disclosed to be isomer **9** (see below).

No further isomerization to form other configurational isomers was detected when the acidic solution was left standing at ambient temperature for a week.

Neutralization of the acidic solution of **1** with aqueous sodium hydrogen carbonate resulted in regeneration of **1**, whose ^{1}H NMR spectra in $CDCl_3$ revealed that the sample was a mixture of three configurational isomers in a ratio of 69:23:8 [Fig. 1(*b*)]. The isomer ratio gradually changed because of isomerization ($\Delta G^{\ddagger} \approx 25$ kcal mol^{-1} at ambient temperature) and the ratio was 21:71:8 after 20 days at ambient temperature, when signals due to a small amount of unidentified decomposition and/or polymerization products were also detected [Fig. 1(*c*)].

The least populated isomer was easily assigned to **4**, the initial one. The structures of the other two isomers **6** and **8** were determined by detailed analysis of the ^{1}H NMR spectra of the mixture (Table 1). The chemical shifts of the isomers moved as the isomer ratio changed as revealed by Fig. 1(*b*) and 1(*c*). The values in Table 1 correspond to those obtained when the isomer ratio of **6**:**8** was *ca.* 3:2. In isomer **6**, the most abundant isomer at the outset, the C(2)=C(3) bond was shown to be in the *Z* configuration while in the other isomer **8** the C(4)=C(5) bond was *Z*. In both isomers fast conformational change occurred at ambient temperature and conformer-averaged signals were observed in the ^{1}H NMR spectra. As the temperature was lowered the signals broadened and then re-sharpened but the slow-exchange limit was not reached even at the lowest temperature of −55 °C (Fig. 5), $\Delta G^{\ddagger}$ was roughly estimated to be about 10 kcal mol^{-1} for **6** and the similar value would be assigned also to **8**.

From the magnitudes of the coupling constants across the single bonds observed at 26 °C which are the weighted averages of those in the respective conformers, the position of the conformer equilibrium can be roughly estimated. Isomer **6** is inferred to be composed of comparable amounts of conformers **6A** and **6B**, because all of $J_{5,6}$, $J_{7,8}$, $J_{15,16}$ and $J_{17,18}$ are in the range of 8.5–9.5 Hz, although contribution of two other conformers which would be formed by flipping of one of the C(6)=C(7) and C(16)=C(17) bonds from **6A** or **6B** is not excluded. On the other hand isomer **8** is inferred to comprise mainly **8A** with minor contributions from other conformers including probably **8B**, because $J_{5,6}$ and $J_{15,16}$ are near the s-*trans* range and $J_{17,18}$ is near the s-*cis* range.

As mentioned before, when **1** composed solely of isomer **4** was left standing as a $CDCl_3$ solution at ambient temperature for a month, formation of only trace amounts of **6** and **8** was detected. Addition of a catalytic amount of iodine to the solution caused rapid isomerization to afford a mixture of **4**, **6** and **8** in a ratio of 6:24:70 together with considerable amounts of decomposition and/or polymerization products within several hours. The similarity of this isomer ratio with the above-mentioned one (8:21:71) suggests that the isomer ratio at equilibrium is close to these values.

The absence of the '4-*Z*' isomer **9** in the acidic solution

seemed puzzling, judging from the fact that under neutral conditions the '4-*Z*' isomer **8** is the most abundant isomer. In order to investigate this point, the sample composed of a mixture of **4**, **6** and **8** (8:21:71) obtained from the above-mentioned process was dissolved again in CF_3CO_2D–CD_2Cl_2 (4:1). Three cationic species in almost the same ratio (5:24:71) as in the precursor mixture were observed by ^1H NMR spectroscopy [Fig. 4(*a*)]. Thus isomers **4** and **6** formed **5** and **7**, respectively, while **8** gave a new species, which was shown to be **9** by analysis of the ^1H NMR spectrum of the isomer mixture.

