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# Odd–Even Effect in the Elastic Modulii of $\alpha,\omega$-Alkanedicarboxylic Acids

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Supporting Information

**ABSTRACT:** Nanoindentation studies on $\alpha,\omega$-alkanedicarboxylic acids reveal that the elastic modulus, $E$, shows an odd–even alternation in exactly the same manner as the melting temperature, $T_m$. These results are consistent with the hypothesis that the strained molecular conformations in the odd diacids are the reasons for these alternations in $T_m$. The same packing features that lower $T_m$ in the odd acids lead to easy accommodation of the deformation during nanoindentation and hence their low $E$.

The $\alpha,\omega$-alkanedicarboxylic acids, $HO_2C(CH_2)_nCO_2H$, which are used as co-formers in the pharmaceutical industry, are of relevance in drug development and formulation.[1] They are also of fundamental interest in view of the odd–even alternation in their melting points, $T_m$, first observed by Baeyer in 1877.[2] In 2000, Thalladi et al. hypothesized that the reason for this alternation is the strained intramolecular geometry in the odd acids.[3] In this Communication, we provide compelling experimental evidence for this hypothesis through the measurement of elastic moduli of seven members of this homologous series ($1 \leq n \leq 7$; malonic through azelaic acids). Our experimental results show that the elastic modulus, $E$, of the single crystals—measured by the nanoindentation technique—varies exactly in the same fashion as $T_m$ and that both $E$ and $T_m$ are strongly dependent on solid-state molecular conformations.

The crystal structures of odd and even dicarboxylic acids result from assembly of one-dimensional chains consisting of infinite carboxyl dimers (Figure 1).[3] The conformational differences between these acids are illustrated in the overlay plot in Figure 2. The structures may be understood as a trade-off between two competing driving forces: dispersive attractions between the $n$-alkyl chains and O⋯O repulsions between the carboxyl groups.[4] The former tend to align the chains and bring them closer together; the latter tend to slide the chains apart. The even acids adopt an offset arrangement along their length and avoid the O⋯O repulsions even as they retain an all-staggered sawtooth molecular conformation. The odd acids are dimorphic ($\alpha$ and $\beta$); the present study is based on the stable $\beta$-form of the acids.[5] Unlike the even acids which have a parallelogram shape in section, the odd acids have a trapezium shape. This prohibits the lateral offset arrangement seen in the even acids. The only way to maintain close packing of infinite chains of these trapezium-shaped molecules, and also avoid the repulsive O⋯O contacts, is for the molecules to adopt twisted molecular conformations. This leads to severe torsional strain in the odd acids, especially at smaller $n$. Thalladi et al. posited that it is this strained geometry in the odd acids, rather than issues related to close-packing, that results in their lower $T_m$.[3] However, this hypothesis was not ascertained experimentally; the strain in the observed molecular geometry in the odd acids was verified via computational studies (average energy difference is 2.4 kJ mol$^{-1}$).

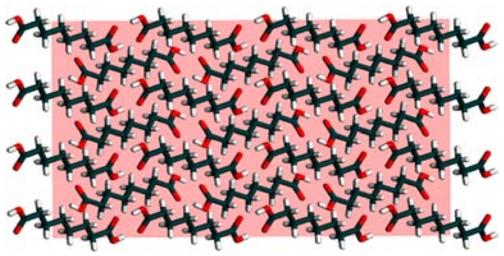

**Figure 1.** Crystal structure of suberic acid ($n = 6$) as a typical example. Notice the infinite hydrogen-bonded chains. The view shows a molecular layer looking down [100], the nanoindentation direction. The plane of the carboxylic groups is approximately 130° to this direction for all the even acids.

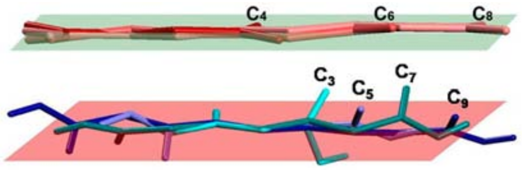

**Figure 2.** Deviation of diacid molecules from the mean plane. For even acids (red) the mean plane was calculated on the basis of the carboxyl group and the first two carbon atoms of the aliphatic chain. For odd acids (blue) the mean plane was calculated on the basis of the central portions of the aliphatic chains.

