

C-11 Acid and the Stereochemistry of Abietic Acid

S N Balasubrahmanyam

The elucidation of the structure and stereochemistry of an acid named 'C-11 Acid' that played a crucial role in the determination of the molecular structure of abietic acid, which is a constituent of violinists' 'rosin', led to a flowering of ideas of conformational analysis.

Introduction

Correlations based on cyclohexane polycarboxylic acids into which terpenic and steroidal natural products¹ were degraded in the laboratory led to the main ideas underlying their biosynthetic origin [1]. To illustrate, abietic acid, a tricyclic diterpene acid, which is the main constituent of acid-treated exudate of trees of the pine species, (better known as violinists' rosin), has been related to lanosterol, a steroidal alcohol isolated from sheeps' wool, and onocerin, a triterpenic alcohol of plant origin, via 2,6,6-trimethyl-2-carboxycyclohexylacetic acid. The derivation of (+)*trans*-2-methyl-2-carboxycyclohexylacetic acid from both abietic acid and ergosterol, a steroidal alcohol of fungal origin, established the common absolute configuration of the mode of A/B ring junction in a terpenoid and in a steroid [2] (*Scheme 1*). In the 'classical period' of developments in the terpenoid field, especially in the school established by Leopold Ruzicka (1939 Chemistry Nobel Prize) at the Eidgenössische Technische Hochschule (ETH) in Switzerland, degradation to cyclohexanecarboxylic acids has played an important part in the establishment of configurational inter-relationships among a host of alicyclic natural products. A list of such acids has been compiled by Jeger *et al* [3] of Ruzicka's school. These studies have led to the recognition of a 'normal' absolute configuration in natural products isolated from large groups of organisms, both from plant and animal kingdoms.



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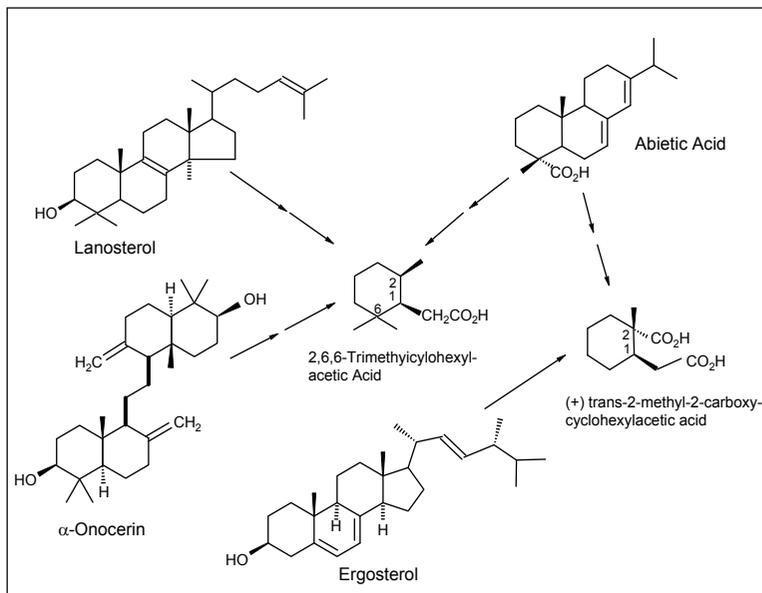
¹ The terms 'terpenic' and 'terpenoid' designate non-aromatic organic compounds – hydrocarbons, alcohols, aldehydes, ketones, acids and the like – isolated originally from exudates of coniferous trees (pine species).

Keywords

Abietic acid, C-11 and C-12 acids, assignment of stereochemical configuration by comparison of acid ionization constants, conformational analysis.



Scheme 1.



The establishment of all aspects of the structure of a cyclohexane tricarboxylic acid, named the 'C-11 acid', isolated from the products of oxidative degradation of abietic acid, (*Figure 1*; stereostructure alongside) was important to the elucidation of the structure of the latter. Historically, this effort figured among the first applications of the ideas of conformational analysis

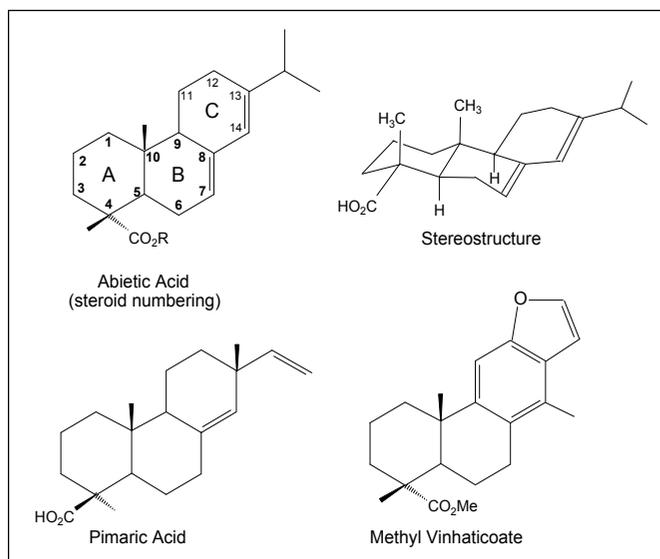


Figure 1.

developed by Barton (1969 Chemistry Nobel Prize) to the solution of an important configurational problem, as we shall see.