Table 2 ^1H NMR spectral data of the isomers of **2** in $CDCl_3$[a]

Proton	Isomer **10B**	**12**	**14**
3-H	5.734 d (11.2)	6.78 d[b]	5.731 d (11.4)
4-H	7.017 dd (15.0, 11.2)	5.75[b]	6.991 t (11.4)
5-H	5.500 dd (15.0, 10.9)	6.80[b]	6.862 t (11.3)
6-H	6.818 dd (15.2, 10.9)	6.378 dd (15.3, 8.4)	5.964 dd (15.3, 11.6)
7-H	5.744 dd (15.2, 11.0)	6.024 dd (15.5, 9.0)	6.527 dd (15.0, 8.3)
8-H	7.023 d (11.0)	6.78 d[b]	6.626 d (8.5)
15-H	6.937 d (11.5)	6.78 d[b]	7.065 d (11.0)
16-H	5.674 dd (14.8, 11.5)	6.30[b]	5.859 dd (15.6, 11.0)
17-H	6.906 dd (14.8, 11.2)	6.30[b]	6.722 dd (15.6, 7.0)
18-H	5.622 dd (16.0, 11.2)	7.776 dd (15.1, 8.1)	7.790 dd (15.2, 7.0)
19-H	6.533 d (16.0)	5.611 d (15.6)	5.634 d (15.2)
2-Me	2.024 s	2.185 s	2.276 s
9-Me	2.094 s	2.193 s	2.364 s
14-Me	2.164 s	2.214 s	2.271 s

[a] Obtained at 26 °C; chemical shifts are given in ppm with tetramethylsilane as the reference. [b] Coupling constants could not be read owing to signal overlap.

Isomer **9** gave broad signals at 26 °C, which sharpened upon lowering the temperature and were analysed to represent a single conformer, *i.e.* **9A** at −22 °C [Fig. 4(*b*), Table 1 and Scheme 1]. The minor conformer(s), *e.g.* **9B**, were not detected at all, indicating that their populations were very low (< 5%). Judging from the temperature range of the signal broadening, the conformational change in **9** has a higher barrier than that in **8**, *i.e.*, higher than *ca.* 10 kcal mol^{-1}.

The ratio of configurational isomers, **5**, **7** and **9**, changed only slightly when the sample was allowed to stand for more than 10 days at ambient temperature (3:28:69). These results together with the aforementioned ones indicate that the energy barrier to isomerization of **7** (or **5**) to **9** is far higher than 27 kcal mol^{-1}, although it is uncertain whether the isomer equilibrium was attained in this medium.

Isomerism in Compound **2**.—Compound **2** synthesized as reported before[5] was shown to exist as a single isomer. The ^1H NMR spectrum indicated the 'all-*E*' configuration with the conformation shown by **10B** [Table 2 and Fig. 6(*a*)].[5] Conformational homogeneity was confirmed by no essential change in the ^1H NMR spectrum in the temperature range of +60 to −60 °C. No sign of configurational isomerization was observed when a solution of **2** in $CDCl_3$ was allowed to stand for 2 weeks at ambient temperature.

The ^1H NMR study at 26 °C of the dark green solution obtained upon dissolution of **2** in CF_3CO_2D–CD_2Cl_2 (3:1) showed that the initially formed species **11** rapidly isomerized to the second species **13**, which then slowly isomerized to the third species **15**, finally affording an equilibrium mixture of the three

Table 3 ^1H NMR spectral data of the isomers of **2** in CF_3CO_2D–CD_2Cl_2 (3:1)[a]

