Mendeleev Communications

Mendeleev Commun., 2026, **36**, 69–71

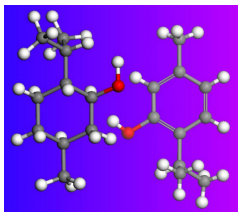
Peculiarities of molecular interactions in the L-menthol–thymol system

Andrey V. Petrov,* Georgii Kh. Misikov and Alexander M. Toikka

Institute of Chemistry, St. Petersburg State University, 199034 St. Petersburg, Russian Federation.
E-mail: a.petrov@spbu.ru

DOI: 10.71267/mencom.7853

Molecular interactions in the L-menthol–thymol system were simulated using classical molecular dynamics. The results were compared with experimental and theoretical published data regarding this system. It was shown that the molecular dynamics simulation data can be an important additional criterion for understanding the nature of molecular interactions in this system.



Keywords: L-menthol, thymol, molecular dynamics, intermolecular interactions, deep eutectic solvents.

Through the last decades significant attention has been paid to the exploration of physicochemical properties of the L-menthol–thymol system. This is due to the fact that this system belongs to the relatively new class (‘type V’) of the deep eutectic solvents (DESs), in which, unlike other types, the interaction between components does not have an explicit ionic nature. Note that the existing DES classification seems to be not quite correct to us, because instead of the main difference between DESs and ‘ordinary’ eutectic systems, *i.e.*, a relatively low temperature of the eutectic point (‘eutectic depth’), the nature of the interaction of components (formation of hydrogen bonds, donor–acceptor interactions, *etc.*) is taken into account. At the same time, DESs based on L-menthol and thymol and other type V DESs can be defined as a separate class from the practical point of view: most of these DESs are formed by natural components or products and have a certain medical and other applications. All these circumstances determine the interest and necessity of a detailed description of the systems forming these DESs. In the present report, the peculiarities in the behavior of the L-menthol–thymol system, which can be attributed to one of the most popular DESs of non-ionic type, as well as natural DESs (NaDESs), are considered.

It is well-known that a binary eutectic is a three-phase system including a liquid phase and two solid solutions (or crystals of two pure components in the case of a simple eutectic). Unfortunately, modern works in the field of DESs hardly ever include the characterization of solid phases, although their data are the necessary characteristics of phase diagrams and, consequently, thermodynamic properties. At the same time, the Schroeder–van Laar equation in the form assuming the absence of solid solutions is often used to evaluate deviations from ideality in the liquid phase, which reflect molecular interactions at the macroscopic level:

$$\ln a_i = \frac{\Delta_f H_i}{R}\left(\frac{1}{T_{m,i}} - \frac{1}{T}\right),$$

where a_i is the activity of the component i in the liquid phase, $\Delta_f H_i$ is the enthalpy of fusion for the pure component i, $T_{m,i}$ is the melting point of the pure component i, T is the thermodynamic temperature, and R is the gas constant. Such a simplified approach, apparently, cannot be considered reliable, even when taking into account the temperature dependence of the fusion enthalpy (according to the well-known Kirchhoff formula). Moreover, some authors,[1] using, in fact, similar data on activities, point out that at small deviations from ideality, ‘deep eutectics’ cannot be considered at all. This seems to be controversial, since even according to the Schroeder–van Laar equation, the values of activity coefficients are not the only parameters that determine the eutectic temperature.

