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Abstract

More than half a century has passed since Drs. Hansch and Fujita proposed a general approach to the formulation of QSAR in 1961. Their approach (Hansch-Fujita analysis) has provided a new perspective for chemical-biological interactions as well as a number of successes in drug discovery. Now it is time to develop a new and promising approach based on their QSAR with the aid of modern, powerful molecular calculations.

We have proposed a novel QSAR procedure called Linear Expression by Representative Energy terms (LERE)-QSAR involving molecular calculations such as an ab initio fragment molecular orbital (FMO) and QM/MM (ONIOM) ones. The first assumption made in formulating the LERE-QSAR equationis that the free-energy terms comprising the overall free-energy change (DG_{obs}) associated with complex formation are all additive ($DG_{obs} = DG_{bind} + DG_{sol} +$ DG ot hers). DG bind and DG sol are the intrinsic binding interaction free-energy of a ligand with a protein, and the solvation free-energy change associated with complex formation, respectively. DG others , the sum of free-energy terms other than representative free-energy terms, DG bind and DG sol , is assumed to be linear with that of representative free-energy terms (DG others = β (DG bind + DG sol) + const, b 0). DG sol is replaceable by its dominant polar contribution DG sol pol , and most of DG sol pol comes from the enthalpic contribution. Combining the above three equations yields the following

concise expression,

$$DG_{obs} = g\,(DE_{bind} + DG_{sol}^{pol}) + const\ [g = (1 - a)\,(1 + b)]$$

where DE_{bind} is computable using ab initio MO calculations such as FMO and ONIOM, and DG_{sol}^{pol} is with continuum solvation models such as GB (generalized Born), PB (Poisson–Boltzmann), and PCM (polarizable continuum model).

We have demonstrated that the LERE-QSAR procedure can excellently reproduce DG_{obs} associated with complex formation of a series of ligands with a protein (carbonic anhydrase, MMP, influenza and human neuraminidases).

We will also discuss newly introduced two approaches for estimating the representative energy terms; (1) hybrid estimation of PCM and GB/PB for DG_{sol}^{pol} and (2) dispersion–corrected Hartree-Fock method (HF–D) for DE_{bind}.

You can download this presentation as a PDF .