Proton	Isomer **11B** (*T*/°C = 47)	(−35)	**13** (47)	**13A** (−35)	**13B** (−35)	**15** (47)	**15A** (−35)
3-H	2.570 d (12.2)	2.442 d (12)	9.555 d (13.0)	9.604 d (13)	*d*	0.033 d (13.2)	−0.237 d (13)
4-H	8.464 dd (14.0, 12.2)	8.533 t (13)	−0.075 t (13.4)	−0.160 t (13)	*d*	9.223 dd (13, 11)	9.33[c]
5-H	2.341 dd (14.0, 11.5)	2.232 t (13)	9.429 dd (13.4, 9.8)	9.32[c]	*d*	9.568 t (11)	9.696 t (11.5)
6-H	8.328 dd (14.5, 11.5)	8.406 t (13)	*e*	8.953 dd −(14.7)	*d*	*e*	−0.349 t (13.5)
7-H	2.034 dd (14.5, 11.4)	1.867 t (13)	*e*	0.615 t (13.5)	*d*	*e*	9.228 dd (15, 9)
8-H	8.386 d (11.4)	8.451 d (11)	8.802 br d[b] (7.9)	*d*	*d*	8.561 d (10)	8.618 d (9)
15-H	8.409 d (11.9)	8.466 d (11)	8.897 br d[b] (8.8)	*d*	*d*	9.197 d (11.6)	9.328 d (12)
16-H	1.881 dd (13.9, 11.9)	1.744 t (13)	*e*	9.07[c]	*d*	*e*	−0.672 t (13.5)
17-H	8.546 dd (13.9, 12.0)	8.603 t (13)	*e*	0.190 t (13)	*d*	*e*	9.054 dd (15, 7)
18-H	1.604 dd (14.2, 12.0)	1.466 t (13)	10.222 br dd (14.3, 9.8)	10.392 t (13)	10.09 br	10.086 dd (14.9, 7.7)	10.164 dd (15, 7)
19-H	8.166 d (14.2)	8.192 d (14)	−0.434 d (14.3)	−0.501 d (14)	*d*	−0.600 d (14.9)	−0.873 d (15)
2-Me	2.792 s	2.796 s	3.276 s	3.297 s	3.297 s	3.471 s	3.517 s
9-Me	2.840 s	2.859 s	3.314 s	3.344 s	3.344 s	3.484 s	3.534 s
14-Me	2.979 s	2.998 s	3.358 s	3.364 s	3.425 s	3.384 s	3.430 s

[a] Chemical shifts are given in ppm. The $CHDCl_2$ signal at δ 5.30 is used as the reference. In parentheses are coupling constants in Hz, reliable to ±0.3 Hz at 47 °C and ±1.0 Hz at −35 °C because of general signal broadening due to viscosity. [b] Mutually interchangeable. [c] Coupling constants could not be read owing to signal overlap. [d] Not identified owing to signal overlap. [e] Too broad to be observed.

Table 4 ^{1}H NMR spectral data of **3**[a]

	Isomer	
Proton	**16A**[b]	**17**[c]
2-H	6.127 d (15.6)	2.95 br*[1]
3-H	7.184 dd (15.6, 5.5)	7.15 br*[1]
4-H	6.602 dd (15.2, 5.5)	8.533 dd (14.6, 8.6)
5-H	5.517 dd (15.2, 11.0)	0.93 br t (*ca.* 13)
6-H	6.839 dd (14.7, 11.0)	8.834 t (12.1)
7-H	5.707 dd (14.7, 11.6)	0.56 br
8-H	7.012 d (11.6)	8.822 d*[2] (12.1)
15-H	7.022 d (11.6)	8.915 d*[2] (12.1)
16-H	5.730 dd (14.5, 11.6)	0.56 br
17-H	7.061 dd (14.5, 11.3)	9.166 t (12.5)
18-H	5.846 d (11.3)	0.622 br d (12.5)
9-Me	2.137 s	3.083 s
14-Me	2.180 s	3.201 s
19-Me	2.118 s	3.186 s

[a] See footnote *a* in Table 1. [b] Measured in $CDCl_3$ at 26 °C. [c] Measured in CF_3CO_2D–CD_2Cl_2 (3:1) at 26 °C. Signals indicated by *1 and *2 are mutually interchangeable.

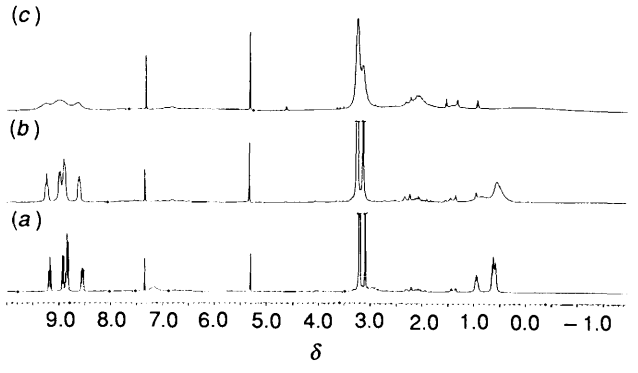


Fig. 9 ^{1}H NMR spectra of **3** in CF_3CO_2D–CD_2Cl_2 (3:1): (*a*) 26 °C—small signals at δ 1.3–2.5 are due to impurities; (*b*) 0 °C; (*c*) −22 °C.

