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Re: Ph.D. Thesis of RNDr. Michal Kolář
“Molecular modelling in drug development”

The cumulative thesis presented by Mr Kolář includes an introductory section of five chapters and a total of seven of his publications, the last of which is written in Czech, so that I cannot comment on it. The seven publications have appeared (or have been submitted to) high-quality journals, usually those of the American Chemical Society.

Chapter 1, the Introduction, provides some background to the development and use of computer-aided drug design (CADD), especially in the context of the pharmaceutical industry. The section entitled Historical Context is refreshing because it regards the pharmaceutical industry critically and does not resort to the usual “crisis” review articles, which paint a very one-sided view of pharmaceutical research. Although short, the sections in this chapter are well chosen and include the necessary background without excessive information.

Chapter 2, which introduces molecular dynamics, is also written very economically and effectively. Mr Kolář perhaps missed an opportunity here to review current practice somewhat more critically and to question some techniques and point out alternatives.

Chapter 3 discusses conformational ensembles. This is an almost impossible task in such an introduction and Mr Kolář uses examples from his own work to
illustrate the main principles.

The final “real” chapter of the Introduction before the short Summary and Outlook (chapter 5) describes a subject close to my heart; halogen bonding. Again, this has become a very large and sometimes controversial area in the past five years of intense interest. Mr Kolář presents the most important facts without going into the interpretational controversies and then goes on to introduce his own work designed to incorporate halogen bonding into a classical force field.

There are some minor typographical errors in these five chapters that I have listed in the Appendix to this report.

The first of the attached papers (J. Phys. Chem. B, 2010, 114, 13446) describes Mr Kolář’s work on the configurational entropy change that occurs when an intercalator complexes with DNA. This is an ambitious undertaking that was attacked using MD simulations and using the quasi-harmonic approximation, which should be reliable as long as significant allosteric rearrangements do not occur. The results reveal an unexpected increase in DNA flexibility when the intercalator binds.

The second paper (J. Phys. Chem. B, 2011, 115, 4718) combines molecular dynamics, the PM6-DH2 semiempirical Hamiltonian and the COSMO implicit solvation model to investigate the conformational flexibility and desolvation energies of a series of nine HIV-1 protease inhibitors. This work uses non-standard techniques refreshingly to shed new light on a well-studied system.

A major, for me unsolved problem in CADD is the representation of the solvent (usually water). A myriad of implicit water models is available and there is no obvious correlation between their physical correctness and their accuracy. The third paper presented in this thesis (submitted to J. Phys. Chem. B) investigates the performance of six such models, three classical and three quantum-mechanical. The conclusions have benchmark character and are likely to be highly cited. Again, Mr Kolář uses MD simulations in order to investigate a conformational ensemble.

The remaining three papers in English are concerned with halogen bonding in drug design. It is remarkable that a bonding interaction remained unrecognised for so long and that not only in modelling but also in the refinement of X-ray structures the
weakly binding interaction of Lewis bases with the heavier halogens was treated as repulsive. Publication 5 (J. Chem. Theor. Comput., 2012, 8, 1325) is one of three that appeared in 2012 to modify conventional force fields to take explicit account of the $\sigma$-hole. Publication 6 (Chem. Commun., 2013, 49, 981) uses this modification to improve docking results for halogenated ligands. Finally, Publication 4 (submitted to J. Phys. Chem. A) uses dispersion-corrected density-functional theory to investigate halogen bonding and other intermolecular interactions in perhalogenated benzene crystals. The trends in enthalpies of sublimation are explained.

Mr Mr Kolář’s thesis reports an impressive body of work. It is clear that he has been involved closely in many of the major topics investigated by Prof. Hobza’s group in recent years and that he has proven himself to be a very competent computational chemist. His writing style is informative and easy to read and the thesis as a whole represents a significant achievement.

I consider this thesis to be suitable for the defense and that its quality fulfils the criteria necessary for the candidate to be awarded the Ph.D. degree.

Erlangen, 24 April 2013
Appendix:

Typographical errors in the thesis:

1. Page 15: last line of the penultimate paragraph: “Equations ?? to 2.7”
2. Page 19: line 16 “pentalty”
3. Page 31: “Figure 3.2.2” should probably be “Figure 3.3”
4. Page 32: above equation 3.8: “Figure ??”
5. Page 41: line 3 “σ-holemodels”
6. Page 43: last line of the penultimate paragraph: “Figure ??”
7. Page 59, reference 153, “σ” is missing