JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 353–367
Published online 17 September 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.856

Assessment of the metabolic stability of the methyl groups in heterocyclic compounds using C—H bond dissociation energies: effects of diverse aromatic groups on the stability of methyl radicals

Su-Wen Zhao, Lei Liu,* Yao Fu and Qing-Xiang Guo*

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Received 29 April 2004; revised 14 July 2004; accepted 18 July 2004

ABSTRACT: The C—H bond dissociation energies (BDEs) of the methyl groups attached to a large number of heterocyclic compounds are calculated using a carefully calibrated B3LYP method. These C—H bond dissociation energies are important for evaluating the metabolic stability of the methyl groups in heterocyclic compounds that may be used as drug candidates. It is found that the C—H BDEs of the methyl groups attached to diverse heterocycles can dramatically vary from ca 80 to ca 100 kcal mol^{-1} (1 kcal = 4.184 kJ). Therefore, the benzylic positions of different heterocycles may have remarkably different metabolic stabilities varying by $\sim 10^{12}$-fold. The heteroatoms in the aromatic rings vary the benzylic BDEs either by delocalizing the spin or by changing the charge carried by the radical center. *N*-Methyl groups have systematically higher C—H BDEs than *C*-methyl groups. NH, O and S groups have similar effects on the benzylic C—H BDEs. A methyl group at the α-position relative to the NH, O and S groups usually has a lower BDE than that at the β-position. On the other hand, the N group has a different effect on the benzylic C—H BDEs. A methyl group at the β-position relative to N has a lower C—H BDE than that at the α-position. There is a special aromatization effect associated with 1-methyl-2*H*-isoindole, 1-methylisobenzofuran, 1-methylbenzo[*c*]thiophene and related compounds. This aromatization effect dramatically decreases the benzylic C—H BDEs. Finally, an interesting QSAR model has been developed. This model not only can successfully predict the benzylic C—H BDEs of diverse heterocyclic compounds, but also can clearly and quantitatively reveal the mechanisms for the variation of the C—H BDEs. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: methyl groups; heterocyclic compounds; metabolic stability; C—H bond dissociation energy; QSAR model

INTRODUCTION

Heterocyclic compounds are widely utilized in medicinal chemistry for several reasons:[1] (1) they have a specific chemical reactivity, e.g. epoxides, aziridines and β-lactams; (2) they resemble essential metabolites and can provide false synthons in biosynthetic processes, e.g. anti-metabolites used in the treatment of cancer and viral diseases; (3) they fit biological receptors and block their normal working; (4) they provide convenient building blocks to which biologically active substituents can be attached; (5) the introduction of heterocyclic groups into drugs may affect their physical properties, e.g. the dissociation constants of sulfonamide drugs, or modify their pattern of absorption, metabolism or toxicity.

Recent advances in synthetic chemistry, especially combinatorial methodology, have increased the number of heterocyclic compounds considered as early drug candidates by several orders of magnitude.[2] However, most of the drug candidates evolved from these technologies possess inappropriate pharmacokinetic properties, such as undesirable metabolic stability, and therefore fail during pre-clinical and clinical trials. In order to make better promotion-to-development decisions, pharmaceutical researchers have learned to utilize ADMET (absorption, distribution, metabolism, excretion and toxicity) screening early in the drug discovery process to minimize undesirable properties, and allow only candidates that pass such tests to be developed further.[3] There is also increasing interest in the potential utility of computational models for the prediction of ADMET drug properties before a compound is ever synthesized.[4]

In the present study, we utilized the computational approach to study the metabolic stability of the methyl groups adjacent to aromatic rings in various heterocyclic compounds. We consider this as an important subject because methyl groups adjacent to aromatic rings are known to undergo metabolic oxidations in many cases.

**Correspondence to:* L. Liu and Q.-X. Guo, Department of Chemistry, University of Science and Technology of China, Hefei 230026, China.
E-mail: leiliu@chemist.com; qxguo@ustc.edu.cn
Contract/grant sponsor: NSFC; *Contract/grant number:* 20332020.

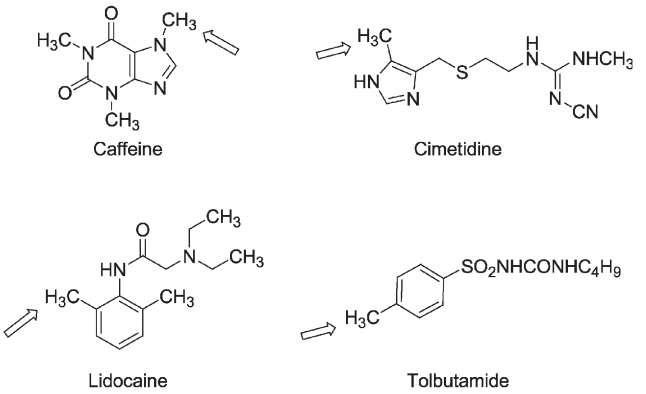


Figure 1. Experimentally confirmed methyl oxidation of common drugs

Some examples of methyl oxidation of common drugs are shown in Fig. 1.[5] These methyl oxidation reactions have been demonstrated by experiments to occur in phase I (oxidative) metabolism where cytochrome P450 is participant (Fig. 2).[6] Experiments have also established that the ease of these cytochrome P450 oxidation reactions parallels the C—H bond dissociation energies (BDEs).[7] Therefore, in order to understand the metabolic stabilities of the methyl groups in heterocyclic compounds, we first need to obtain accurate C—H BDEs.

There were two major purposes of the present study. First, we wished to obtain reliable C—H BDEs of the methyl groups in diverse heterocyclic compounds. Since there has been very little work on these BDEs in the past, we hope to provide systematic, comprehensive and high-quality data that can help pharmaceutical researchers evaluate the metabolic stability of candidate compounds.

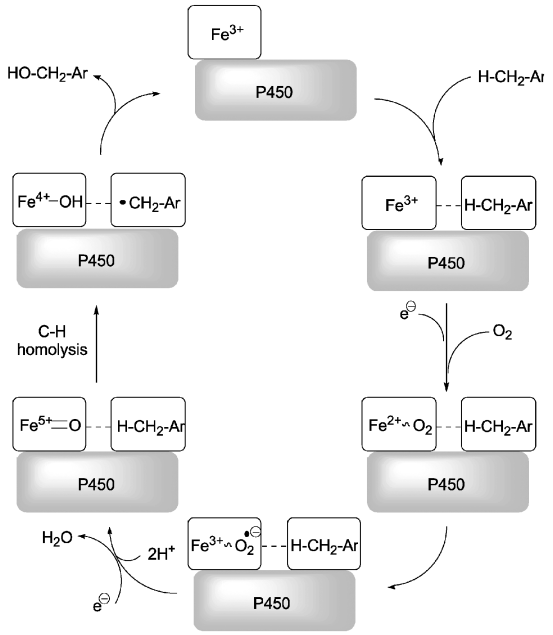


Figure 2. Proposed mechanism for the cytochrome P450-Catalyzed oxidation of the methyl groups attached to aromatic rings

Second, the structure–activity relationships (SARs) for radical systems remain a challenging subject that has not been fully elucidated.[8] Systematic data for the C—H BDEs of the methyl groups in heterocyclic compounds present a unique opportunity to study the SARs of the methyl radicals attached to diverse aromatic rings. The present work is the first in our long-term series of studies on *the applications of modern quantum chemistry methods to the chemoinformatics of biologically active molecules*.

METHOD

All the quantum chemistry calculations were performed using the Gaussian 03 program.[9] Geometry optimization was conducted using the UB3LYP/6–31G(d) method without any constraint. Each optimized structure was confirmed by frequency calculation to be the real minimum without any imaginary vibrational frequency. The enthalpy of each species was calculated using the following equation:

$$H_{298} = E + ZPE + H_{\text{trans}} + H_{\text{rot}} + H_{\text{vib}} \qquad (1)$$

where ZPE is the zero point energy and H_{trans}, H_{rot} and H_{vib} are the standard temperature correction terms calculated using equilibrium statistical mechanics with harmonic oscillator and rigid rotor approximations.