(Fig. 7). After two weeks at ambient temperature, the isomer ratio **11**:**13**:**15** was 38:22:40 and no further change was observed, while gradual decomposition and/or polymerization of the sample took place as shown by the gradual increase of the broad hump spreading over the δ 1.8–2.3 region.

The fast isomerization of **11** to **13** took place with the rate constant of *ca.* 1.3×10^{-4} s^{-1} (half-life ≈140 min and $\Delta G^{\ddagger}$ ≈22.3 kcal mol^{-1}) at 26 °C, while the formation of **15** had the rate constant ≈1.6×10^{-6} s^{-1} at 20–22 °C ($\Delta G^{\ddagger}$ ≈25.0 kcal mol^{-1}).

The initial species **11** was shown to retain the geometry of the precursor **10**, thus existing as conformer **11B** [Table 3, Fig. 7(*a*) and Scheme 2]. The ^{1}H NMR spectrum showed no fundamental change in the temperature range of +47 to −35 °C confirming the conformational homogeneity, although the signals of the inner alkenic protons moved upfield and those of the outer ones downfield upon lowering the temperature (*ca.* 0.1 ppm/70 °C).

The second species **13** was shown to be a mixture of two conformers. At 47 °C the conformational change was fast and averaged, sharp signals were observed except for 6-H, 7-H, 16-H and 17-H, whose signals were still buried under the baseline, indicating that these four protons exchange their sites between the inside and the outside of the ring [Fig. 8(*a*)]. The resonance of 3-H at the low field of δ 9.56 indicated that this proton is located outside of the ring and thus the C(2)=C(3) bond is in the *Z* configuration. At −35 °C, the conformational change became considerably slower, though not completely frozen. The presence of two conformers in a ratio of *ca.* 2:1 was detected [Fig. 8(*b*)]. For the major conformer the signals were unambiguously analysed and the geometry of **13A** was assigned (Table 3). The signals due to the minor conformer were still broad and no definite assignment was made for the geometry but the structure **13B** could reasonably be deduced based on the spectral features observed at 47 °C. The $\Delta G^{\ddagger}$ value for the **13B** ⟶ **13A** conversion was estimated as 13.2 kcal mol^{-1} at 7 °C from the coalescence of the 18-H signals.

The third species **15** was also a rapidly equilibrating mixture of conformers at 47 °C and rather sharp signals were observed except for 6-H, 7-H, 16-H and 17-H, whose signals were too broad to be detected [Fig. 8(*a*)]. The *Z* configuration of the C(4)=C(5) bond was easily deduced (Table 3). When the temperature was lowered, the signals broadened and then re-sharpened and at −35 °C the signals of the major conformer were definitely identified and the geometry of **15A** was elucidated for the conformer (Table 3). The signals ascribed to the minor conformer(s) were not detected at all because of the very low population (<5%). The spectral feature at 47 °C reasonably suggested the geometry of **15B** for the minor conformer if only one minor conformer contributed.