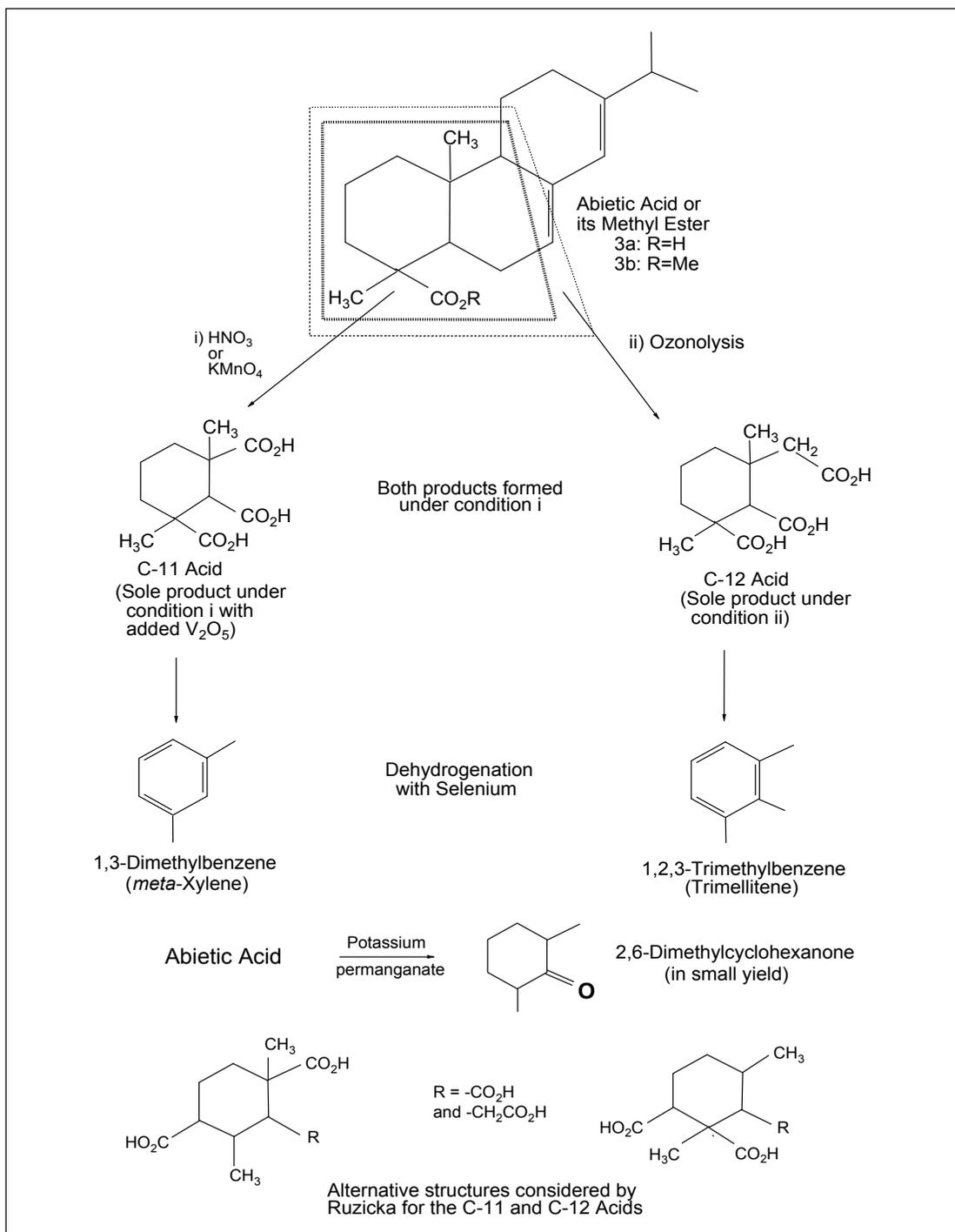
The presently accepted structure of abietic acid is the result of intensive chemical researches extending over a period of more than a century. The subject is an important part of authoritative treatises by well known researchers in the field of the chemistry of alicyclic terpenic natural products [4]. Much of that work is now standard material in textbooks of organic chemistry. The history of investigations into the structure of abietic acid is a microcosm of the development of organic chemistry itself. Starting from early-type of what would now be regarded as crude degradative experiments, it stretches to a period that routinely employs instrumentation for performing what were earlier distinguished as 'physico-chemical investigations'. These latter encompass a host of developments in practical aspects like chromatographic separation/purification methods, routine recording of ultraviolet, infrared and Raman spectra, use of continuous wave and multiple irradiation nuclear magnetic resonance spectroscopy, etc. In the case of abietic acid itself, the determination of its absolute configuration through optical rotatory dispersion² methods has only fairly recently been confirmed by single-crystal X-ray crystallography [5]. But most importantly, the investigations led to the development of ideas of 'conformational analysis' and what used to be earlier known as 'electronic theory of organic chemistry' and of the theoretical treatment of the chemical bond, essential to an understanding of how natural products are formed through biosynthetic processes (enzyme mediated synthesis of complex structures from substrates of primary structure).

C-11 and C-12 Acids

Oxidation of abietic acid or its methyl ester with potassium permanganate [6] or with nitric acid [7] gives a tricarboxylic acid $C_{11}H_{16}O_6$, the C-11 acid, mp 219° , and its homologue $C_{12}H_{18}O_6$, the C-12 acid, mp 213° (Scheme 2). As recommended by Ruzicka *et al* [6c], a specific rate of heating of the sample must be used to arrive at a sharp melting point. Otherwise, the formation of anhydrides leads to a range of softening of the sample. The use of vanadium

² Optical rotatory dispersion (ORD) uses the phenomenon of a change in the magnitude of optical rotation in the vicinity of an absorption band of a substance, called the Cotton Effect. In a wavelength region where the light is absorbed, the absolute magnitude of the optical rotation at first varies with wavelength, crosses zero at absorption maximum, and again varies with wavelength but in the opposite direction. This can be most easily observed of an optically active substance that has a single chromophore e.g., a C = O group. The effect is positive if the optical rotation first increases as the wavelength decreases and negative if the rotation first decreases. A protein structure such as a short polypeptide chain made up of L-amino acids shows a negative effect. A similar structure made up of D-amino acids will show a positive effect, virtually a mirror image of the curve of the former.