RESULTS AND DISCUSSION

BDEs of five- and six-membered ring systems

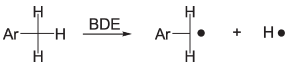
Bond dissociation energy is defined as the gas-phase enthalpy change of the following reaction at 298 K:[10]

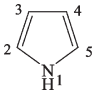
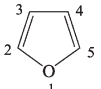
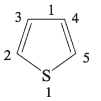
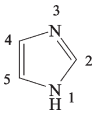
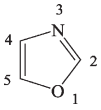
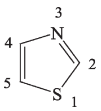
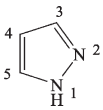
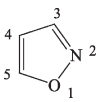
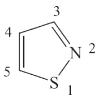
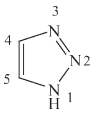
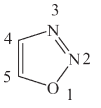
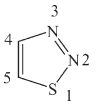
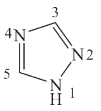
$$\text{A—B (g)} \rightarrow \text{A}^{\bullet}\text{(g)} + \text{B}^{\bullet}\text{(g)} \qquad (2)$$

We have demonstrated recently using a large number of experimental data that composite *ab initio* methods including G3, CBS-Q and G3B3 can predict reliable BDE values accurate to ca $1\,\text{kcal mol}^{-1}$ ($1\,\text{kcal} = 4.184\,\text{kJ}$).[11] We have also shown that most current density functional theory methods significantly underestimate the BDEs by 4–5 kcal mol^{-1}.[11] Here we calculate the C—H BDEs of the methyl groups attached to diverse five- and six-membered heterocycles using both the G3B3 and UB3LYP/6–311 + + G(2df,2p)//UB3LYP/6–31G(d) (abbreviated to B3LYP below) methods. The results are given in Table 1.

Very few experimental or theoretical data can be found to assess our theoretical results in Table 1. In fact, after a careful literature research we only found the benzylic C—H BDE of $PhCH_3$, which is $89.6 \pm 1.0\,\text{kcal mol}^{-1}$ according to the most recent experimental measurement.[12] G3B3 provides a prediction of $91.1\,\text{kcal mol}^{-1}$, which is $1.5\,\text{kcal mol}^{-1}$ higher than the experimental

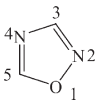
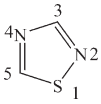
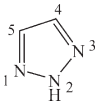
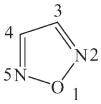
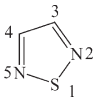
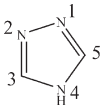
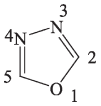
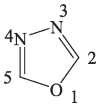
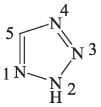
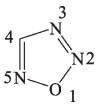
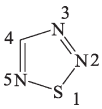
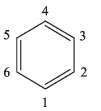
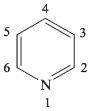
Table 1. C—H BDEs of the methyl groups attached to diverse five- and six-membered heterocycles (kcal mol^{-1})



Parent molecule	Structure	Bond	G3B3 (recommended)	B3LYP[a]	Charge (CH_3)[b]	Charge $(CH_2^{\bullet})$[c]	Spin[d]	BDE from Eqn (5)
Pyrrole		N1—CH_2—H	93.6	89.9	0.255	0.197	0.813	94.3
		C2—CH_2—H	87.2	82.9	0.031	−0.020	0.638	89.0
		C3—CH_2—H	90.2	86.7	0.033	0.015	0.740	90.9
Furan		C2—CH_2—H	87.4	82.9	0.037	0.010	0.599	89.4
		C3—CH_2—H	90.9	87.3	0.042	0.040	0.720	91.8
Thiophene		C2—CH_2—H	87.8	82.9	0.048	0.035	0.590	88.9
		C3—CH_2—H	90.5	86.8	0.046	0.052	0.700	91.1
Imidazole		N1—CH_2—H	94.7	91.4	0.260	0.215	0.822	95.2
		C2—CH_2—H	90.4	85.7	0.039	0.018	0.649	90.6
		C4—CH_2—H	91.3	87.6	0.036	0.042	0.738	92.4
		C5—CH_2—H	88.7	84.3	0.037	−0.002	0.659	90.0
Oxazole		C2—CH_2—H	91.3	86.2	0.048	0.061	0.615	90.9
		C4—CH_2—H	91.6	87.9	0.048	0.066	0.719	93.3
		C5—CH_2—H	88.9	84.2	0.044	0.033	0.619	90.3
Thiazole		C2—CH_2—H	90.0	85.0	0.053	0.073	0.577	90.5
		C4—CH_2—H	91.5	87.5	0.052	0.080	0.693	92.7
		C5—CH_2—H	89.2	84.2	0.053	0.059	0.607	89.8
Pyrazole		N1—CH_2—H	94.9	91.3	0.269	0.232	0.799	95.8
		C3—CH_2—H	92.5	88.7	0.040	0.063	0.748	92.4
		C4—CH_2—H	91.6	87.7	0.040	0.038	0.767	91.8
		C5—CH_2—H	90.3	85.8	0.044	0.030	0.682	90.0
Isoxazole		C3—CH_2—H	94.1	90.2	0.058	0.108	0.738	93.3
		C4—CH_2—H	92.5	88.4	0.053	0.060	0.739	92.7
		C5—CH_2—H	90.9	86.1	0.053	0.073	0.640	90.3
Isothiazole		C3—CH_2—H	92.2	88.4	0.052	0.097	0.707	92.7
		C4—CH_2—H	91.5	87.4	0.053	0.072	0.714	92.1
		C5—CH_2—H	89.8	85.0	0.055	0.081	0.623	89.8
1,2,3-Triazole		N1—CH_2—H	96.5	92.3	0.279	0.266	0.804	96.8
		C4—CH_2—H	93.7	89.4	0.048	0.067	0.756	93.4
		C5—CH_2—H	91.7	86.8	0.053	0.052	0.692	90.9
1,2,3-Oxadiazole		C4—CH_2—H	93.9	88.7	0.058	0.080	0.731	94.6
		C5—CH_2—H	92.4	87.6	0.063	0.087	0.632	92.0
1,2,3-Thiadiazole		C4—CH_2—H	93.9	88.6	0.060	0.095	0.697	94.2
		C5—CH_2—H	91.0	85.6	0.066	0.107	0.623	91.6
1,2,4-Triazole		N1—CH_2—H	95.7	92.1	0.276	0.268	0.804	96.8
		C3—CH_2—H	93.7	89.9	0.049	0.093	0.750	94.0
		C5—CH_2—H	92.8	88.3	0.033	0.085	0.702	91.5

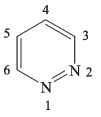
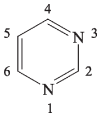
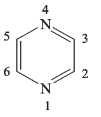
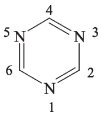
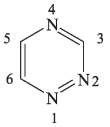
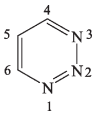
Continues

Table 1. Continued

Parent molecule	Structure	Bond	G3B3 (recommended)	B3LYP[a]	Charge (CH_3)[b]	Charge $(CH_2^{\bullet})$[c]	Spin[d]	BDE from Eqn (5)
1,2,4-Oxadiazole		C3—CH_2—H	94.8	91.2	0.067	0.134	0.721	94.9
		C5—CH_2—H	94.4	89.5	0.065	0.127	0.686	91.9
1,2,4-Thiadiazole		C3—CH_2—H	93.3	89.5	0.062	0.129	0.704	94.3
		C5—CH_2—H	91.6	86.8	0.064	0.124	0.632	91.4
2*H*-1,2,3-Triazole		N2—CH_2—H	95.3	91.1	0.287	0.278	0.764	97.4
		C4—CH_2—H	93.3	89.2	0.049	0.077	0.747	93.4
1,2,5-Oxadiazole		C3—CH_2—H	94.6	90.1	0.068	0.119	0.712	94.3
1,2,5-Thiadiazole		C3—CH_2—H	92.5	88.0	0.061	0.106	0.691	93.6
4*H*-1,2,4-Triazole		N4—CH_2—H	95.9	92.4	0.269	0.236	0.836	96.2
		C3—CH_2—H	92.9	88.2	0.050	0.059	0.691	91.5
1,3,4-Oxadiazole		C2—CH_2—H	93.6	88.7	0.060	0.093	0.666	91.9
1,3,4-Thiadiazole		C2—CH_2—H	92.8	87.4	0.064	0.114	0.641	91.4
2*H*-Tetrazole		N2—CH_2—H	96.9	92.5	0.298	0.312	0.761	98.3
		C5—CH_2—H	95.4	90.8	0.060	0.109	0.760	94.9
1,2,3,5-Oxatriazole		C4—CH_2—H	95.6	90.3	0.076	0.138	0.698	95.8
1,2,3,5-Thiatriazole		C4—CH_2—H	94.8	89.4	0.070	0.138	0.674	95.2
Benzene		C1—CH_2—H	91.1	86.6	0.039	0.069	0.700	90.9
Pyridine		C2—CH_2—H	92.9	88.1	0.042	0.113	0.705	92.4
		C3—CH_2—H	91.9	86.9	0.045	0.082	0.702	91.8
		C4—CH_2—H	92.6	87.8	0.047	0.108	0.722	91.4