Nanoindentation is a technique with which the mechanical properties of small volumes of materials can be measured with high precision. It has recently been applied to study the mechanical response of molecular crystals, which are typically available only in small sizes.[6] In addition to the fact that these properties are of importance, especially in the handling of bulk materials in the pharmaceutical industry, one can uncover features associated with interaction anisotropy,[7] solid-state

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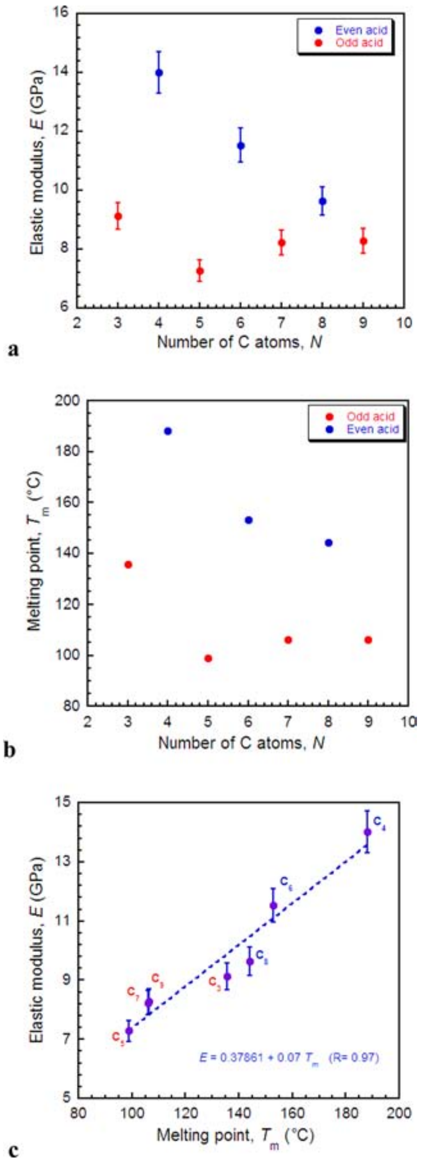

**Figure 3.** Variation of (a) $E$ and (b) $T_m$ with $N$ in $\alpha,\omega$-alkanedicarboxylic acids. (c) Linear correlation between $E$ and $T_m$.

phase transformations,[8] and molecular migration under stress[9] by employing this technique, allowing in turn new insights into the structural features of molecular crystals. In this study, we utilized nanoindentation to measure $E$ of the major face of carefully grown single crystals of the dicarboxylic acids $HO_2C(CH_2)_nCO_2H$ ($1 \leq n \leq 7$) (Figure 1). $E$ is an intrinsic property of a material and is determined, as is $T_m$, by the underlying crystal structure, which includes the intermolecular interactions and molecular arrangements. For example, it is well known that for inorganic materials (metals and ceramics) a higher $T_m$ of a material is associated with a higher $E$.[10] Therefore, our primary interest was to look for any possible relationship between $T_m$ of odd−even alternations in the diacids and their $E$. For evaluating $E$, a nanoindenter (Triboindenter of Hysitron, Minneapolis, MN) with a three-sided pyramidal Berkovich diamond tip (end radius ∼100 nm) and in situ imaging capability was employed. Since single crystals tend to be anisotropic, indentations were performed such that the loading axis is always normal to the major face (100), which is equivalent in all the different crystals examined (Figure 1). Crystal surfaces were imaged prior to indentation using the same indenter tip to identify flat regions that were probed. The loading and unloading rates were maintained at 0.6 mN/s with a hold time of 30 s at the peak load of 6 mN. The resulting load vs depth of penetration curves were analyzed by employing the standard Oliver−Pharr method[11] to extract $E$. Further experimental details are provided in the Supporting Information (SI).