For the L-menthol–thymol system, there is some information about the equilibrium with solid phases, although rather contradictory.[1–4] The direct experimental data[1–6] have been obtained by thermal analysis methods (DSC). The formation of co-crystals in the middle range of concentration has been noted, which is associated with the appearance of two eutectic points on the phase diagram.[4] The interactions in the liquid solution have been studied in detail by NMR, X-ray, and Raman spectroscopy methods with the application of molecular dynamics (MD) simulation focusing on the formation of hydrogen bonds and the temperature dependence.[3] The same dependence has also been investigated by means of MD.[7] In addition, such properties as activities and liquid–vapour equilibrium parameters, *i.e.* macroscopic characteristics of the interaction of components in the solution, have been discussed in a number of papers.[3,4] Note that in most of these and other works, such as ref. 8, the presence of an eutectic on the phase diagram of the L-menthol–thymol system is associated with the formation of hydrogen bonds, which, of course, affects the thermodynamic parameters, but cannot serve as a necessary criterion of DESs. Nevertheless, in modern works, the definition of a DES, as it was mentioned above, is based on the presence of hydrogen bond donors and acceptors in the system rather than on the type of the phase diagram. Recent works, including the analysis of type V DES properties, and among others, the L-menthol–thymol system, reflect the contradictory views on the formal definition and classification of DESs.[9,10]

Thus, so far, a significant amount of experimental data on the L-menthol–thymol system has been obtained. At the same time, certain experimental difficulties did not permit obtaining completely reliable results.[4] This is mainly due to the problems with obtaining solid phase samples, primarily the crystallization rate.[11] Slow crystallization, which provides equilibrium data, in

the composition range corresponding to the low concentrations of thymol ($x_{thymol} < 0.67$), as noted in ref. 4, was not possible due to the high viscosity of the melts at these concentrations. Therefore, the authors had to perform X-ray studies using samples obtained by rapid crystallization, which could lead to certain errors in the results.

In general, the most comprehensive diagrams given, among others, in refs. 1–5 include both experimental and calculated results. Therefore, despite the relatively intensive investigation of this system, additional studies should be carried out, primarily to evaluate the features of molecular interactions and their dependence on the composition. In this communication, we present the results of MD analysis of the L-menthol–thymol system, complementing the characteristics of structural and physicochemical parameters obtained earlier by other methods. We should note the general accordance and certain differences between our results and those obtained in other works using MD simulation,[3,7,12] where the temperature dependences of the modeling results were considered, while the concentration dependences were only partially taken into account.

In this work, the molecular interactions between thymol and L-menthol molecules were evaluated at T = 343 K, when the system is definitely liquid. Under these conditions, molecules can move and take positions relative to each other at optimal spatial and energetic factors. This enables quantitative tracking of the most likely mutual arrangement configurations using radial distribution functions. With this assessment of the mutual arrangement of thymol and L-menthol molecules, conclusions can be drawn about the preferential molecular interactions based on non-valent interatomic bonds, depending on the composition of the system.

At the first stage, the electronic structures of thymol and L-menthol molecules were calculated using the DFT method in the DMol^3 program and the COSMO model from the Materials Studio software package.[13] The data on charges on atoms obtained by the Mulliken scheme were necessary for subsequent calculations of the electrostatic interactions between molecules. Calculations by the classical MD simulation were also carried out using the Materials Studio package (FORCITE module). Short-range interactions were calculated using the Universal Force Field.[13] An isobaric–isothermal NPT ensemble was used at 343 K (Nose thermostat) and a pressure of 0.00 GPa (Berendsen barostat) with a total system calculation time of 1 ns and a step of 1 fs. Calculation cells with periodic boundary conditions were constructed with a total number of thymol and L-menthol molecules equal to 100. The following molar fractions of thymol were chosen: 0.01, 0.10, 0.20, 0.33, 0.40, 0.45, 0.50, 0.60, 0.70, 0.80, 0.90, and 0.99. The radial distribution functions (RDFs) between oxygen atoms of thymol and L-menthol served as a parameter of the observed molecular interaction, and the evaluation criteria were the distances of the first maxima, reflecting the closest mutual arrangement, and their intensities as a quantitative measure of the number of interacting molecules.

Figure 1 shows an example of the RDFs obtained for the L-menthol–thymol mixture (x_{thymol} = 0.5) at 343 K. The results of calculations, namely, the values of the RDF, have shown that there are no significant changes in the values of distances between the molecules of the components in the full concentration range of the L-menthol–thymol system. The same conclusions (similar values) can be drawn regarding the peak intensities and coordination numbers. The absence of the dependence of r_{Max1} or r_{Min1} on the composition indirectly indicates a really weak molecular interactions in the system.