Continues

Table 1. Continued

Parent molecule	Structure	Bond	G3B3 (recommended)	B3LYP[a]	Charge (CH_3)[b]	Charge $(CH_2^{\bullet})$[c]	Spin[d]	BDE from Eqn (5)
Pyridazine		C3—CH_2—H	94.8	88.8	0.052	0.125	0.723	93.4
		C4—CH_2—H	93.3	87.5	0.055	0.124	0.701	92.3
Pyrimidine		C2—CH_2—H	94.3	89.5	0.049	0.150	0.722	94.0
		C4—CH_2—H	94.1	89.2	0.051	0.143	0.727	93.0
		C5—CH_2—H	92.6	87.4	0.052	0.099	0.709	92.7
Pyrazine		C2—CH_2—H	93.4	87.9	0.048	0.120	0.691	93.4
1,3,5-Triazine		C2—CH_2—H	95.5	90.5	0.060	0.182	0.742	94.5
1,2,4-Triazine		C3—CH_2—H	96.2	89.8	0.059	0.161	0.720	94.9
		C5—CH_2—H	94.8	88.6	0.060	0.164	0.692	93.9
		C6—CH_2—H	95.1	88.7	0.059	0.141	0.705	94.3
1,2,3-Triazine		C4—CH_2—H	95.9	89.2	0.062	0.162	0.711	93.9
		C5—CH_2—H	94.0	87.5	0.064	0.145	0.684	93.3

[a] B3LYP means the UB3LYP/6–311 + + G(2df,2p)//UB3LYP/6–31G(d) method.
[b] NPA charge carried by the CH_3 group before homolysis.
[c] NPA charge by the $CH_2^{\bullet}$ group after homolysis.
[d] Spin carried by $CH_2^{\bullet}$. NPA charges and spins were obtained using the UB3LYP/6–311++G(2df,2p)//UB3LYP/6–31G(d) method.

value. B3LYP provides a prediction of 86.6 kcal mol^{-1}, which is 3.0 kcal mol^{-1} lower than the experimental value. This is in agreement with our previous finding that G3B3 is superior to B3LYP in predicting BDEs.

Further analysis of Table 1 reveals that all the B3LYP BDE values are lower than the G3B3 data. The average difference between them is 4.6 kcal mol^{-1}, indicating that the B3LYP method significantly underestimate the BDEs. Nonetheless, the underestimation by the B3LYP method is largely systematic because the B3LYP BDEs correlate well with the G3B3 BDEs. The correlation equation is

$$\mathrm{BDE(G3B3)} = 10.2 + 0.936\mathrm{BDE(B3LYP)} \quad (3)$$

The correlation coefficient (r) is 0.938 and the standard deviation of the correlation is 0.8 kcal mol^{-1} for 69 BDE values (see Fig. 3). Therefore, we can still use the relatively cheap B3LYP method to calculate the BDEs by using Eqn (3).

BDEs of bicyclic systems

In addition to monocyclic heterocycles, bicyclic heterocyclic compounds are also widely utilized in pharmaceutical chemistry. Hence it is important to know the C—H BDEs of the methyl groups attached to these systems. Unfortunately, because these systems contain more than nine non-hydrogen atoms, the G3B3 method cannot be used to handle them. We can only use the B3LYP method to calculate the BDEs. By using Eqn (3), we correct the B3LYP data to the 'recommended' BDEs as shown in Table 2. Adding the error of the G3B3 method

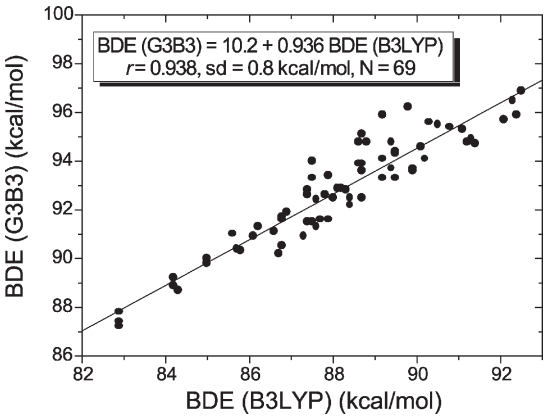
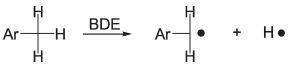
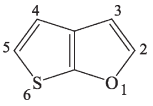
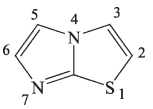
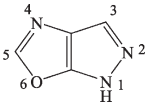
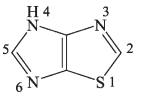
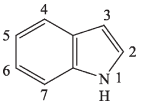
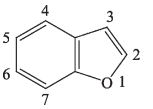
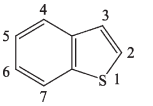
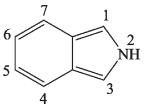
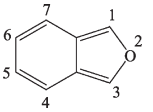
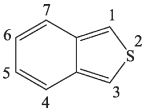


Figure 3. The correlation between the G3B3 and B3LYP BDEs for the C—H bond on the methyl group attached to five- and six-membered heterocycles

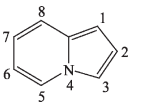
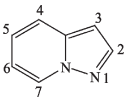
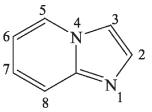
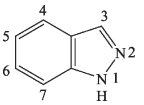
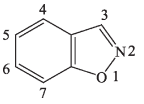
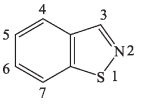
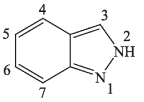
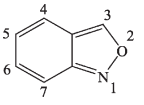
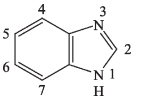
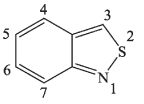
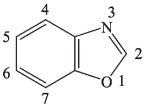
Table 2. C—H BDEs of the methyl groups attached to diverse bicyclic heterocycles (kcal mol^{-1})



Name of the parent molecule	Structure	Bond	Recommended BDE[a]	B3LYP[b]	Charge (CH_3)[c]	Charge ($CH_2^{\bullet}$)[d]	Spin[e]	BDE from Eqn (5)
Thieno[2,3-*b*]furan		C2—CH_2—H	87.0	82.1	0.041	0.010	0.546	88.1
		C3—CH_2—H	91.2	86.5	0.049	0.047	0.680	90.0
		C4—CH_2—H	90.2	85.5	0.051	0.057	0.646	89.6
		C5—CH_2—H	87.0	82.1	0.045	0.022	0.556	87.8
Imidazo[2,1-*b*]thiazole		C2—CH_2—H	88.7	83.9	0.057	0.041	0.582	88.8
		C3—CH_2—H	89.1	84.3	0.061	0.033	0.563	88.7
		C5—CH_2—H	88.2	83.3	0.041	−0.012	0.639	88.2
		C6—CH_2—H	91.6	87.0	0.042	0.048	0.680	91.2
1*H*-Pyrazolo[4,3-*d*]oxazole		N1—CH_2—H	95.4	91.0	0.278	0.233	0.807	96.2
		C3—CH_2—H	92.8	88.2	0.055	0.091	0.709	91.8
		C5—CH_2—H	88.8	84.0	0.054	0.053	0.532	90.1
4*H*-Imidazo[4,5-*d*]thiazole		C2—CH_2—H	86.2	81.2	0.053	0.045	0.464	89.8
		N4—CH_2—H	96.0	91.7	0.274	0.235	0.819	94.4
		C5—CH_2—H	88.4	83.5	0.049	0.025	0.539	89.9
1*H*-Indole		N1—CH_2—H	93.4	88.9	0.251	0.175	0.795	92.9
		C2—CH_2—H	87.9	83.0	0.038	0.001	0.559	88.1
		C3—CH_2—H	90.0	85.3	0.032	0.008	0.690	89.5
		C4—CH_2—H	89.8	85.1	0.033	0.049	0.641	89.2
		C5—CH_2—H	91.0	86.3	0.032	0.043	0.707	90.0
		C6—CH_2—H	89.9	85.2	0.033	0.042	0.674	89.7
		C7—CH_2—H	90.2	85.5	0.029	0.022	0.642	89.8
Benzofuran		C2—CH_2—H	87.6	82.7	0.044	0.027	0.535	88.4
		C3—CH_2—H	91.1	86.4	0.042	0.039	0.677	90.0
		C4—CH_2—H	90.2	85.5	0.037	0.061	0.656	89.3
		C5—CH_2—H	91.4	86.8	0.037	0.057	0.717	90.4
		C6—CH_2—H	90.2	85.5	0.039	0.061	0.673	89.5
		C7—CH_2—H	91.1	86.4	0.048	0.075	0.677	90.6
Benzo[*b*]thiophene		C2—CH_2—H	88.1	83.2	0.049	0.050	0.559	88.0
		C3—CH_2—H	90.4	85.7	0.048	0.047	0.646	89.7
		C4—CH_2—H	90.4	85.7	0.037	0.065	0.636	89.1
		C5—CH_2—H	91.4	86.7	0.039	0.063	0.694	90.1
		C6—CH_2—H	90.3	85.6	0.040	0.064	0.672	89.3
		C7—CH_2—H	91.2	86.5	0.046	0.072	0.663	90.0
2*H*-Isoindole		N2—CH_2—H	94.6	90.2	0.262	0.233	0.787	93.3
		C1—CH_2—H	82.4	77.2	0.029	−0.050	0.461	82.5
		C4—CH_2—H	88.1	83.2	0.029	0.027	0.542	89.2
		C5—CH_2—H	89.3	84.5	0.031	0.032	0.612	90.4
Isobenzofuran		C1—CH_2—H	80.3	74.9	0.038	−0.008	0.359	82.9
		C4—CH_2—H	87.4	82.5	0.036	0.047	0.496	89.3
		C5—CH_2—H	88.6	83.8	0.037	0.052	0.566	90.4
Benzo[*c*]thiophene		C1—CH_2—H	81.8	76.5	0.045	0.028	0.371	82.4
		C4—CH_2—H	88.0	83.1	0.034	0.049	0.515	89.1
		C5—CH_2—H	88.8	84.0	0.038	0.058	0.584	90.1

