COMMUNICATION

Computer simulations to calculate accurate molecular properties: are the widely reported densities of coumarin and indole erroneous?

Prem K. C. Paul,*[a] Stuart Fraser[a] and David Rigby[b]

[a] *Unilever Research, Portsunlight Laboratory, Wirral, UK CH63 3JW*
[b] *Accelrys Inc., 9685 Scranton Road, San Diego 92121, CA, USA*

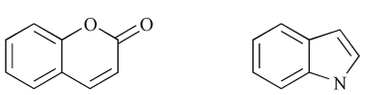
Received (in Cambridge, UK) 20th November 2001, Accepted 12th December 2001
First published as an Advance Article on the web 2nd January 2002

Molecular dynamics simulations on coumarin and indole indicate that their widely reported densities are incorrect and this was vindicated by subsequent measurements.

Our recent research suggests a significant error in the widely reported† density of coumarin, and a slightly smaller discrepancy for indole.

In an effort to calculate various bulk properties of molecules, and to test the validity of force fields, molecular dynamics simulations were performed on a series of small organic molecules. The simulations were done under the NPT protocol where the number of particles (N), the pressure (P) and temperature (T) are kept constant, using the pressure control algorithm developed by Berendsen and coworkers,[1] and applying temperature control using the stochastic collision approach of Andersen and coworkers.[2,3] This enables the simulated system to 'find' its own density and provides an excellent benchmark for testing the validity of the simulations and the force field. The main objective here is to compare the density obtained from the simulations with the reported values. The force field used was COMPASS,[4] a so-called 'class II' force field, which uses high level calculations to determine valence parameters, combined with experimental condensed phase PVT and cohesive property data to determine nonbond parameters, and which includes coverage for a wide variety of organic systems.

While most of the simulations‡ using COMPASS[4,5] and the NPT protocol reproduce correctly the reported densities of the molecules, the results of molecular dynamics simulations for coumarin and indole (Fig. 1), showed that the densities of



Coumarin Indole

Fig. 1

the supercooled equilibrated systems§ at 298 K were 1.222 and 1.108 g cm^{-3}, and differed from the reported values of 0.935 g cm^{-3} (coumarin) and 1.22 g cm^{-3} (indole) by about 30% and 10% respectively.

Therefore a series of investigative density calculations using molecular dynamics simulations were performed for coumarin and indole from 473 K down to 273 K and the main results are captured in the upper curves (a) and (b) of Fig. 2. From this a linear model linking the density ρ to T can be made. Clearly the simulation data in Fig. 2 suggest predicted densities of coumarin and indole quite different from the reported values, especially for coumarin.

In order to further establish the validity of the simulations and to investigate this observation in more detail, density calculations were performed on a series of systems analogous to coumarin and indole, and on simple molecules with similar basic chemical features. The structures are as follows: pyran-2(2*H*)-one (coumarin without the attached aromatic ring), coumaran-2-one (has five-membered lactone ring with no C=C

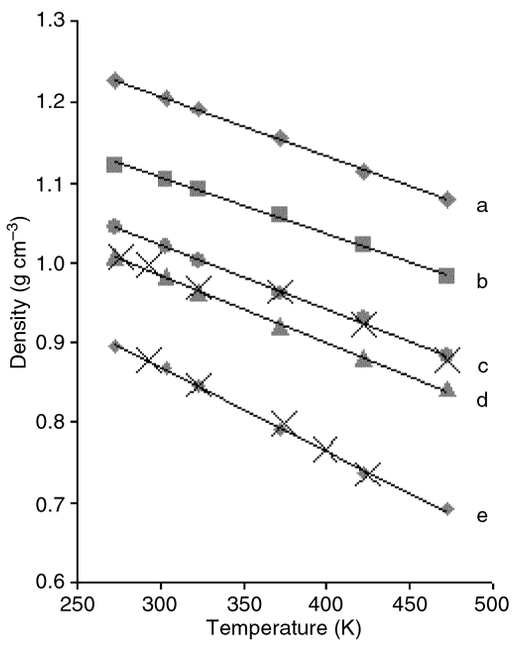


Fig. 2 Calculated densities at various temperatures (K) of coumarin (a) and indole (b). For comparison, the calculated and experimental densities of naphthalene (c), indene (d), and benzene (e) are also given. Calculated densities are represented by filled symbols, while the symbol X represents experimental values.[6]

bonds), coumaran (as coumaran-2-one but with the –C=O replaced by CH_2), hydrocoumarin (coumarin with C–C instead of C=C in lactone ring), indene (a CH_2 in place of the NH in indole), tetrahydrofuran, naphthalene and benzene.