Scheme 2.

pentoxide as a catalyst, when nitric acid is employed as the oxidizing agent, affords predominantly the C-11 acid [8] while ozonolysis, followed by suitable work-up, yields the C-12 acid [6b]. While many features, like the phenanthrene-type of fusion of the three constituent rings, the positions of substituents, etc., were found by independent investigations, the knowledge of the gross structures of the C-11 and C-12 acids was essential to the establishment not only of the constitution of diterpenoid natural products (made up of four isoprene units) such as pimaric and vinhaticoic acids (*Figure 1*) but also of the configuration of the A/B ring fusion in these and related natural products.

Structures of C-11 and C-12 Acids

The structures of C-11 and C-12 acids, grossly taken, were thought to contain the original ring A of abietic acid, retaining the 'nuclear methyl groups' characteristic of most polycyclic terpenic natural products. Dehydrogenation and decarboxylation of the two acids with selenium gave, respectively, *m*-xylene and 1,2,3-trimethylbenzene [6c] (*Scheme 2*), indicating the 1,3-relationship between the tertiary methyl and angular methyl groups (at C-4 and C-10, respectively, in abietic acid). Ruzicka and Waldmann [9], who isolated 1,3-dimethylcyclohexane-2-one in small yield in the oxidation of abietic acid with potassium permanganate (*Scheme 2*), provided further evidence confirming this feature. Ruzicka tried to explain his esterification and saponification experiments considering possible structures (*Scheme 2*) taking two of the carboxyl groups as representing the remnants of ring B of abietic acid and the third as retention of the original carboxyl group positioned in different ways in ring A [6c, 6d]. The implied, resulting structures of abietic would not have been, however, consistent with the Isoprene Rule³ [1].

Ruzicka observed the lack of optical activity on the part of the C-11 acid [6c] but reported a small laevorotation (-5°), later corrected to 0° , for the C-12 acid [10]. However, he did not immediately draw an appropriate structural conclusion, one based on the possible presence of symmetry (optical inactivity due to presence

³ The 'Isoprene Rule' is a generalization from observations that structures of most natural products of the terpenic/alicyclic type can be analyzed as those of head-to-tail, and sometimes as head-to-head or tail-to-tail, unions of isoprene (2-methyl butadiene) units, forming chains that, in most cases, cyclise to the many products that may bear diverse functional groups on the rings. 'Isoprenoid' or 'polyisoprenoid' are terms often used in this context.



of a feature that renders the structure symmetrical); it is interesting to note here that if structures like those of the alternatives shown in *Scheme 2* were that of a product derived from natural sources, they would, most likely, have been optically active.

Investigations by Vocke led to the correct structures of the two homologous tricarboxylic acids and, hence, to a solution of the abietic acid structural problem [11]. He first applied a diagnostic test: secondarily bound carboxyl groups (carboxyl groups bound to a carbon bearing a hydrogen atom) are stable to warm concentrated sulphuric acid while tertiary carboxylic acids often lose carbon monoxide [12]. Both tetrahydroabietic acid (abietic acid with both double bonds saturated) and the C-11 acid evolved carbon monoxide showing both incorporated tertiary carboxyl groups. Vocke's other investigations are detailed in the sequences shown in *Scheme 3*. On the basis of the final, known product, α -methylglutaric acid, Vocke concluded that the C-11 acid could only be represented as 1,3-dimethyl-1,2,3-cyclohexanetricarboxylic acid and the C-12 acid, its homologue, logically, as 2-carboxymethyl-1,3-dimethyl-1,3-cyclohexane-dicarboxylic acid.

Proof, by synthesis, for the structure of Vocke's unsaturated acid and lactone was furnished by Rydon [13] (*Scheme 3*).

Barton's Work and Beginnings of Conformational Analysis

The C-11 and C-12 acids can have three possible configurations, probably preferring the conformations **A**, **B**, and **C** shown in *Figure 2*. Absence of optical activity in acids which are isolated

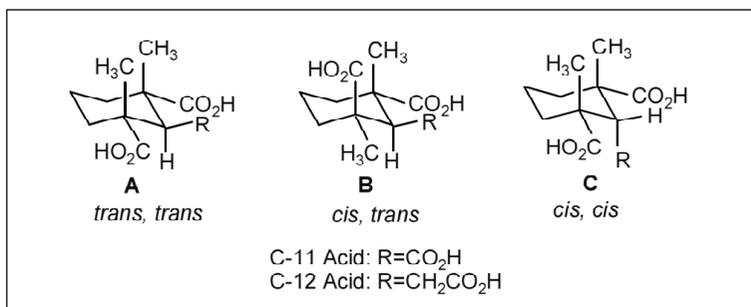
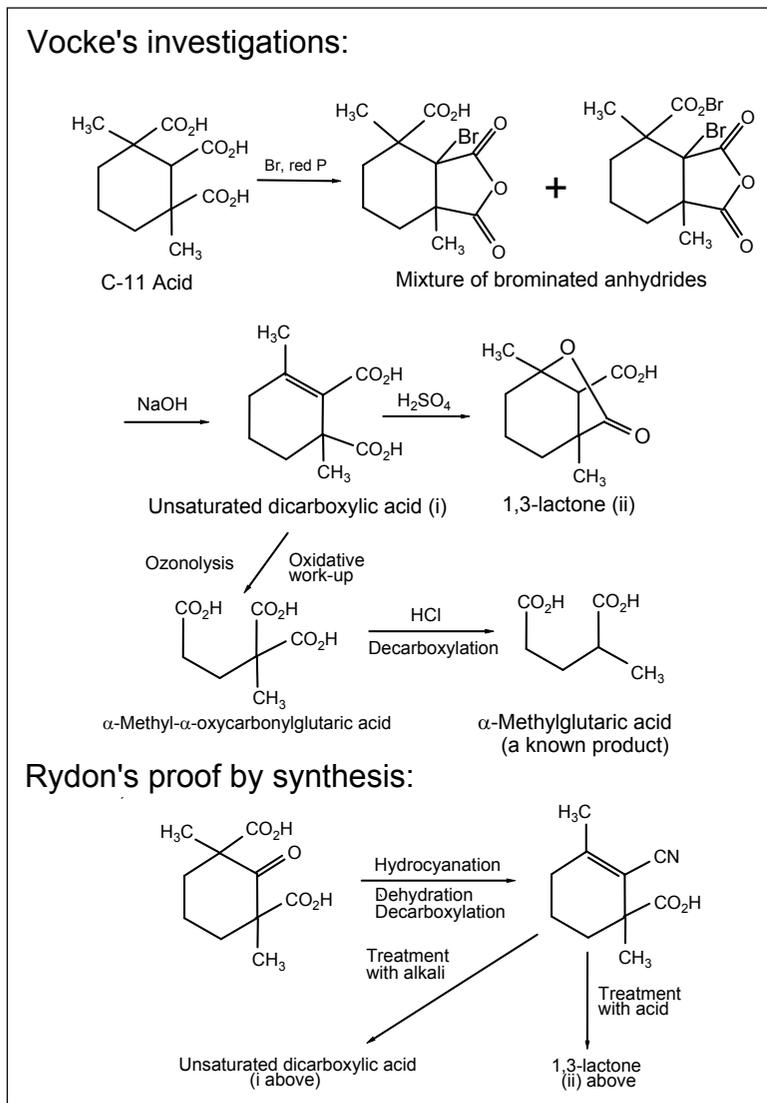