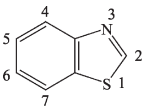
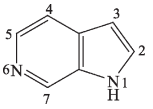
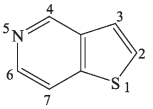
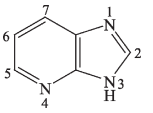
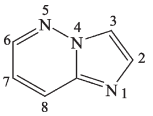
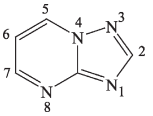
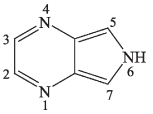
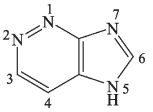
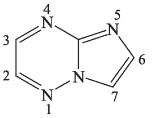
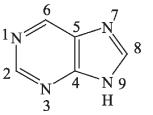
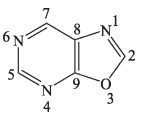
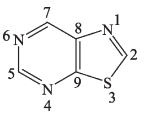
Continues

Table 2. Continued

Name of the parent molecule	Structure	Bond	Recommended BDE[a]	B3LYP[b]	Charge (CH_3)[c]	Charge ($CH_2^{\bullet}$)[d]	Spin[e]	BDE from Eqn (5)
Indolizine		C1—CH_2—H	88.4	83.5	0.034	−0.007	0.639	89.5
		C2—CH_2—H	91.6	87.0	0.039	0.047	0.715	90.3
		C3—CH_2—H	86.3	81.3	0.030	−0.041	0.553	87.6
		C5—CH_2—H	87.0	82.1	0.043	0.000	0.446	87.9
		C6—CH_2—H	90.5	85.8	0.044	0.038	0.652	89.9
		C7—CH_2—H	87.6	82.7	0.039	0.027	0.559	89.3
		C8—CH_2—H	89.0	84.2	0.048	0.058	0.553	89.8
Pyrazolo[1,5-*a*]pyridine		C2—CH_2—H	93.2	88.7	0.047	0.080	0.738	91.5
		C3—CH_2—H	90.1	85.4	0.041	0.014	0.692	90.4
		C4—CH_2—H	89.4	84.6	0.052	0.070	0.587	90.3
		C5—CH_2—H	89.7	84.9	0.045	0.063	0.621	89.8
		C6—CH_2—H	91.0	86.4	0.048	0.056	0.691	90.5
		C7—CH_2—H	89.1	84.3	0.067	0.083	0.525	88.8
Imidazo[1,2-*a*]pyridine		C2—CH_2—H	92.6	88.0	0.042	0.068	0.704	91.5
		C3—CH_2—H	88.3	83.4	0.037	−0.024	0.600	89.0
		C5—CH_2—H	88.4	83.6	0.049	0.033	0.519	88.5
		C6—CH_2—H	91.4	86.7	0.048	0.059	0.690	90.4
		C7—CH_2—H	89.5	84.7	0.045	0.060	0.618	89.9
		C8—CH_2—H	89.8	85.0	0.064	0.111	0.590	90.7
1*H*-Indazole		N1—CH_2—H	94.0	89.6	0.264	0.209	0.783	94.4
		C3—CH_2—H	91.4	86.8	0.044	0.060	0.658	91.0
		C4—CH_2—H	89.9	85.2	0.040	0.072	0.633	89.7
		C5—CH_2—H	91.2	86.5	0.038	0.052	0.699	90.4
		C6—CH_2—H	90.7	86.0	0.040	0.070	0.674	89.8
		C7—CH_2—H	90.1	85.4	0.039	0.049	0.633	90.3
Benzo[*d*]isoxazole		C3—CH_2—H	93.4	88.9	0.063	0.109	0.682	91.9
		C4—CH_2—H	90.3	85.6	0.048	0.089	0.647	89.8
		C5—CH_2—H	91.7	87.1	0.043	0.069	0.708	90.8
		C6—CH_2—H	91.0	86.3	0.047	0.090	0.673	89.9
		C7—CH_2—H	91.1	86.4	0.059	0.101	0.660	91.2
Benzo[*d*]isothiazole		C3—CH_2—H	91.7	87.1	0.053	0.096	0.652	91.3
		C4—CH_2—H	90.5	85.8	0.043	0.077	0.623	89.7
		C5—CH_2—H	91.4	86.8	0.043	0.070	0.701	90.5
		C6—CH_2—H	91.0	86.3	0.046	0.087	0.660	89.7
		C7—CH_2—H	91.2	86.6	0.051	0.082	0.643	90.6
2*H*-Indazole		N2—CH_2—H	94.9	90.5	0.277	0.271	0.747	94.9
		C3—CH_2—H	85.6	80.6	0.046	0.001	0.521	83.5
		C4—CH_2—H	88.6	83.8	0.036	0.053	0.573	89.7
		C5—CH_2—H	89.9	85.2	0.035	0.052	0.642	90.4
		C6—CH_2—H	90.2	85.5	0.037	0.063	0.650	90.5
		C7—CH_2—H	88.7	83.9	0.047	0.083	0.569	90.1
Benzo[*c*]isoxazole		C3—CH_2—H	84.0	78.9	0.056	0.041	0.404	83.8
		C4—CH_2—H	87.8	82.9	0.046	0.078	0.514	89.8
		C5—CH_2—H	89.0	84.2	0.043	0.073	0.588	90.8
		C6—CH_2—H	89.8	85.0	0.046	0.089	0.601	90.9
		C7—CH_2—H	87.9	83.0	0.056	0.111	0.513	90.2
Benzo[*c*]isothiazole		C3—CH_2—H	84.5	79.4	0.054	0.063	0.415	83.3
		C4—CH_2—H	88.4	83.6	0.038	0.066	0.537	89.7
		C5—CH_2—H	89.5	84.7	0.042	0.078	0.593	90.5
		C6—CH_2—H	89.6	84.8	0.044	0.085	0.599	90.6
		C7—CH_2—H	88.4	83.6	0.053	0.110	0.531	90.1
1*H*-Benzoimidazole		N1—CH_2—H	95.3	90.9	0.257	0.201	0.812	93.8
		C2—CH_2—H	91.1	86.4	0.047	0.050	0.615	89.6
		C4—CH_2—H	90.4	85.7	0.050	0.093	0.657	90.1
		C5—CH_2—H	91.4	86.7	0.036	0.055	0.706	89.8
		C6—CH_2—H	90.5	85.8	0.037	0.053	0.679	90.5
		C7—CH_2—H	90.5	85.8	0.035	0.040	0.664	90.3
Benzoxazole		C2—CH_2—H	91.2	86.6	0.056	0.077	0.577	90.0
		C4—CH_2—H	91.4	86.8	0.055	0.087	0.684	90.2
		C5—CH_2—H	90.7	86.0	0.042	0.070	0.676	90.9
		C6—CH_2—H	91.6	87.0	0.041	0.068	0.715	89.9
		C7—CH_2—H	91.4	86.7	0.055	0.087	0.684	91.2