Figure 3a shows the variation of the measured $E$ with the number of C atoms, $N$ (where $N = n + 2$). Several points are noteworthy. (i) $E$ for even acids is much higher than those observed in odd acids. (ii) For the even acids $E$ decreases markedly with increasing $N$. (iii) The divergence between the $E$ for odd and even acids is large at smaller $N$. For example, $E$ of succinic acid ($N = 4$) is nearly twice that measured for glutaric acid ($N = 5$). As $N$ increases, the divergence decreases and an extrapolation indicates that there might not be much difference in the $E$ values of odd and even acids for $N \geq 10$. These trends in $E$ vs $N$ are remarkably similar to those observed for $T_m$ vs $N$, which are displayed in Figure 3b. To further ascertain the existence of a one-to-one correspondence between $E$ and $T_m$, they are cross-plotted in Figure 3c. An excellent linear fit between $E$ and $T_m$ confirms that both of them depend on the same structural factors.

Having established a direct correlation between $E$ and $T_m$, we discuss below the possible structural origins for the observed trends in $E$ with $N$. As mentioned earlier, $E$ of a material is determined by its crystal structure and intramolecular bonding characteristics. Thalladi et al.[3] attempted to correlate $T_m$ with the density of the crystals, $\rho$, which generally depends on the close packing of molecules within the crystal. The absence of a correlation between $T_m$ and $\rho$, led them to conclude that the observed alternation in $T_m$ is due to "a factor other than the closest packing". Variation of $\rho$ with $N$, displayed in Figure 4, shows a continuous reduction in $\rho$ with $N$, which is a consequence of the increase in the chain length with $N$. The trends in the specific modulus ($E/\rho$) vs $N$ (Figure 4) are similar to those seen in Figure 3a. It is worth noting here that, in general, within any structural family and all other things being equal, the denser the solid, the higher will be $E$.[12] However, such an expectation is found to be true here only for the even acids whereas no such correlation could be found for the odd acids. Thus, our experimental observations on $E$ vs $N$ further validate the surmise of Thalladi et al.[3] that the even−odd alternation in $T_m$ is not due to variations in close packing.

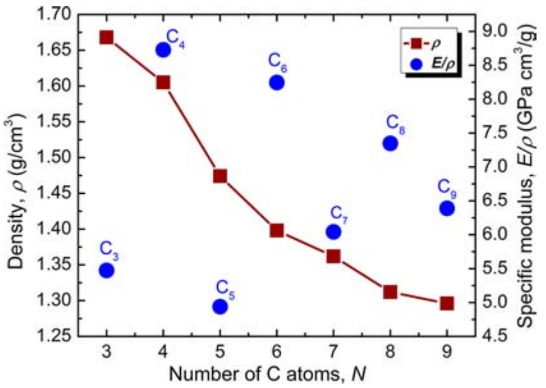

**Figure 4.** For $\alpha,\omega$-alkanedicarboxylic acids, $E/\rho$ vs $N$ and variation in $\rho$ and $E$ with $N$.

We now turn our attention to intramolecular factors. On the basis of computational results, Thalladi et al.[3] hypothesized that the high-energy molecular conformation in the odd acids could be the reason for their low $T_{\mathrm{m}}$. In terms of mechanical behavior such conformations in fact make it easier for stress induced rearrangement, which consequently results in a lower $E$ than in related structures with stable intramolecular geometries. For higher $N$, where the alkyl chains are sufficiently long and inherently more flexible, the destabilizing effect of the high-energy molecular conformations is more or less compensated by the stabilizing intermolecular interactions. It is to be further noted that the orientations of the molecular layers of the even members are around 130° to the indentation direction (Figure 1). This allows for the compression of the two-dimensional layers through weak nondirectional dispersion forces existing in the interlayer region. For the odd acids, the oblique orientation of the layers (~145° to the indenter) provides the layers with an energetically feasible mechanism to deform relatively easily.[9a] This is the reason, we believe, for the lower $E$ of the odd acids.