Results of these calculations are listed in Table 1, where they are compared with the limited data available in the literature. In the case of the common compounds naphthalene, indene and benzene, for which density data are widely available at a variety of temperatures,[6] calculated and experimental data from 273–473 K are illustrated by the lower curves c, d and e in Fig. 2. It is clear from Table 1 that for systems analogous to coumarin and indole, the densities obtained from molecular dynamics simulations match the literature values extremely well. The difference in most of the densities is less than 1%. This conclusion applies similarly to the data plotted in Fig. 2 over quite extended temperature ranges. Moreover, for most temperatures of practical interest it is again observed that the data can be satisfactorily fitted by a linear function of temperature as seen by the trend lines in the figure.

The calculations reported in Table 1 and Fig. 2 further reinforce the conclusions that the widely reported values for the density of coumarin and indole are simply incorrect.

In the laboratory, an initial measurement of the density of solid coumarin yielded a value of 1.28 g cm^{-3} at 25 °C. This supported our opinion that the reported value might well be

DOI: 10.1039/b110649j

Table 1 Densities from simulations of analogous molecules

Molecule	T [a]/K	Mp [b]	Density [c] MD	Density [d] Literature	
Pyran-2(2*H*)-one	293	281	1.182	1.197	Aldrich
Coumaran-2-one	287	323	1.197	1.224	CRC
Coumaran	298	252	1.058	1.058	CRC
Hydrocoumarin	291	298	1.164	1.169	CRC
Indene	293	271	0.9975	0.996	CRC
Tetrahydrofuran	293	165	0.8627	0.889	CRC
Naphthalene	373	354	0.9635	0.9625	CRC
Benzene	293	279	0.8804	0.879	CRC

[a] Temperature at which the literature densities are reported. [b] The approximate melting points reported in the literature. [c] Density (g cm^{-3}) from molecular dynamics using linear fit with temperature. [d] Density (g cm^{-3}) reported in Aldrich or CRC Handbook.

Table 2 Densities of coumarin and indole

Molecule	Measured density/g cm^{-3}	Density from simulations/g cm^{-3}	
Coumarin	1.237 at 75 °C	1.172 at 75 °C	1.222 at 25 °C
Indole	1.086 at 60 °C	1.083 at 60 °C	1.108 at 25 °C

inaccurate. To achieve a more accurate value, the densities of liquid coumarin and liquid indole were measured using standardised techniques¶ and these are given in Table 2. For comparison the densities obtained from simulations are also included. The table shows that the measured densities of coumarin and indole compare well with the predicted densities. The differences between the newly measured and simulated values are 5.2% for coumarin and 0.3% for indole.

In conclusion, given proper force fields, it is possible to reproduce to a high level of accuracy, often only rivaled by good quality experiments, the bulk properties of materials, using computer simulations. Furthermore we would like to publicise a better value for the densities of coumarin and indole.

Notes and references

† By this we mean the values found in the most common and widely used resources of chemical data; like the CRC Handbook, Aldrich catalogue and various websites on the Internet. For coumarin and indole, a thorough search of the literature, especially that published in the early part of the 20th century, also gives other values. For some reason only the incorrect values have been propagated in the common and widely used resources.

‡ All simulations were performed using the Discover simulation program (Discover User Guide, Accelrys Inc., 1994–2001). The NPT (P = 0.0) protocol was used with sharp group-based cut-offs set at 9.5 Angstroms for all nonbonds. Pressure and energy tail corrections were added. All structures were double-checked to ensure freedom from pathological defects such as catenations. 40–50 pico-second (ps) of equilibration was performed prior to the density production stages of duration 100 ps. Statistical uncertainties in computed densities for 100 ps dynamics runs are typically ± 0.3–0.5%.

§ Since coumarin and indole are solids at room temperature, the density values from simulations actually correspond to the density of super cooled liquids at 298 K

¶ Densities were measured, using a pyknometer to a precision of ± 0.001, by SGS Redwood Services, Rossmore Business Park, Ellesmere Port, Cheshire, UK CH65 3EN using Institute of Petroleum methods, reference IP 189-190/98.

1 H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola and J. R. Haak, *J. Chem. Phys.*, 1984, **81**, 3684–3690.
2 H. C. Andersen, *J. Chem. Phys.*, 1980, **72**, 2384–2393.
3 T. A. Andrea, W. C. Swope and H. C. Andersen, *J. Chem. Phys.*, 1983, **79**, 4576.
4 H. Sun, *J. Phys. Chem. B*, 1998, **102**, 7338–7364.
5 D. Rigby, H. Sun and B. E. Eichinger, *Polym. Int.*, 1997, **44**, 311–330.
6 C. F. Beaton and F. G. Hewitt, *Physical Property Data for the Design Engineer*, Hemisphere Publishing, New York, 1989.