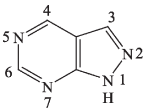
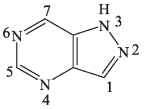
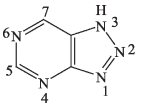
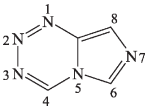
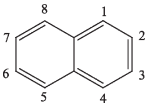
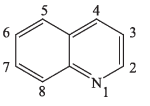
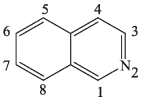
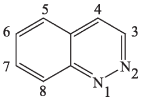
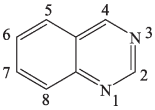
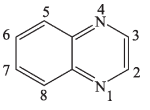
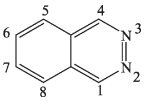
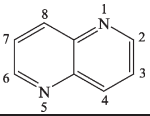
Continues

Table 2. Continued

Name of the parent molecule	Structure	Bond	Recommended BDE[a]	B3LYP[b]	Charge (CH_3)[c]	Charge ($CH_2^{\bullet}$)[d]	Spin[e]	BDE from Eqn (5)
Benzothiazole		C2—CH_2—H	90.7	86.0	0.057	0.093	0.584	89.5
		C4—CH_2—H	91.2	86.6	0.055	0.076	0.674	90.1
		C5—CH_2—H	90.7	86.0	0.042	0.073	0.677	90.6
		C6—CH_2—H	91.5	86.9	0.043	0.073	0.710	89.7
		C7—CH_2—H	91.4	86.7	0.049	0.076	0.674	90.6
1*H*-Pyrrolo[2,3-*c*]pyridine		N1—CH_2—H	94.2	89.8	0.257	0.189	0.803	93.4
		C2—CH_2—H	89.0	84.2	0.045	0.029	1.224	88.5
		C3—CH_2—H	90.7	86.0	0.038	0.024	0.708	89.9
		C4—CH_2—H	90.3	85.6	0.041	0.062	0.636	90.1
		C5—CH_2—H	92.4	87.8	0.034	0.071	0.700	91.5
		C7—CH_2—H	91.8	87.2	0.033	0.067	0.656	91.3
Thieno[3,2-*c*]pyridine		C2—CH_2—H	88.3	83.4	0.053	0.062	0.554	88.4
		C3—CH_2—H	90.8	86.1	0.054	0.062	0.649	90.3
		C4—CH_2—H	91.7	87.1	0.043	0.103	0.667	90.7
		C6—CH_2—H	91.5	86.9	0.042	0.094	0.670	90.9
		C7—CH_2—H	91.4	86.8	0.052	0.082	0.666	91.0
3*H*-Imidazo[4,5-*b*]pyridine		C2—CH_2—H	91.1	86.4	0.052	0.067	0.604	90.2
		N3—CH_2—H	95.8	91.5	0.271	0.231	0.828	94.7
		C5—CH_2—H	91.2	86.6	0.040	0.088	0.672	91.3
		C6—CH_2—H	92.2	87.6	0.043	0.065	0.720	91.5
		C7—CH_2—H	91.4	86.7	0.058	0.126	0.669	90.6
Imidazo[1,2-*b*]pyridazine		C2—CH_2—H	92.3	87.7	0.046	0.083	0.682	92.0
		C3—CH_2—H	89.2	84.4	0.055	0.041	0.631	89.5
		C6—CH_2—H	92.8	88.3	0.056	0.115	0.683	91.9
		C7—CH_2—H	89.5	84.7	0.052	0.075	0.599	90.8
		C8—CH_2—H	90.7	86.0	0.073	0.151	0.605	91.2
[1,2,4]Triazolo [1,5-*a*]pyrimidine		C2—CH_2—H	94.7	90.3	0.058	0.124	0.726	93.6
		C5—CH_2—H	92.4	87.8	0.056	0.141	0.662	91.9
		C6—CH_2—H	92.5	87.9	0.061	0.087	0.708	91.8
		C7—CH_2—H	91.4	86.8	0.082	0.143	0.615	89.9
6*H*-Pyrrolo[3,4-*b*]pyrazine		C1—CH_2—H	90.2	85.5	0.042	0.096	0.576	92.5
		C5—CH_2—H	83.7	78.5	0.047	0.013	0.452	84.0
		N6—CH_2—H	94.8	90.4	0.271	0.261	0.751	94.4
5*H*-Imidazo[4,5-*c*]pyridazine		C3—CH_2—H	92.7	88.1	0.049	0.106	0.709	92.2
		C4—CH_2—H	91.6	87.0	0.052	0.096	0.662	91.8
		N5—CH_2—H	96.1	91.8	0.267	0.220	0.821	94.8
		C6—CH_2—H	92.3	87.7	0.058	0.098	0.630	90.6
Imidazo[1,2-*b*][1,2,4]triazine		C2—CH_2—H	92.3	87.7	0.062	0.130	0.654	92.9
		C3—CH_2—H	89.6	84.8	0.057	0.115	0.531	92.4
		C6—CH_2—H	91.9	87.3	0.052	0.109	0.644	92.6
		C7—CH_2—H	88.9	84.1	0.059	0.056	0.601	90.0
9*H*-Purine		N9—CH_2—H	96.2	91.9	0.277	0.244	0.832	95.2
		C8—CH_2—H	91.5	86.9	0.057	0.084	0.610	90.6
		C6—CH_2—H	92.5	87.9	0.061	0.158	0.675	92.2
		C2—CH_2—H	92.9	88.4	0.048	0.128	0.693	92.9
Oxazolo[5,4-*d*]pyrimidine		C2—CH_2—H	91.7	87.1	0.067	0.113	0.582	90.9
		C5—CH_2—H	93.0	88.5	0.056	0.146	0.679	93.0
		C7—CH_2—H	92.8	88.2	0.067	0.168	0.678	92.3
Thiazolo[5,4-*d*]pyrimidine		C2—CH_2—H	91.1	86.4	0.063	0.121	0.598	90.5
		C5—CH_2—H	93.1	88.6	0.055	0.146	0.674	92.8
		C7—CH_2—H	92.7	88.1	0.066	0.171	0.677	92.2

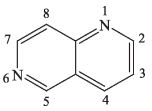
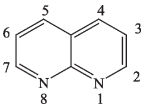
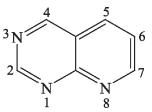
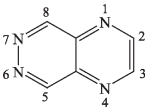
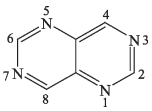
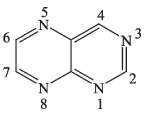
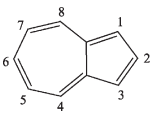
Continues