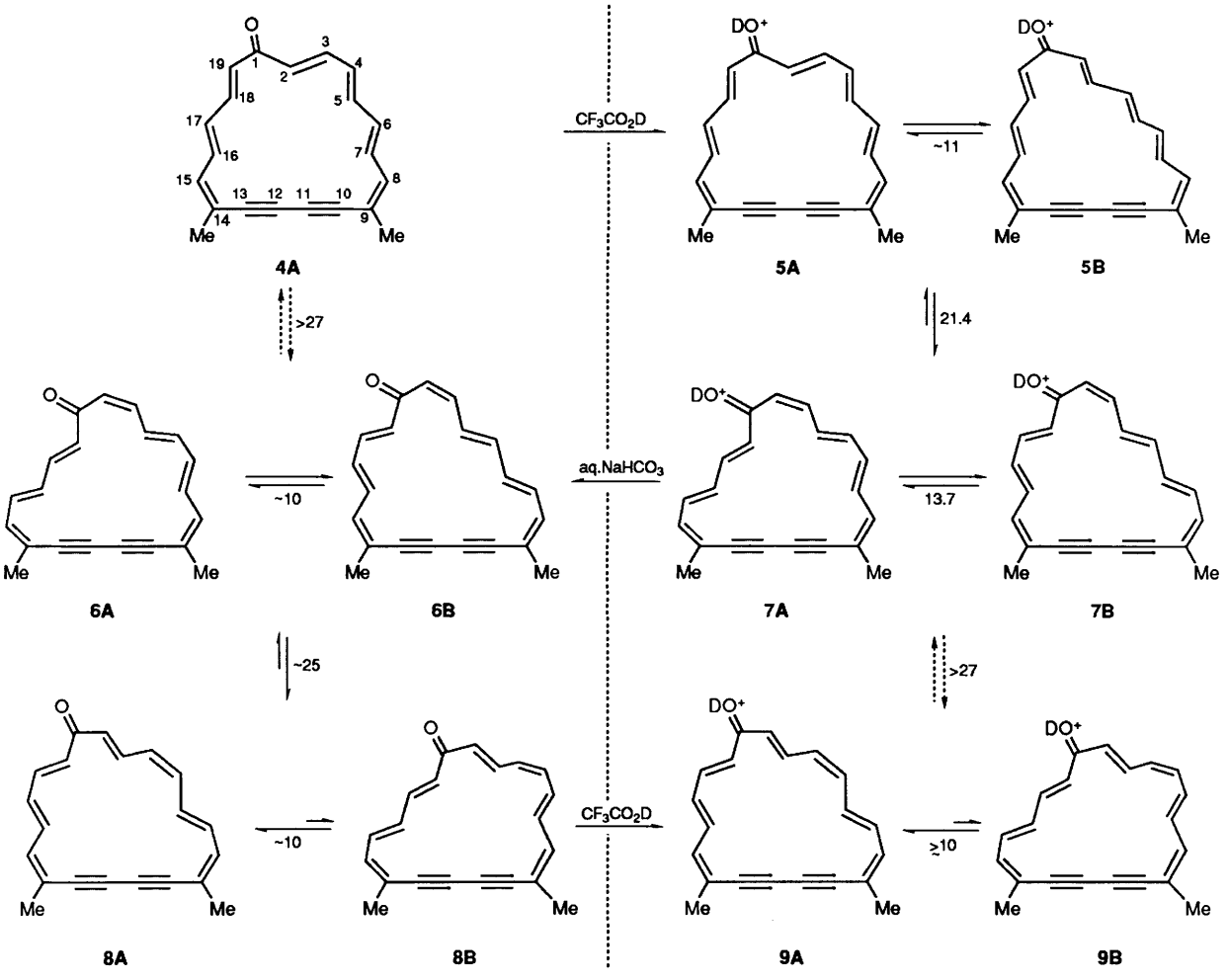
Quenching of the above-mentioned TFA solution of **2** with aqueous sodium hydrogen carbonate regenerated **2**. The immediate ^{1}H NMR measurement of the recovered **2** in $CDCl_3$ revealed that the sample consisted of three configurational isomers in a ratio of *ca.* 2:2:1 [Fig. 6(*b*)]. The population of the least populated isomer decreased at a rate of *ca.* 1×10^{-4} s^{-1} at 26 °C and a 1:1 mixture of the other two isomers resulted one day later [Fig. 6(*c*)]. Disappearance of the isomer might be due to selective decomposition and/or polymerization because the complementary increase of the population of the other isomers was not detected. The reason for the particular instability of this isomer remains uncertain.

One of the major isomers was the original 'all-*E*' isomer **10**, while the other major isomer was shown to be the '4-*Z*' isomer **14** (Table 2). Although the ^{1}H NMR signals ascribable to **14** at 26 °C were fully analysed in terms of conformer **14A**, they broadened and re-sharpened upon lowering the temperature indicating that facile equilibration with a small amount of another conformer, presumably **14B**, was occurring at 26 °C. The signals due to the minor conformer(s) were not detected at −55 °C.

As for the least-populated isomer, the geometrical assignment was difficult because of the overlap of the signals with those of the major isomers, but the appearance of the signal assignable to 3-H at the low field of δ 6.78 of the outer proton region suggested that **12** with the '2-*Z*' configuration could be assigned to this isomer, which might be reasonable because the isomer was thought to derive from **13**.

Isomerism in Compound **3**.—Compound **3** synthesized as reported[5] existed as a single isomer. The ^{1}H NMR spectrum indicated the 'all-*E*' geometry with the conformation shown by **16A** (Table 4).[5] No sign of isomerization was observed when a solution of **3** in $CDCl_3$ was left standing for 2 weeks at ambient temperature.