Figure 2 shows the selected values of the indicated parameters (distances between molecules) together with the liquidus curves according to ref. 4. For the better illustrative clarity, we present a

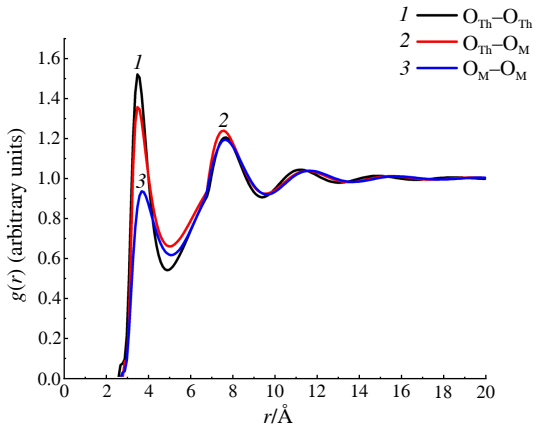


Figure 1 Example of O–O RDFs [$g(r)$ – probability density] for the equimolar mixture of L-menthol and thymol at 343 K: (*1*) thymol–thymol (black line), (*2*) thymol–L-menthol (red line), (*3*) L-menthol–L-menthol (blue line).

comparison only with the calculated data.[4] Note that the MD simulation was performed for a constant temperature, 343 K, although, as pointed out in ref. 3, the values of activity coefficients depend significantly on temperature. Nevertheless, it can be assumed that the type of the dependence of intermolecular distances on the concentration will not change significantly within a small temperature range, that is, this concentration dependence will remain insignificant at the temperature under consideration. This is also consistent with the data on RDFs at different temperatures obtained in refs. 7 and 12 for the system under consideration.

The obtained result additionally confirms the data,[4] which indicate the possibility to describe the liquidus curves in the L-menthol–thymol system neglecting the non-ideality of the liquid phase.

Thus, the conducted MD simulation of the L-menthol–thymol system made it possible to evaluate some characteristics of molecular interactions that complement the current experimental and calculated data. In particular, insignificant changes in the intermolecular bonds with the composition allow the application of thermodynamic modeling methods under the assumption that the non-ideality of the liquid phase can be neglected. This conclusion is rather specific, since we limit ourselves to the consideration of one system, where the experimental data require additional clarification. In general, regarding the importance of continuing the exploration of this system as one of the most demanded and promising representatives of non-ionic DESs (type V), we believe that the above MD simulation results can be

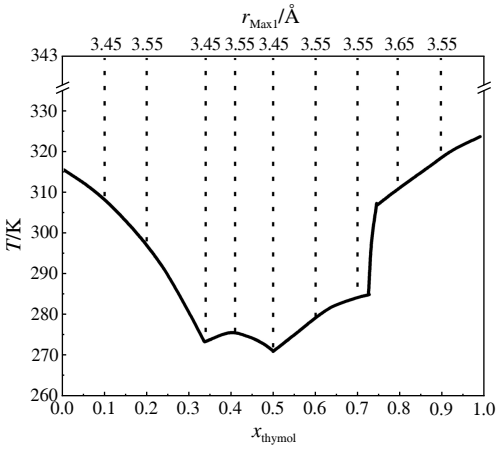


Figure 2 Values of intermolecular distances (r) determined from the data on the first maximum of the RDF of the L-menthol–thymol system at 343 K for the corresponding concentrations from the liquidus curves.[4]

useful for the development of fundamental ideas about the physicochemical features of organic eutectics and DES components.[14] In particular, it is desirable to continue these investigation using *ab initio* MD simulation.[15,16]

This work was supported by the Russian Science Foundation (grant no. 25-23-00021). The research was carried out using the computing resources of the Resource Center 'Computer Center of St. Petersburg State University' (http://cc.spbu.ru).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7853.