Figure 2.

Scheme 3.



from the oxidation products of abietic acid suggests the presence of a plane of symmetry (*meso*- configuration, as in *meso*-tartaric acid), ruling out the configuration implied by **B**. Both conformations, **A** and **C** (which are loosely described in *Figure 2* as having, respectively, *trans, trans*- and *cis, cis*-vicinal (next to each other) relationship of the carboxylic functions) have a plane of symmetry. Change of configuration at C-2 in the C-11 acid under oxidative conditions is only a remote possibility and the C-12 acid cannot undergo epimerization (change in configuration) at any of the three centers.

⁴In 1948, Barton wrote, "It is now generally accepted that the chair configuration of cyclohexane is appreciably more stable than the boat configuration. In the former, all arrangements of the valency directions about the carbon atoms correspond to the staggered configuration in ethane, in which there are two distances between hydrogen atoms not bonded to the same carbon atom, a 'short' distance and a 'long' distance." At the present time, a third, twist-boat conformation where the chair configuration of cyclohexane has become 'twisted' to various degrees has been recognized in certain cases.

⁵Change to a possible different conformation without breaking and reconstituting a bond can change the energy content based on 'Conformational Free-energy Difference'. In 4-methylcyclohexane, e.g., the chair conformation having axial methyl group will have more energy content than its chair-to-chair ring transform that has equatorial methyl group.

Attribution of *cis*, *cis*- and the *trans*, *trans*- configurations **C** and **A** to the C-11 acid would respectively imply *cis*- and *trans*- fusion of the A and B rings of abietic acid. A *cis*- junction would indeed have been the case had it been shown that the easily-formed anhydride (mp 175°) is generated by loss of water from vicinal carboxyl groups of the C-11 acid.

We now take a little digression in order to look into a classic case of how science corrects itself as it advances.

Campbell and Todd [14] looked into a possible difference in the stereochemistry of A/B ring fusion in podocarpic and dehydroabietic acids after establishing the general structural features and relationships between them (*Figure 3*). They first confirmed an observation reported earlier that podocarpic esters were more resistant to hydrolysis than dehydroabietic esters. They then used molecular models to look into a possible steric reason for this difference in behavior. Their assessment showed greater steric hindrance in the *cis*-fused case than in the *trans*-fused case (that could cause higher resistance to hydrolysis in the case of dehydroabietic acid), the opposite of the experimental finding. The conclusion from this was that the A/B ring junction was not *cis* but *trans*.

Barton⁴ suspected that Campbell and Todd had used the two-boat Sachse–Mohr conformation (*Figure 3*) for modeling decalin *cis*-fusion and the two-chair decalin *trans*-fusion for assessing and comparing the relative degree of steric hindrance. He pointed out [15] that while the two-chair *cis*-fusion, is also close to the *trans*-fusion in conformational free-energy content⁵, using the Sachse–Mohr type *cis*-conformation [16] would invalidate their arguments even if they had been correct in saying that the A/B junction in both natural products had the *trans*-configuration. We can set down pairs of *cis*-two-chair conformations for A/B *cis* junction, Podo-a and Podo-b for podocarpic acid and Dha-a and Dha-b for dehydroabietic acid (*Figure 3*). While a comparison of the models of Podo-a with Dha-a would again make a wrong