In the diacids studied here an inverse relationship exists between the magnitude of layer separation and $E$ (see SI) mostly for the even acids (Figure S10). Succinic acid ($N = 4$) with the least interlayer separation (3.27 Å) accounts for the largest $E$ (14.01 GPa) in the series. Interestingly the layer separation in diacids also exhibits odd−even alternation with the separation diminishing with increasing chain length (Figure S8). In the higher members the attractive van der Waals interactions in the interlayer region[13] constitute a major contributing factor in reducing the layer separation, and also play a significant role in determining the observed elastic response. Hirshfeld surface analysis shows ~237% enhancement of the dispersive H···H contacts in the series ($3 \leq N \leq 9$; see the SI). As mentioned above, the layers in the even acids are around 130° to the indentation direction. The measured elastic response therefore contains contributions from the stiff carboxylic acid O−H···O dimers. Hence, a higher $E$ is measured in the even acids. In the odd acids, however, the oblique layer orientation (~145°) results in a relatively smaller contribution from the acid dimers to the mechanical response, since the indenter mainly experiences the response from the weak nondirectional dispersion forces. Also there is a substantial decrease (~89%) in the contribution of O−H···O hydrogen bonds to the total available interactions in the higher members. These subtle variations in the interaction characteristics act as significant contributing elements to the observed $E$ alternations in the diacids studied here.

The parallelogram and trapezium model proposed by Thalladi et al.[3] to represent columnar and lateral arrangements of the acid molecules, and also invoked by Bond in his study of $n$-alkanemonocarboxylic acids[14] (Figure 5), can be used to further rationalize the observed mechanical response. The even members inherently possess relatively longer O···O contacts. The lateral movement of the layers, induced by the stress applied during indentation, leads to structures with still longer O···O contacts. Being at equilibrium separation distance, a further increase in O···O contacts is not helpful from the crystal packing point of view. The applied stress only pushes the intermolecular energy up into the attractive regime of the potential energy curve and is mildly disadvantageous. However, when stress is applied to the odd acids, the lateral movement induced by the applied stress pushes the molecules up the repulsive hill and is strongly disfavored. This compels the layer to slide away in the most energetically feasible direction.

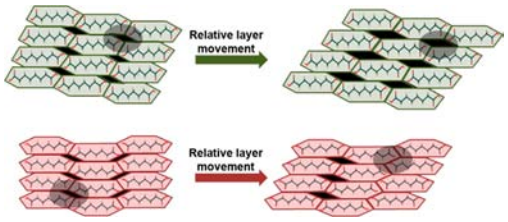

**Figure 5.** Schematic representation of the relative layer movement in even (light green) and odd (pink) acids according to the parallelogram and trapezium model.

At a fundamental level, the melting temperature $T_{\mathrm{m}}$ depends on enthalpic and entropic factors.[15] Within a family of chemically related substances, the entropic factors may be reasonably assumed to be constant,[16] allowing $T_{\mathrm{m}}$ to depend on enthalpy, which includes the crystal and molecular energy components. A higher $T_{\mathrm{m}}$ is associated with efficient three-dimensional close packing and higher density. A crystal with a higher $E$ has a similarly larger set of restoring forces between molecules that may be measured with nanoindentation. The even diacids have a crystal packing that is dominated by alkyl chain close packing and the melting points and $E$ values are correspondingly high. In the odd acids, the packing follows from a high-energy strained conformation. Relief of this strain energy is provided by melting or by mechanical flexing. This accounts for their anomalously low $T_{\mathrm{m}}$ and $E$ values.

In summary, systematic measurements of $E$ of dicarboxylic acids as a function of increasing aliphatic chains by employing nanoindentation reveal that $E$ varies in exactly the same manner as $T_{\mathrm{m}}$. This one-to-one correspondence suggests that the same factors—strained molecular conformations in odd acids and a trade-off between attractive dispersive forces and O···O repulsions—govern both $E$ and $T_{\mathrm{m}}$. Our results are consistent with the strained molecular conformation hypothesis for the odd−even $T_{\mathrm{m}}$ alternations put forth by Thalladi et al.[3] These results are of general interest because they show that nanoindentation may be used as a direct measure of molecular and crystal energies in molecular crystals. Ongoing studies, including further computational work, are in progress.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental details and supplementary figures, graphs, and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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