Dissolution of **3** in CF_3CO_2D–CD_2Cl_2 (3:1) gave a dark green solution. The ^{1}H NMR spectrum of the solution at 26 °C (Table 4) indicated the presence of a single configurational



Scheme 1

isomer **17** which was undergoing a rapid conformational change [Fig. 9(*a*)]. The spectral feature was similar to that observed for **5** described before. Three rather sharp singlets were observed for the methyl protons. As for the alkenic protons, very broad signals were observed at δ 2.95 and 7.15, one proton for each, together with the well-resolved five-proton signals at δ 8.5–9.3 and the somewhat broadened four-proton signals at δ 0.5–1.1 (Fig. 9 and Table 4). Upon lowering the temperature, all the signals further broadened and at -22 °C only an extremely broad spectrum was observed. The spectral features together with the analogy with **5** suggested that conformers **17A** and **17B** were contributing and the equilibrium might be slightly more inclined to one side (*ca.* 3:1) than in the case of **5** because the chemical shift difference between the 2-H and 3-H signals were larger in **17** than in **5**.

Compound **3** in the acidic solution was unstable and after one day at ambient temperature considerable decomposition/polymerization had occurred and broad signals appeared in the δ 1.5–3.5 region. Although new small signals probably assignable to a configurational isomer of **17** were observed in the methyl proton region at δ 3.10, 3.20 and 3.21, the structural assignments could not be made because the signals of the alkenic protons were broad owing to fast conformational interchange and thus further study was abandoned.

Discussion

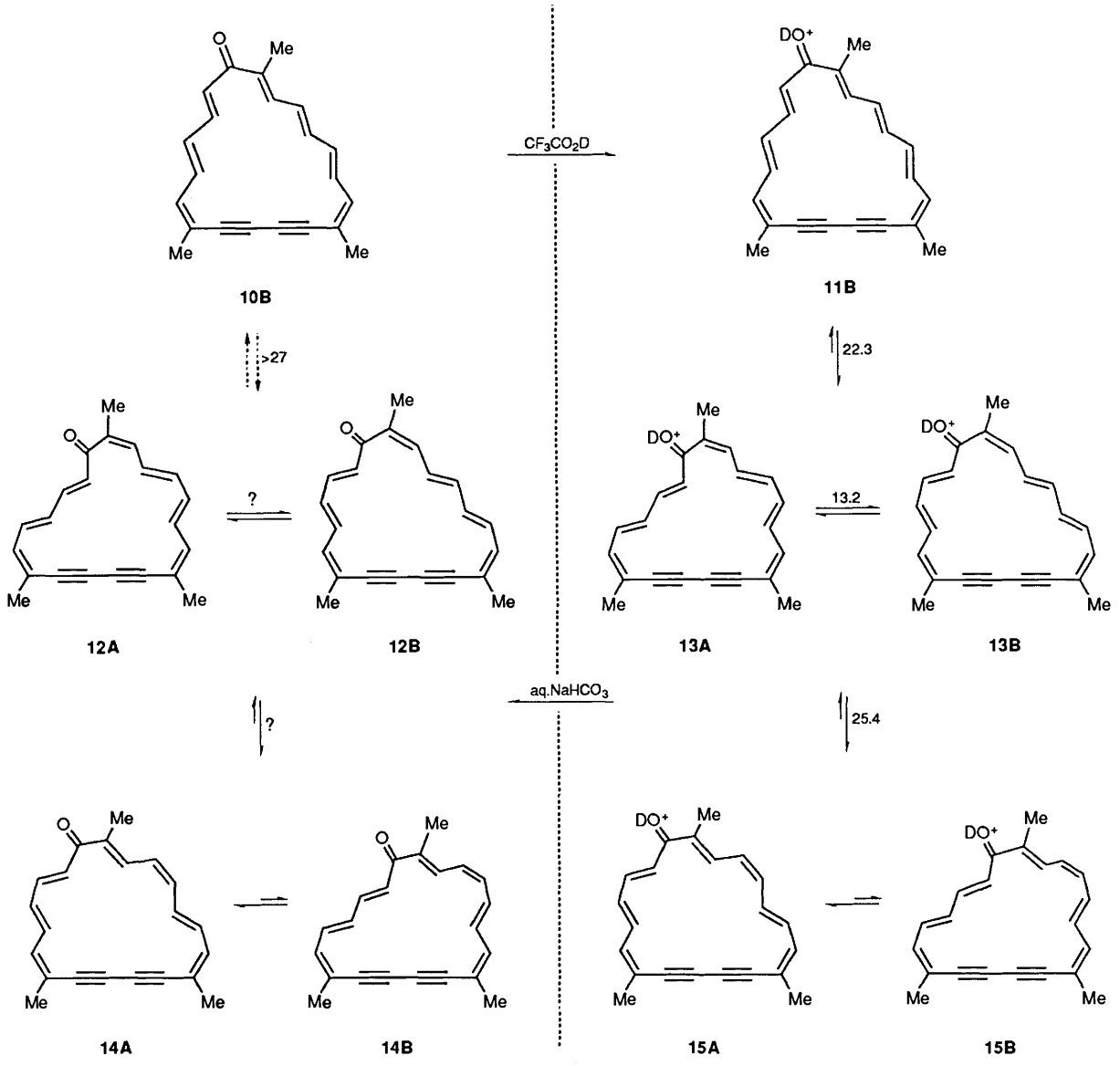
The configurational and conformational isomers of compounds **1**–**3** and their interconversion pathways in $CDCl_3$ and TFA solutions are shown in Schemes 1–3, respectively, together with the energy barriers to various processes in terms of free energies of activation.