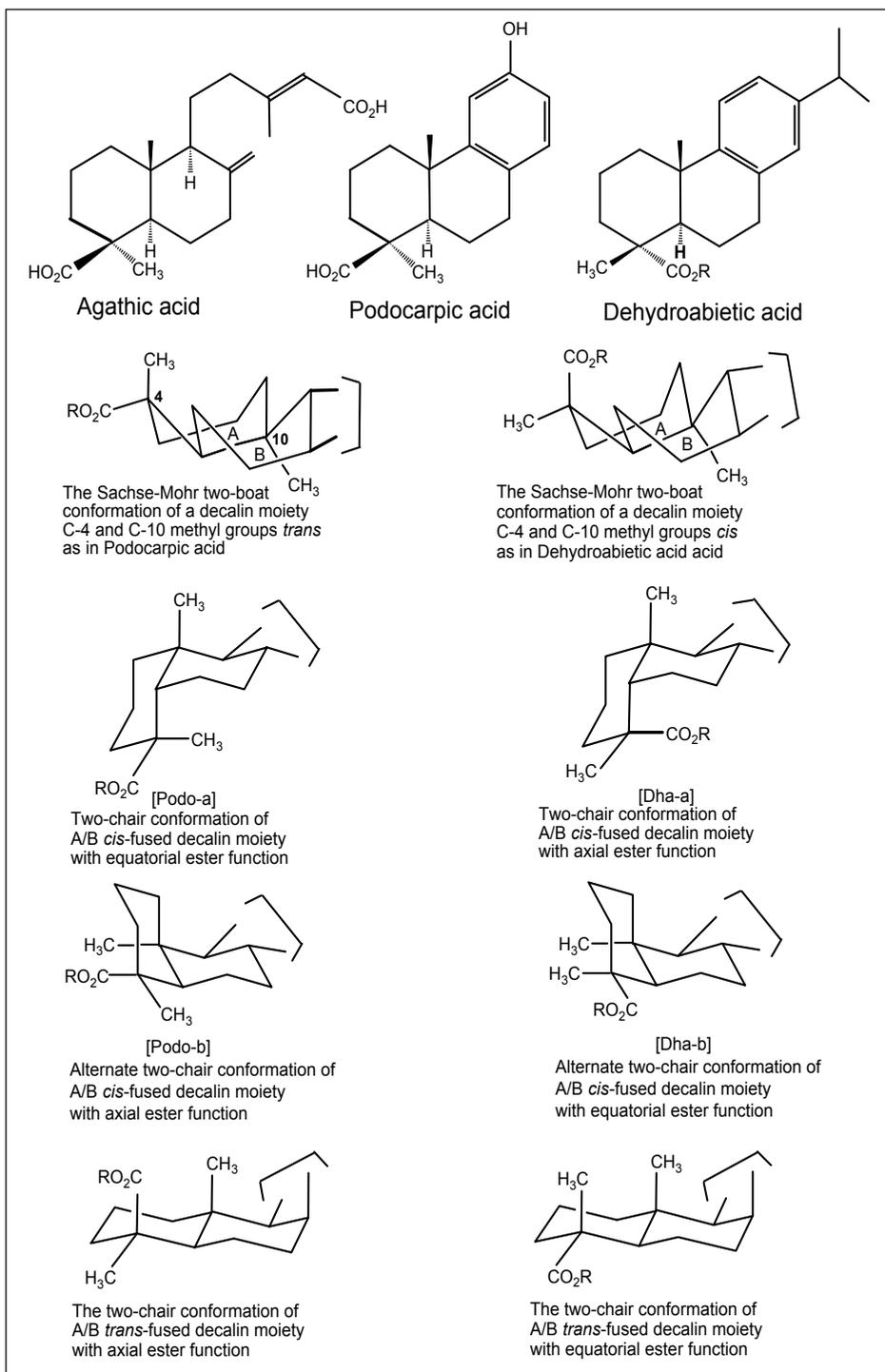


Figure 3.

prediction of the difference in the rates of hydrolysis of their esters, it would be difficult to make qualitative assessments of pertinent steric hindrance from similar models in the case of the other pair, Podo-b with Dha-b (Figure 3).

Thinking that the anhydride he had obtained by the action of heat on the C-11 acid was the 1,2-anhydride (Figure 4), Lombard [8] had concluded that the configuration of A/B ring junction is *cis*. Barton noted [15] that Ruzicka *et al* had not only separated two anhydrides (mp's $\sim 100^\circ$ and $\sim 171^\circ$) that are formed on treating the C-11 acid with acetyl chloride but had also shown that the higher melting one had the C-1 and C-3 carboxyl groups in *cis* relationship. On the basis of the ease of its formation, similar to the formation of the anhydride of *cis*-cyclohexane-1,3-dicarboxylic acid, as well as on symmetry grounds, Barton said that it must be given the 1,3-anhydride structure. This view received support from the later work of Norin [17] who found that the unsymmetric mono-methyl ester (structural formula in Table 1) of the C-11 acid shows little or no tendency to form the 1,2-anhydride when heated to its melting point. And, from even later developments in conformational analysis, it has come to be known that 5- and 6-membered rings condense in *cis*-fashion more easily than they can fuse in *trans*-fashion [18].

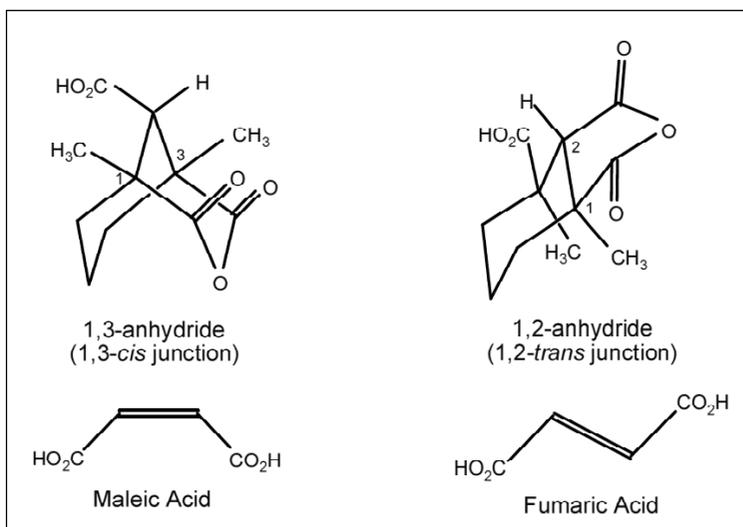


Figure 4.

Electrostatic Energy Differences to Assign Configuration

Contending that the ease of formation of the 1,3-anhydride does not provide evidence towards the stereochemistry of the C-2 carboxyl group, Barton sought to obtain independent evidence for the relative configuration of the three carboxyl groups in the C-11 acid in order to demonstrate clearly that the A/B junction had the *trans*- configuration in abietic and certain known diterpenic acids of related structure. His method was based on 'electrostatic energy differences' measured by comparing the dissociation constants of the C-11 acid and its mono- and dimethyl esters, as elaborated below.