Table 2. Continued

Name of the parent molecule	Structure	Bond	Recommended BDE[a]	B3LYP[b]	Charge (CH_3)[c]	Charge ($CH_2^{\bullet}$)[d]	Spin[e]	BDE from Eqn (5)
1*H*-Pyrazolo[3,4-*d*]pyrimidine		N1—CH_2—H	95.6	91.2	0.283	0.255	0.796	95.8
		C3—CH_2—H	91.7	87.1	0.054	0.090	0.657	92.1
		C4—CH_2—H	92.8	88.2	0.056	0.154	0.686	91.8
		C6—CH_2—H	93.3	88.8	0.052	0.145	0.687	92.9
1*H*-Pyrazolo[4,3-*d*]pyrimidine		C1—CH_2—H	92.0	87.4	0.274	0.108	0.657	92.4
		N3—CH_2—H	94.7	90.3	0.061	0.234	0.777	95.5
		C7—CH_2—H	91.9	87.3	0.049	0.129	0.655	92.4
		C5—CH_2—H	94.2	89.7	0.051	0.129	0.701	93.5
1*H*-[1,2,3]Triazolo [4,5-*d*]pyrimidine		N3—CH_2—H	96.3	92.0	0.291	0.287	0.795	96.5
		C7—CH_2—H	92.7	88.1	0.070	0.187	0.672	93.0
		C5—CH_2—H	93.6	89.1	0.058	0.159	0.677	94.1
Imidazo[5,1-*d*][1,2,3,5]tetrazine		C4—CH_2—H	91.9	87.3	0.073	0.107	0.626	91.5
		C6—CH_2—H	88.9	84.1	0.059	0.057	0.519	90.7
		C8—CH_2—H	89.1	84.3	0.067	0.130	0.507	92.9
Naphthalene		C1—CH_2—H	90.2	85.5	0.033	0.054	0.592	89.5
		C2—CH_2—H	90.4	85.7	0.041	0.070	0.669	90.0
Quinoline		C2—CH_2—H	92.3	87.7	0.043	0.112	0.676	91.5
		C3—CH_2—H	90.6	85.9	0.047	0.080	0.648	90.9
		C4—CH_2—H	91.2	86.6	0.045	0.101	0.627	90.0
		C5—CH_2—H	90.1	85.4	0.037	0.066	0.606	90.0
		C6—CH_2—H	90.6	85.9	0.043	0.078	0.661	90.4
		C7—CH_2—H	90.9	86.2	0.037	0.086	0.663	90.5
		C8—CH_2—H	89.8	85.1	0.044	0.114	0.615	90.4
Isoquinoline		C1—CH_2—H	90.5	85.8	0.040	0.092	0.653	91.0
		C3—CH_2—H	92.8	88.2	0.042	0.080	0.601	91.5
		C4—CH_2—H	90.2	85.5	0.042	0.068	0.606	90.4
		C5—CH_2—H	90.0	85.3	0.038	0.092	0.661	89.9
		C6—CH_2—H	90.9	86.2	0.045	0.067	0.657	90.2
		C7—CH_2—H	91.4	86.7	0.044	0.085	0.606	90.4
		C8—CH_2—H	89.8	85.0	0.044	0.105	0.610	90.0
Cinnoline		C3—CH_2—H	92.1	87.5	0.050	0.112	0.675	92.5
		C4—CH_2—H	90.5	85.8	0.052	0.114	0.596	90.9
		C5—CH_2—H	89.9	85.2	0.040	0.083	0.604	90.4
		C6—CH_2—H	90.6	85.9	0.049	0.106	0.643	90.6
		C7—CH_2—H	90.9	86.2	0.049	0.100	0.661	90.9
		C8—CH_2—H	89.8	85.1	0.061	0.136	0.562	90.9
Quinazoline		C3—CH_2—H	93.3	88.8	0.049	0.142	0.678	90.8
		C4—CH_2—H	93.0	88.5	0.048	0.146	0.644	90.7
		C5—CH_2—H	90.0	85.3	0.042	0.085	0.615	90.8
		C6—CH_2—H	90.8	86.1	0.047	0.088	0.668	92.5
		C7—CH_2—H	91.2	86.5	0.049	0.109	0.663	90.9
		C8—CH_2—H	90.0	85.3	0.055	0.122	0.602	90.9
Quinoxaline		C2—CH_2—H	91.6	87.0	0.050	0.126	0.646	91.9
		C5—CH_2—H	89.9	85.2	0.052	0.111	0.587	90.4
		C6—CH_2—H	90.8	86.1	0.047	0.099	0.648	90.6
Phthalazine		C1—CH_2—H	92.8	88.2	0.048	0.128	0.647	93.1
		C5—CH_2—H	90.6	85.9	0.045	0.093	0.626	91.6
		C6—CH_2—H	91.2	86.6	0.050	0.103	0.666	90.5
[1,5]Naphthyridine		C2—CH_2—H	92.4	87.8	0.046	0.124	0.671	92.0
		C3—CH_2—H	91.7	87.1	0.061	0.101	0.644	91.5
		C4—CH_2—H	90.3	85.6	0.050	0.148	0.616	90.9

Continues

Table 2. Continued

Name of the parent molecule	Structure	Bond	Recommended BDE[a]	B3LYP[b]	Charge (CH_3)[c]	Charge ($CH_2^{\bullet}$)[d]	Spin[e]	BDE from Eqn (5)
[1,6]Naphthyridine		C2—CH_2—H	92.7	88.1	0.049	0.137	0.688	91.7
		C3—CH_2—H	90.7	86.0	0.051	0.091	0.647	91.3
		C4—CH_2—H	91.4	86.8	0.052	0.121	0.633	90.5
		C5—CH_2—H	91.5	86.9	0.040	0.112	0.623	91.6
		C7—CH_2—H	91.7	87.1	0.045	0.111	0.655	92.1
		C8—CH_2—H	90.0	85.3	0.058	0.123	0.608	91.3
[1,8]Naphthyridine		C2—CH_2—H	92.5	87.9	0.047	0.131	0.687	92.1
		C3—CH_2—H	90.9	86.2	0.050	0.094	0.648	91.3
		C4—CH_2—H	91.4	86.7	0.047	0.106	0.642	90.5
Pyrido[2,3-*d*]pyrimidine		C2—CH_2—H	93.6	89.1	0.054	0.160	0.687	93.6
		C4—CH_2—H	93.1	88.6	0.050	0.151	0.665	92.1
		C5—CH_2—H	91.5	86.9	0.053	0.128	0.652	91.1
		C6—CH_2—H	91.0	86.3	0.054	0.104	0.654	91.7
		C7—CH_2—H	92.9	88.4	0.053	0.155	0.692	92.3
Pyrazino[2,3-*d*]pyridazine		C2—CH_2—H	92.2	87.6	0.062	0.158	0.638	93.1
		C5—CH_2—H	91.9	87.3	0.067	0.178	0.629	94.1
Pyrimido[5,4-*d*]pyrimidine		C2—CH_2—H	93.6	89.1	0.058	0.165	0.663	93.9
		C4—CH_2—H	91.9	87.3	0.231	0.201	0.638	92.9
Pteridine		C2—CH_2—H	93.4	88.9	0.057	0.172	0.677	94.1
		C4—CH_2—H	92.6	88.0	0.068	0.169	0.656	93.0
		C6—CH_2—H	91.8	87.2	0.058	0.149	0.633	93.3
		C7—CH_2—H	92.5	87.9	0.062	0.169	0.656	93.2
Azulene		C1—CH_2—H	86.6	81.6	0.040	0.101	0.473	90.0
		C2—CH_2—H	84.9	79.8	0.032	0.015	0.477	89.2
		C4—CH_2—H	90.1	85.4	0.050	0.115	0.554	89.7
		C5—CH_2—H	86.8	81.8	0.041	0.041	0.488	89.9
		C6—CH_2—H	88.3	83.4	0.046	0.101	0.507	90.0

[a] Recommended BDEs are calculated using Eqn (3).
[b] B3LYP means the UB3LYP/6–311++G(2df,2p)//UB3LYP/6–31G(d) method.
[c] NPA charge carried by the CH_3 group before homolysis.
[d] NPA charge carried by the $CH_2^{\bullet}$ group after homolysis.
[e] Spin carried by $CH_2^{\bullet}$. NPA charges and spins were obtained using the UB3LYP/6–311++G(2df,2p)//UB3LYP/6–31G(d) method.

(ca 1 kcal mol^{-1})[11] and the standard deviation of Eqn (3) (0.8 kcal mol^{-1}) together, we consider that the error for the 'recommended' BDEs in Table 2 is about 2 kcal mol^{-1}.

Structure–activity relationships

From the data in Tables 1 and 2, we find that the C—H BDEs of the methyl groups attached to diverse heterocycles vary dramatically. The lowest C—H BDE (80.3 kcal mol^{-1}) is observed for 1-methylisobenzofuran and the highest (96.9 kcal mol^{-1}) for 2-methyl-2*H*-tetrazole. The difference between these two values is 16.6 kcal mol^{-1}, which means that the H-abstraction reaction for 1-methylisobenzofuran is about 1.5×10^{12} times faster than that for 2-methyl-2*H*-tetrazole. The transition-state theory with the transmission coefficient equated to unity [i.e. $k = (k_B T/\mathrm{h})\exp(-\Delta G^{\neq}/\mathrm{RT})$] was used calculate the H-abstraction reaction rates. Therefore, the stability of the methyl group towards metabolic oxidation reactions is very different when it is attached to different positions of heterocycles. This is clearly an important piece of information for drug design.

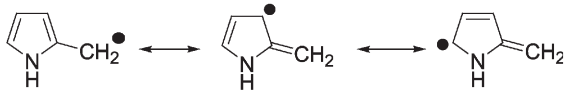
What factors change the benzylic C—H BDEs of different heterocycles so dramatically? First, we find that increasing the ring size generally decreases the C—H BDEs. For example, the benzylic C—H BDE of toluene is 91.1 kcal mol^{-1}, whereas those of naphthalene are 90.2 (α-position) and 90.4 kcal mol^{-1} (β-position), respectively. Also, the average benzylic C—H BDE for monocyclic heterocycles (i.e. BDEs in Table 1) is 92.8 kcal mol^{-1}, whereas the average benzylic C—H

BDE for bicyclic heterocycles (i.e. BDEs in Table 2) is 90.7 kcal mol^{-1}. The ring size effect on benzylic C—H BDEs can be readily explained by the spin delocalization effect.[13] Since all the ring atoms can participate in delocalizing the spin of the benzylic radical, more ring atoms clearly result in a lower C—H BDE.