As these compounds have seven C=C double bonds and seven C–C single bonds that are flanked by double bonds, there are $2^7 \times 2^7 = 16\,384$ choices of *E*/*Z* and *s-trans*/*s-cis* geometries to form planar structures, though most of them can be excluded because they do not form a ring with reasonable bond lengths and angles. Construction of molecular models was at first thought helpful to identify plausible isomers and conformers, but later it was revealed that too much reliance on molecular model considerations might be dangerous: the molecular model of **8A**, for example, appeared to suggest that **8A** would be unstable causing inevitable opening of some of the C–C–C angles, nonetheless **8A** actually exists as the most stable of the observed isomers.

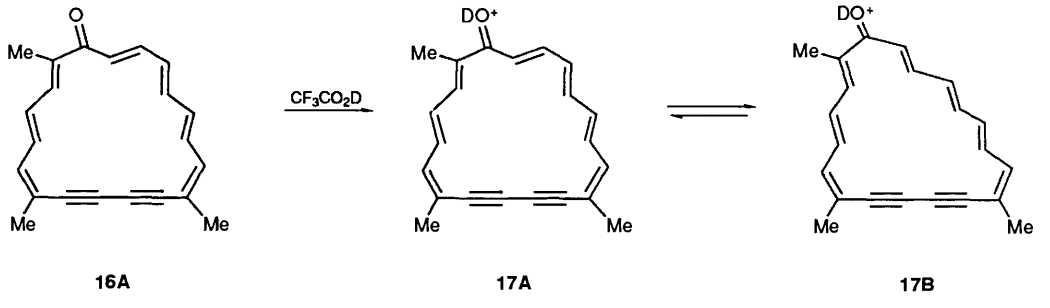
The relative stabilities of the various geometries comprise a balance of steric factors (including constraints of bond lengths, bond angles and torsional angles as well as non-bonded interactions) and electronic factors such as π-delocalization. It would be difficult to predict the lowest-energy of various geometries without the aid of theoretical considerations such as molecular-orbital calculations.

In our present investigation, an extensive study of configurational isomerization was restricted because of the instability of the samples toward heat or catalysts necessary for isomerization. Therefore the possibility should be admitted that some configurational isomers have escaped detection because of their excessively high isomerization energy barriers (>27 kcal mol^{-1}) even if they are of comparable thermodynamic stability to those detected in this study.

In compounds **1** and **2**, three configurational isomers, 'all-*E*', '2-*Z*' and '4-*Z*' are found. On the other hand, only the 'all-*E*' isomer is found for compound **3** even in the acidic medium.