Barton obtained the 1,3-anhydride (mp 175°; *Figure 4*) from the C-11 acid, identical with the one reported earlier by Ruzicka [6c] and by Lombard [8]. On even prolonged hydrolysis by treatment with potassium hydroxide, the anhydride gave the original C-11 acid, showing that the secondary carboxyl group in the C-11 acid does not undergo configurational isomerization on treatment with alkali. The stability of the acid towards basic reagents was further demonstrated by Rao and Bagchi [19] who treated the trimethyl ester of the C-11 acid with potassium powder in ether and also with sodium methoxide in methanol and found no isomerization. They prepared the 1,3- and 1,2-anhydrides (*Figure 4*) according to reported methods and observed, in the respective cases, infrared absorption bands, which are characteristic of 6- and 5-membered anhydrides [20].

The use of dissociation constant measurements⁶ in the determination of the configuration of isomeric entities with active hydrogen has received much attention, both theoretical and practical, particularly from the investigations of Ingold [21] and Kirkwood and Westheimer [22]. Taking the instance of the *cis*- and *trans*-ethylene-1,2-dicarboxylic acids (maleic and fumaric acids, respectively; *Figure 4*), maleic acid shows a greater difference between the first and second ionization constants than fumaric acid⁷. These investigations led also to the idea of cocooning of ions and molecules in a 'dielectric cavity' within which the dielectric

⁶The second proton will be harder to pull away because of the presence of the negative charge already situated on the carboxylate group which is nearer in maleic acid than in fumaric acid.

⁷Dissociation constants which measure how easily an active hydrogen is abstracted from the organic entity to which it is bound (for example, how easily the proton is separated from a carboxylic group in a carboxylic acid R-COOH to form R-COO⁻ and H⁺ ions) can be measured by potentiometric or colourimetric titration against dilute alkali.



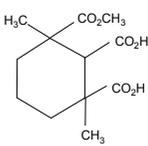
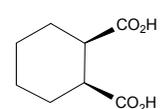
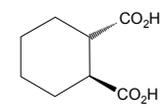
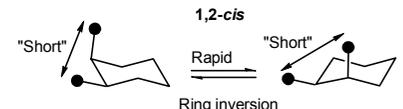
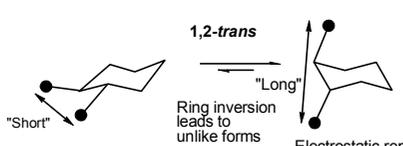
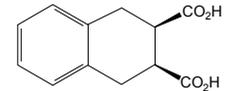
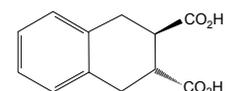
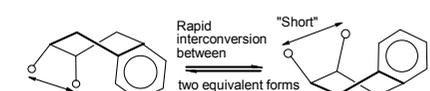
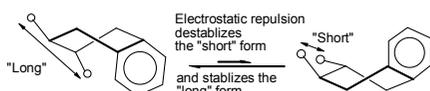
constant (which indicates how well the through-space effect of a charge, or dipolar separation of charges, is conveyed) is different from the general dielectric constant of the medium.

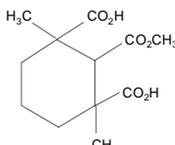
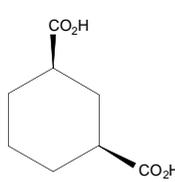
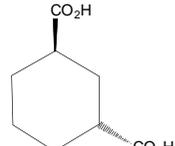
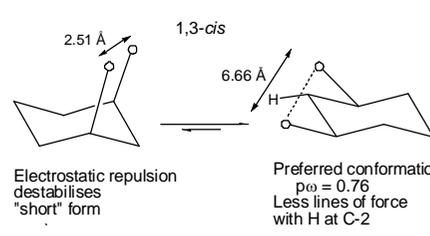
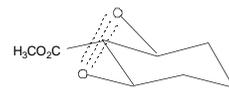
Proceeding from first principles that they detail in their paper, Barton and Schmeidler [15] obtained experimental values of the differential quantity $p\omega$ for the sym. and unsym. monomethyl esters of the C-11 acid (Tables 1a, 1b) and the first two-thirds of the titration curve of the latter from dissociation constants obtained by potentiometric titration. On the basis of what has been said in previous paragraph one can see that larger the value of $p\omega$, shorter is the distance between the carboxyl groups in question. The value of $p\omega$ is related to the first and second measured dissociation constants $K_{a'}^2$ and $K_{a''}^2$, respectively, by:

$$p\omega = -\log_{10} K_{a'}^2 / 4 K_{a''}^2$$

Table 1a. The '1-2' case.

A measure of the distance, ' r ', between the two carboxyl groups

Compound	Comparison systems	Conformations of derived anions
 <p>Asymmetric monomethyl ester [$p\omega_{1,2} = 1.11$; expected $p\omega_{1,2} \approx 1.85$ for 1,2-<i>cis</i> and ≈ 1.13 for 1,2-<i>trans</i>]</p>	 <p><i>cis</i> Cyclohexane-1,2-dicarboxylic acid [$p\omega_{1,2}(\text{H}_2\text{O}) = 1.80$; $p\omega_{1,2}(\text{H}_2\text{O}/\text{MeOH}) = 2.34$]</p>  <p><i>trans</i> Cyclohexane-1,2-dicarboxylic acid [$p\omega_{1,2}(\text{H}_2\text{O}) = 1.15$; $p\omega_{1,2}(\text{H}_2\text{O}/\text{MeOH}) = 1.33$]</p>	<p>1,2-<i>cis</i></p>  <p>Rapid Ring inversion leads to like forms</p> <p>1,2-<i>trans</i></p>  <p>Ring inversion leads to unlike forms</p> <p>Electrostatic repulsion stabilizes the "long" form in the <i>trans</i>-case</p>
	 <p>Tetralin-<i>cis</i>-2,3-dicarboxylic acid [$p\omega_{1,2}(\text{H}_2\text{O}) = 1.89$]</p>  <p>Tetralin-<i>trans</i>-2,3-dicarboxylic acid [$p\omega_{1,2}(\text{H}_2\text{O}) = 1.10$]</p>	 <p>Rapid interconversion between two equivalent forms in the <i>cis</i>-case</p> <p>Electrostatic repulsion destabilizes the "short" form and stabilizes the "long" form in the <i>trans</i>-case</p> 