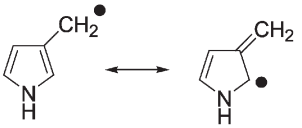
The second factor for the variation of the benzylic C—H BDEs is atom to which the methyl group is attached. Two choices are available for the methyl group in the usual aromatic heterocycles, namely the carbon atom and nitrogen atom, respectively. It is found that a *C*-methyl group usually has a lower BDE than an *N*-methyl group. For instance, the benzylic C—H BDE of *N*-methylpyrrole is 93.6 kcal mol^{-1} whereas those of 2- and 3-methylpyrrole are 87.2 and 90.2 kcal mol^{-1}, respectively. Also, the average C—H BDE for the *C*-methyl groups in Tables 1 and 2 is 90.8 kcal mol^{-1}, whereas that for the *N*-methyl groups atom is 95.5 kcal mol^{-1}. The reason for the higher C—H BDEs in the *N*-methyl compounds is that the radical center is electron deficient. Since nitrogen is more electronegative than carbon, attaching N to an electron-deficient radical is less favorable than attaching C to the same place. (For a more detailed explanation about the destabilization effect of attaching electronegative atoms to radical centers, see Ref. 14).

The third factor affecting for the variation of the benzylic C—H BDEs is the relative position of the methyl group with respect to the heteroatoms in the ring. Four types of heteroatom groups are identified, namely NH, O, S and N. It is worth noting that NH is different from N. It is found that the methyl group at the α-position relative to the NH, O and S groups usually has a lower BDE than that at the β-position. For example, the benzylic C—H BDE of 2-methylpyrrole is 87.2 kcal mol^{-1} whereas that of 3-methylpyrrole is 90.2 kcal mol^{-1}. Also the benzylic C—H BDE of 2-methylfuran is 87.4 kcal mol^{-1} whereas that of 3-methylfuran is 90.9 kcal mol^{-1}. This α- and β-effect is readily explained by resonance theory. As shown in Fig. 4, the 2-methylpyrrole radical has three major resonance forms whereas the 3-methylpyrrole radical has only two.

Compared with NH, O and S, the N group has a different effect on the benzylic C—H BDEs. Here, a

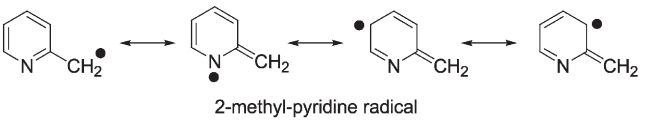


2-methyl-pyrrole radical

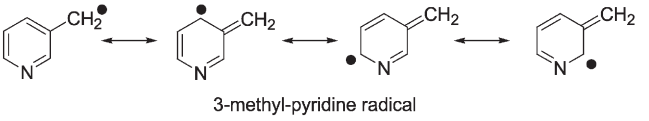


3-methyl-pyrrole radical

Figure 4. Resonance forms of 2- and 3-methylpyrrole radicals



2-methyl-pyridine radical



3-methyl-pyridine radical

Figure 5. Resonance forms of 2- and 3-methylpyridine radicals

methyl group at the β-position relative to N has a lower C—H BDE than that at the α-position. For instance, the benzylic C—H BDE of 3-methylpyridine is 91.9 kcal mol^{-1} whereas that of 2-methylpyridine is 92.9 kcal mol^{-1}. The reason for this special α- and β-effect is again readily explained by resonance theory. As shown in Fig. 5, the 2-methylpyridine radical has one resonance form in which the radical is located at the nitrogen atom, but this does not occur with the 3-methylpyridine radical. Since it is easier to oxidize carbon than nitrogen, it is understandable that a radical on nitrogen is not as favorable as a radical on carbon. Hence 2-methylpyridine has a higher benzylic C—H BDE than 3-methylpyridine.

It is worth noting that the α- and β-effect can also be seen at the remote positions. Here, instead of considering the α- or β-effect, we count the shortest distance between the methyl group and the heteroatom as the number of chemical bonds. For instance, in both 4- and 6-methyl-1*H*-indole, the shortest distance between the methyl group and the NH group is four chemical bonds (see Fig. 6). Similarly, in both 3- and 7-methyl-1*H*-indole, the shortest distance between the methyl group and the NH group is three chemical bonds. Because of these distances, 4- and 6-methyl-1*H*-indole have very similar benzylic C—H BDEs, i.e. 89.8 and 89.9 kcal mol^{-1}, respectively. Also, 3- and 7-methyl-1*H*-indole have very similar benzylic C—H BDEs, i.e. 90.0 and 90.2 kcal mol^{-1}, respectively. Compared with these values, the benzylic C—H BDEs of 2-methyl-1*H*-indole (methyl–NH distance = two bonds) and 5-methyl-1*H*-indole (methyl–NH distance = five bonds) are 87.9 and 91.0 kcal mol^{-1}, respectively.

In addition to the above factors, we find that the benzylic C—H BDEs for 1-methyl-2*H*-isoindole (82.4 kcal mol^{-1}), 1-methylisobenzofuran (80.3 kcal mol^{-1}),

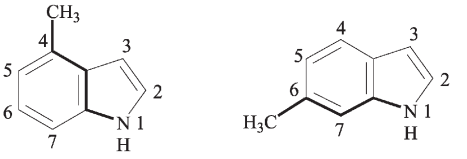


Figure 6. Counting the shortest distance between the methyl group and heteroatoms

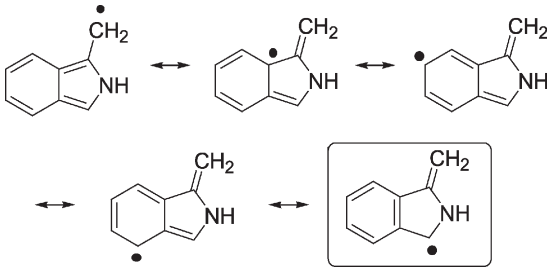


Figure 7. Resonance forms of the 1-methyl-2*H*-isoindole radical

1-methylbenzo[*c*]thiophene (81.8 kcal mol^{-1}) and compounds similar to them are considerably lower than those for any other types of heterocyclic compounds. Further analysis of these compounds reveals a special resonance effect, as shown in Fig. 7, namely that in the radical form the compound may have a full benzene ring in one of its resonance forms. However, this full benzene ring resonance form is not available to the parent compound before homolysis. Therefore, from the parent molecule to the radical there is some 'aromatization' effect, which lowers the benzylic C—H BDEs of these compounds significantly.

Charges and spins

In order to obtain a better understanding of the C—H BDEs, we use the natural bond orbital (NBO) partitioning technique developed by Reed *et al.*[15] to analyze the charge and spin distributions of the heterocyclic systems. First we obtain the NPA (natural population analysis) charges carried by the CH_3 groups in the heterocyclic compounds before homolysis. The results are shown in Fig. 8. It is found that the C—H BDEs should be categorized into two dramatically different groups, one containing all the *C*-methyl heterocycles and the other all the *N*-methyl heterocycles. There appears to be some positive correlation between the charges and the BDEs.