References

1 M. A. R. Martins, E. A. Crespo, P. V. A. Pontes, L. P. Silva, M. Bülow, G. J. Maximo, E. A. C. Batista, C. Held, S. P. Pinho and J. A. P. Coutinho, *ACS Sustainable Chem. Eng.*, 2018, **6**, 8836; https://doi.org/10.1021/acssuschemeng.8b01203.

2 D. O. Abranches, M. A. R. Martins, L. P. Silva, N. Schaeffer, S. P. Pinho and J. A. P. Coutinho, *Chem. Commun.*, 2019, **55**, 10253; https://doi.org/10.1039/C9CC04846D.

3 N. Schaeffer, D. O. Abranches, L. P. Silva, M. A. R. Martins, P. J. Carvalho, O. Russina, A. Triolo, L. Paccou, Y. Guinet, A. Hedoux and J. A. P. Coutinho, *ACS Sustainable Chem. Eng.*, 2021, **9**, 2203; https://doi.org/10.1021/acssuschemeng.0c07874.

4 A. Alhadid, C. Jandl, L. Mokrushina and M. Minceva, *Cryst. Growth Des.*, 2021, **21**, 6083; https://doi.org/10.1021/acs.cgd.1c00306.

5 A. Alhadid, L. Mokrushina and M. Minceva, *J. Mol. Liq.*, 2020, **314**, 113667; https://doi.org/10.1016/j.molliq.2020.113667.

6 F. Bergua, M. Castro, C. Lafuente and M. Artal, *J. Mol. Liq.*, 2022, **368**, **Part B**, 120789; https://doi.org/10.1016/j.molliq.2022.120789.

7 D. K. Panda and B. L. Bhargava, *J. Mol. Graphics Modell.*, 2022, **113**, 108152; https://doi.org/10.1016/j.jmgm.2022.108152.

8 C. D'Hondt and D. Morineau, *J. Mol. Liq.*, 2022, **365**, 120145; https://doi.org/10.1016/j.molliq.2022.120145.

9 A. van den Bruinhorst and M. Costa Gomes, *Curr. Opin. Green Sustainable Chem.*, 2022, **37**, 100659; https://doi.org/10.1016/j.cogsc.2022.100659.

10 D. O. Abranches and J. A. P. Coutinho, *Curr. Opin. Green Sustainable Chem.*, 2022, **35**, 100612; https://doi.org/10.1016/j.cogsc.2022.100612.

11 I. A. Solonina, M. N. Rodnikova, M. R. Kiselev, A. V. Khoroshilov and S. V. Makaev, *Mendeleev Commun.*, 2019, **29**, 693; https://doi.org/10.1016/j.mencom.2019.11.031.

12 C. Benito, R. Alcalde, M. Atilhan and S. Aparicio, *J. Mol. Liq.*, 2023, **376**, 121398; https://doi.org/10.1016/j.molliq.2023.121398.

13 *BIOVIA Materials Studio*, ver. 7, Dassault Systèmes; https://www.3ds.com/products/biovia/materials-studio.

14 A. K. Rappé, C. J. Casewit, K. S. Colwell, W. A. Goddard, III and W. M. Skiff, *J. Am. Chem. Soc.*, 1992, **114**, 10024; https://doi.org/10.1021/ja00051a040.

15 M. A. Krestyaninov and A. V. Kustov, *Mendeleev Commun.*, 2020, **30**, 522; https://doi.org/10.1016/j.mencom.2020.07.040.

16 A. M. Toikka and A. V. Petrov, *Mendeleev Commun.*, 2023, **33**, 413; https://doi.org/10.1016/j.mencom.2023.04.036.

17 A. M. Toikka and A. V. Petrov, *Mendeleev Commun.*, 2024, **34**, 134; https://doi.org/10.1016/j.mencom.2024.01.041.

Received: 20th June 2025; Com. 25/7853