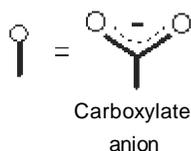
Compound	Comparison systems	Conformations of derived anions
 <p>Symmetric monomethyl ester [$p\omega_{1,3} = 0.96$]</p>	 <p><i>cis</i>-Cyclohexane-1,3-dicarboxylic acid [$p\omega_{1,3}(\text{H}_2\text{O}) = 0.76$; $p\omega_{1,3}(\text{H}_2\text{O}/\text{MeOH}) = 0.98$]</p>  <p><i>trans</i>-Cyclohexane-1,3-dicarboxylic acid [$p\omega_{1,3}(\text{H}_2\text{O}) = 1.15$; $p\omega_{1,3}(\text{H}_2\text{O}/\text{MeOH}) = 1.33$]</p>	 <p>Electrostatic repulsion destabilises "short" form</p> <p>Preferred conformation $p\omega = 0.76$ Less lines of force with H at C-2</p>  <p>More lines of force with ester group at C-2 $p\omega = 0.96$</p>

can be had from the equation:

$$p\omega = -\log_{10}\omega = N_0\varepsilon^2/2.3RTD_Er,$$

where, N_0 is the Avogadro number, ε is the electronic charge, R is the molar gas constant, T is the absolute temperature (in kelvins), and D_E is the 'effective' dielectric constant between the two carboxyl groups separated by distance, ' r '.

Barton's intricate arguments based on the application of the method of electrostatic energy differences led to deductions on the basis of conformational analysis. He unimpeachably demonstrated why the C-11 acid has the 1,2-*trans*, 2,3-*trans* configuration and preferred the conformation shown, hence establishing that the A/B ring junction in abietic and numerous, similarly constituted, naturally-occurring terpenic acids have the *trans*-configuration. In *Tables 1a, b and c*, Barton's argument is detailed in a simplified manner. In the column headed 'Conformations', the following symbolism has been used.



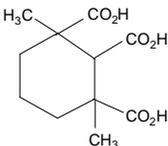
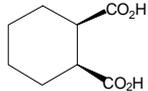
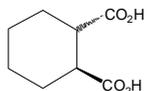
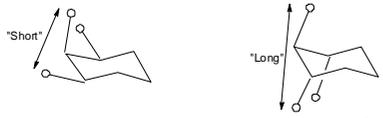
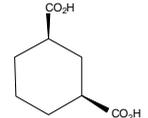
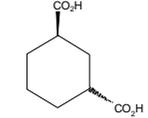
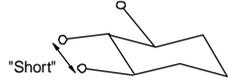
Compound	Comparison systems		Conformations of derived anions
 <p>$p\omega_{1,2} = 1.37$</p>	 <p><i>cis</i>-Cyclohexane-1,2-dicarboxylic acid</p>	 <p><i>trans</i>-Cyclohexane-1,2-dicarboxylic acid</p>	 <p><i>cis,cis</i>-form <i>trans,trans</i>-form</p> <p>Logical extensions to tervalent anion of the corresponding cases of 1,2-divalent anions</p>
	 <p><i>cis</i>-Cyclohexane-1,3-dicarboxylic acid (see Table 1b)</p>	 <p><i>trans</i>-Cyclohexane-1,3-dicarboxylic acid (see Table 1b)</p>	 <p>"Short"</p> <p>Tervalent anion can adopt this ring-transformed conformation stabilised by electrostatic repulsion by about 1 kcal./mole compared with the <i>trans,trans</i> triaxial case (above right) where the distance is shorter</p>

Table 1c. Possible types of behavior of the 1,2,3-trianion.

In places, parlance that came into use in later times in the development of conformational analysis has been used in discussing the data.

The $p\omega_{1,2}$ values of *cis*-cyclohexane-1,2-dicarboxylic acid (1.80 in water and 2.34 in 1:1 MeOH-H₂O) are greatly different from those of the *trans*-acid (1.15 in water and 1.33 in 1:1 MeOH-H₂O). Similar is the case with the tetralin-2,3-carboxylic acid, clearly indicating that the larger contribution to the conformational equilibrium is from those forms where a 'long' distance that can separate the anionic centres prevails. The 1,2-diaxial orientation is possible only for the *trans*-case.

The measured $p\omega_{1,2}$ value of 1.11 for the asymmetric monomethyl ester is close to the *trans*- and not the *cis*-configuration of the comparison systems.

The measured $p\omega_{1,3}$ value of 0.96 for the symmetric monomethyl ester is clearly closer to the values for the *cis*-cyclohexane-1,3-dicarboxylic acid⁸. Looking at the conformational equilibrium for the *cis*-case, the 1,3-diequatorial dianion can be expected to be the greater contributor. Barton explains the somewhat higher value for the symmetric monomethyl ester on the basis that more lines of force can travel through the bulky C-2 ester function than the smaller hydrogen in the case of the model, thus lowering the

⁸ $p\omega_{1,3}$ for *cis*-cyclohexane-1,3-dicarboxylic acid is 0.76 in water and 0.98 in MeOH:H₂O whilst the values for the *trans* acid are 1.15 and 1.33 in the respective media.

dielectric constant (D_E). Additionally, the relative values of $p\omega_{1,2}$ and $p\omega_{1,3}$, 1.11 and 0.96, are consistent with the greater distance that may separate the anionic centers in the 1,3-case.

Barton and Schmeidler determined $p\omega_{1,2}$ for the C-11 tricarboxylic acid from two-thirds of its potentiometric titration curve against alkali⁹. Making the necessary assumptions regarding the values of the parameters involved, the authors calculated $p\omega_{1,2}$ values for the ‘*cis,cis*-’ and ‘*trans,trans*-’ cases as 1.85 and 1.13 and judged that the latter was only in fair agreement with the value measured for the C-11 acid (1.37). They took the discrepancy as arising from cumulative errors in certain measurements and in the values taken for the parameters (e.g., the local D_E) used in the calculations.