Scheme 2



Scheme 3

Judging from the fact that in the '2-*Z*' and '4-*Z*' isomers of **1** and **2** the 19-H always resides inside the ring, it may be reasonable that the '2-*Z*' and '4-*Z*' isomers are absent in **3** which has a methyl group at the 19-position, because a methyl group is too bulky to reside inside the ring. In any of **1**–**3**, only the 'all-*E*' isomer is present upon synthesis and the energy barrier to isomerization of this isomer is very high under neutral conditions with $\Delta G^{\ddagger}$ of far higher than 27 kcal mol^{-1}. In the acidic medium the isomerization barrier considerably decreases to 21.4 and 22.3 kcal mol^{-1} for **1** and **2**, respectively. This is understood in terms of the decrease of bond alternation on going from the neutral to deuteriated species, resulting in the decrease of the double bond character of the C(2)=C(3) bond. Catalytic isomerization by deuteriation–dedeuteriation of the double bond in the acidic medium may be another explanation.

It is therefore interesting that the **6** ⟶ **8** isomerization in the neutral medium is faster than the **7** ⟶ **9** isomerization in the acidic medium. This may suggest the presence of a concerted pathway in which two double bonds simultaneously isomerize (**2***Z*,**4***E* ⇌ **2***E*,**4***Z*) and which is favoured under neutral conditions. This problem is left to further study.

The '2-*Z*' and '4-*Z*' isomers of compounds **1** and **2** exist as a

mixture of conformers in both neutral and acidic media. Geometries of the conformers are definitely determined for **7** and **13**, the '2-*Z*' isomers in the acidic medium, while slight ambiguity is left for the other systems.

The conformational changes in the acidic medium occur faster than the corresponding ones in the neutral medium, as typically shown in compound **1** (**7A** ⇌ **7B** *vs.* **6A** ⇌ **6B** and **9A** ⇌ **9B** *vs.* **8A** ⇌ **8B**). This may also be ascribed to the decrease in the bond alternation in the deuteriated species, affording some double bond character to formal single bonds.

The 'all-*E*' isomers of **1** and **2** exist in a different conformational state because of the presence of the 2-methyl group in **2** which cannot reside inside of the ring.

It is noted that the more abundant isomer generally has higher diatropicity in either medium. Typically, the methyl proton signals appear at a lower field in a more abundant isomer, the δ-values being in the order of **8** > **6** > **4**, **9** > **7** > **5**, **14** > **10** and **15** > **13** > **11**, namely, in the order '4-*Z*' > '2-*Z*' > 'all-*E*'. This suggests that the π-conjugative stabilization plays an important role in the relative stability of the isomers, although it remains uncertain why the '4-*Z*' isomer is the most stable.

Experimental

^{1}H NMR spectra were obtained on a Bruker AM-500 spectrometer operating at 500.14 MHz in the pulse-FT mode equipped with a variable temperature accessory. Temperatures were calibrated with a methanol sample and are reliable to ± 1 °C. In the spectra obtained in CF_3CO_2D solutions the chemical shifts were referenced with the $CHDCl_2$ signal at δ 5.30.

Syntheses of compounds **1**–**3** have been reported previously.[4,5] No efforts were made to isolate and characterize the respective configurational isomers formed by isomerization.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 03214103) from the Ministry of Education, Science and Culture of Japan and by a grant from CIBA-GEIGY Foundation (Japan) for the Promotion of Science.

References

1 For example: P. J. Garratt, *Aromaticity*, Wiley, New York, 1986, pp. 84–124; A. T. Balaban, M. Banciu and V. Ciorba, *Annulenes, Benzo-, Hetero-, Homo-Derivatives, and Their Valence Isomers*, CRC Press, Florida, 1988, vol. I, pp. 67–191.
2 For example: F. Sondheimer, *Proc. R. Soc. (London), Ser. A*, 1967, **297**, 173.
3 Part of this work has appeared in the preliminary form: G. Yamamoto, H. Higuchi, H. Yamamoto and J. Ojima, *Tetrahedron Lett.*, 1991, **32**, 5129.
4 J. Ojima, Y. Shiroishi, K. Wada and F. Sondheimer, *J. Org. Chem.*, 1980, **45**, 3564.
5 J. Ojima, K. Wada, Y. Nakagawa, M. Terasaki and Y. Juni, *J. Chem. Soc., Perkin Trans. 1*, 1982, 31.
6 L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon, London, 1969, pp. 280–304.

Paper 1/05502J
Received 29*th October* 1991
Accepted 3*rd December* 1991