From the results of these experiments Barton concluded that the configuration of A/B ring junction is *trans*- in abietic acid.

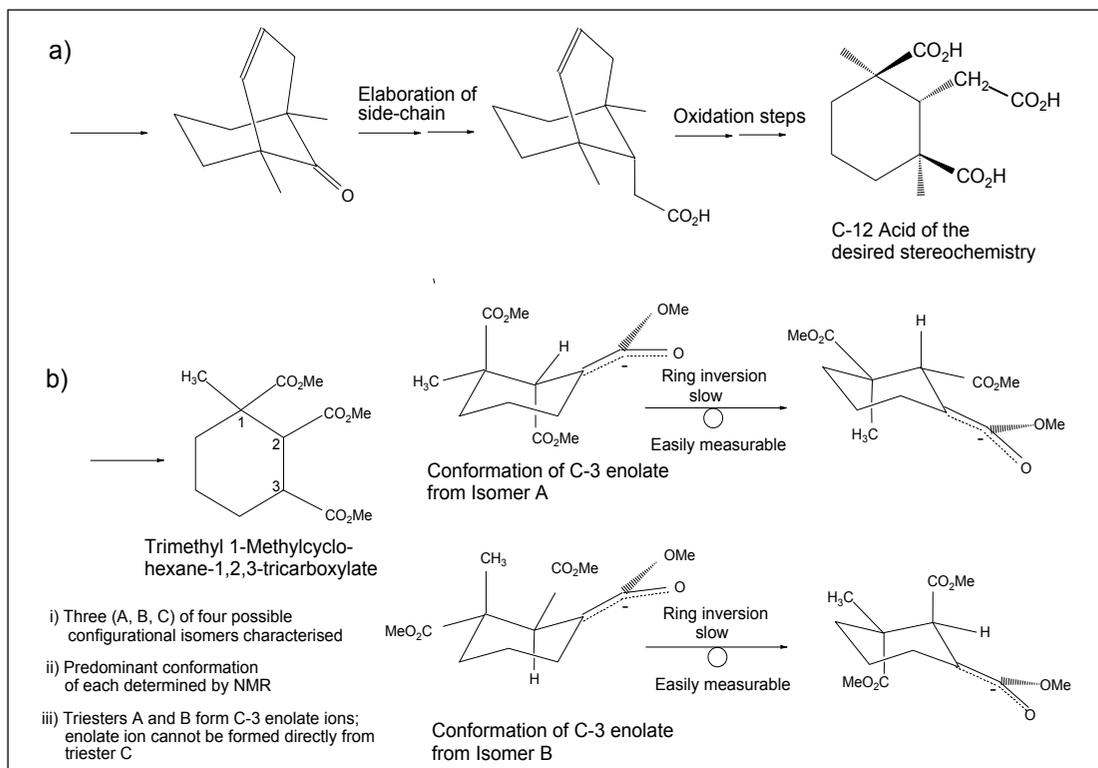
Synthetic Investigations

Much of the work in the ‘Classical Period’ of arriving at the structures of natural products consisted in initial degradation, often by drastic means like oxidation with strong reagents, applied to substances considered to be ‘pure’. Isolated from natural sources, they would have been processed through fractional crystallization of solid extracts, fractional distillation of oils, etc. The aim of the degradation experiments was to arrive at simpler or known structures, the constituent ‘bricks’. The intention was to put the fragments, now of a known structure, together in ways that appeared ‘logical’ to the organic chemist so s(h)e could build the full, naturally occurring structures. Synthesis, or attempts thereof, came later, in the process of completing the picture.

From what has been discussed above, it would appear that a formal total synthesis of the C-11 and C-12 acids would be of little value since determination of the stereochemistry of these acids – assignment of the stereochemistry of A/B ring junction in abietic acid and a host of terpenic and alicyclic natural products – had already been achieved. Nevertheless, there have been

⁹ The change of pH for the addition of a known small amount of dilute alkaline titrant against an acid reaches a maximum at the equivalence (neutralization) point. A plot of the titration curve will have the familiar slanting S-shape, a double S for a dicarboxylic acid and a three-stage S for the tricarboxylic acid. The first two S's would give a measure of $p\omega_{1,2}$ in the case of a tricarboxylic acid.





Scheme 4.

several attempts to synthesise them [23]. These have been challenging and only two were successful, one in the case of the C-11 acid [24] and the other in the case of the C-12 acid [25].

Raphael and his coworkers ensured the desired *trans,trans*-configuration by starting with the rigid bridged bicyclic intermediate of known stereochemistry (Scheme 4a). They achieved highly stereoselective elaboration of the carbonyl group to the acetic acid side-chain. Further oxidation steps gave the C-12 acid.

The attempt by Banerjee, Balasubrahmanyam and Ranganathan that proved successful for the case of the C-11 acid (Scheme 4b) preceded that of Raphael *et al* for the C-12 acid. It illustrates how the easily obtainable nuclear magnetic resonance-based stereochemical information could be used for the syntheses, separately, of both the *trans,trans*- and *cis,trans*-C-11 acids (respectively, *meso* and *dl*), which are the degradation products originally obtained from abietic and agathic acids. The C-3 enolate

ions were prepared from the configurationally different triesters A and B. Methylation immediately after their formation occurred regio- and stereospecifically (at C-3), yielding the *trans,trans*- and *cis,trans*-C-11 acids respectively, as their trimethyl esters.

It is known that ring inversion processes in conformationally mobile systems are usually very fast. However, the C-3 enolates from the configurationally different triesters, A and B, exhibited strange behavior in that both underwent ring inversion at rates amenable to being measured by conventional methods normally employed for following the kinetics of chemical reactions. We hope to publish a detailed explanation of this very interesting and unusual phenomenon in the near future.

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