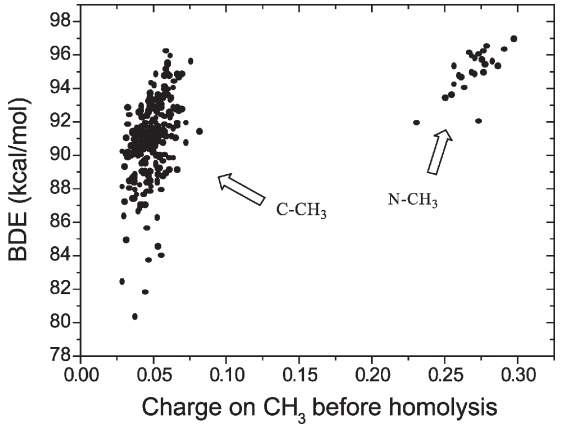


Figure 8. C—H BDEs vs the NPA charges carried by the CH_3 groups in heterocyclic compounds before homolysis

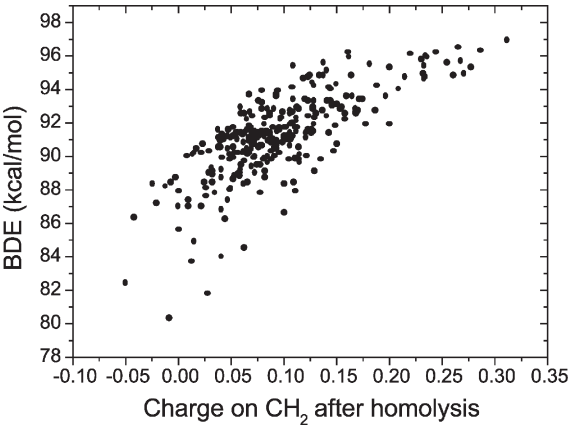


Figure 9. C—H BDEs vs the NPA charges carried by the $CH_2^{\bullet}$ groups in the heterocyclic compounds after homolysis

Next we calculate the charge carried by the $CH_2^{\bullet}$ groups after the homolysis. The results are shown in Fig. 9. It is clear that the benzylic C—H BDEs have a positive correlation with the charges on $CH_2^{\bullet}$. Comparing Fig. 9 with Fig. 8, we find that the charges on $CH_2^{\bullet}$ are usually more positive than the charges on CH_3. This demonstrates that the radical center is electron deficient. Since it is energetically unfavorable to put more positive charge on an electron-deficient center, it is understandable that more positive charges on $CH_2^{\bullet}$ lead to higher C—H BDEs.

Finally, we calculate the spins carried by the $CH_2^{\bullet}$ groups after homolysis. The results are shown in Fig. 10. It is clear that most $CH_2^{\bullet}$ groups carry a spin of only 0.6–0.8 a.u. Hence the remaining spin must be delocalized into the heterocyclic ring. More spin delocalization results in a more stable radical.[13] Therefore, it is not surprising to observe a clear positive correlation between the benzylic C—H BDEs and the spins on $CH_2^{\bullet}$ in Fig. 10. In an extreme case (1-methyl-isobenzofuran radical), the spin carried by the $CH_2^{\bullet}$ group is only as large as 0.36 a.u. This is again due to the highly favorable 'aromatization' effect that occurs in the homolysis.

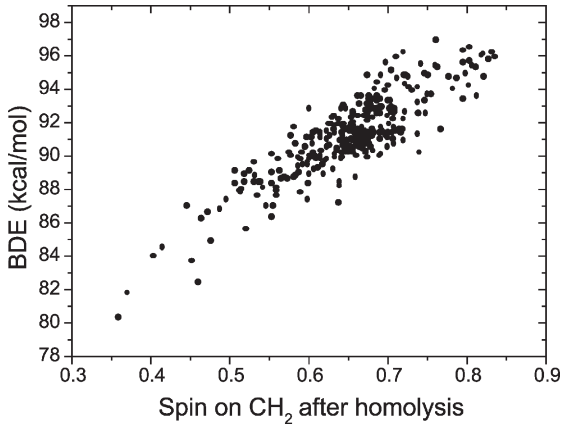


Figure 10. C—H BDEs vs the spins carried by the $CH_2^{\bullet}$ groups in the heterocyclic compounds after homolysis

Since both the charges and spins on the $CH_2^{\bullet}$ groups have a positive correlation with the benzylic C—H BDEs, it is interesting to construct a dual-parameter correlation equation using the charge and spin as independent variables. The following equation is then obtained:

$$\mathrm{BDE} = 78.8 + 20.5 \times \mathrm{Charge}(\mathrm{CH_2}) + 15.9 \times \mathrm{Spin}(\mathrm{CH_2}) \quad (4)$$

There are a total of 303 BDE data in the correlation. The correlation coefficient is 0.893 and the standard deviation is 1.1 kcal mol^{-1}.

QSAR model for benzylic C—H BDEs

Earlier we discussed the structure–activity relationships for the benzylic C—H BDEs in a qualitative fashion. Here we wish to develop these qualitative relationships into a quantitative structure–activity relationship (QSAR) model. Using this model, we hope to gain further insights into the dramatic variations of the C—H BDEs among diverse heterocyclic compounds.

In order to develop the QSAR model, we have the following definitions:

1. We define five types of ring atoms: C, NH, N, O and S. It is necessary to differentiate NH and N.
2. For a heterocyclic compound we assume it has n ring atoms: atom(1), atom(2), ..., atom(n). For any atom (i), it can be any one of the five types of ring atoms, i.e. C, NH, N, O or S.
3. For each ring atom we calculate its shortest distance (D) to the methyl group. This distance is either an odd number or an even number.
4. If the distance is an odd number (i.e. $D = 1, 3, 5, \ldots$) and the type of ring atom is known, we assume that this ring atom increase or decrease the C—H BDE by a value, $\delta^{\mathrm{odd}}_{\mathrm{atom\,type}} \cdot \gamma_{\mathrm{odd}}^{\frac{D-1}{2}}$, where $\delta^{\mathrm{odd}}_{\mathrm{atom\,type}}$ is a coefficient that is dependent only on the atom type, i.e. C, NH, N, O or S, and γ_{odd} is a degradation coefficient. By using γ_{odd}, we assume that the atom with a distance of $D = 3, 5, \ldots$ shows a similar effect on the C—H BDE to that with a distance of $D = 1$, but with some degradation.
5. Similarly, if the distance is an odd number (i.e. $D = 2, 4, 6, \ldots$) and the type of the ring atom is known, we assume that this ring atom increases or decreases the C—H BDE by a value, $\delta^{\mathrm{even}}_{\mathrm{atom\,type}} \cdot \gamma_{\mathrm{even}}^{\frac{D-2}{2}}$. Here $\delta^{\mathrm{even}}_{\mathrm{atom\,type}}$ is also a coefficient that is dependent only on the atom type, i.e. C, NH, N, O or S, and γ_{even} is again a degradation coefficient.
6. For the *N*-methyl compounds, we add one more parameter, Δ_{N}, to adjust the difference between the *C*- and *N*-methyl compounds.
7. For 1-methyl-2*H*-isoindole, 1-methyl-isobenzofuran, 1-methyl-benzo[*c*] thiophene and those compounds in which the extra 'aromatization effect' can occur during the homolysis, we add one more parameter, $\Delta_{\mathrm{aromatization}}$, to correct this special effect.
8. The C—H BDE is finally calculated as

$$\mathrm{BDE} = \mathrm{BDE}_0 + \sum_{\mathrm{odd}-D\ \mathrm{atoms}} \delta^{\mathrm{odd}}_{\mathrm{atom\,type}} \cdot \gamma_{\mathrm{odd}}^{\frac{D-1}{2}} + \sum_{\mathrm{even}-D\ \mathrm{atoms}} \delta^{\mathrm{even}}_{\mathrm{atom\,type}} \cdot \gamma_{\mathrm{even}}^{\frac{D-2}{2}} + \Delta_N + \Delta_{\mathrm{aromatization}} \quad (5)$$

where BDE_0 is the hypothetic C—H BDE without any ring atom. It is worth noting that in Eqn (5) there are 15 independent, unknown parameters.

In order to optimize the above 15 parameters, we have developed a small energy-minimization program using Mathematica software. By using the 303 C—H BDE data we obtain the following optimum values for the parameters:

$$\begin{aligned}
\delta^{\mathrm{odd}}_{\mathrm{C}} &= -1.80 \pm 0.70;\ \delta^{\mathrm{even}}_{\mathrm{C}} = -0.61 \pm 0.81\\
\delta^{\mathrm{odd}}_{\mathrm{NH}} &= -2.02 \pm 0.90;\ \delta^{\mathrm{even}}_{\mathrm{NH}} = -3.69 \pm 1.05\\
\delta^{\mathrm{odd}}_{\mathrm{N}} &= +0.34 \pm 0.19;\ \delta^{\mathrm{even}}_{\mathrm{N}} = +2.09 \pm 0.85\\
\delta^{\mathrm{odd}}_{\mathrm{O}} &= -0.04 \pm 0.18;\ \delta^{\mathrm{even}}_{\mathrm{O}} = -3.40 \pm 1.18\\
\delta^{\mathrm{odd}}_{\mathrm{S}} &= -1.46 \pm 1.13;\ \delta^{\mathrm{even}}_{\mathrm{S}} = -4.20 \pm 1.12\\
\gamma_{\mathrm{odd}} &= +0.71 \pm 0.17;\ \gamma_{\mathrm{even}} = +0.58 \pm 0.06\\
\Delta_{\mathrm{N}} &= +3.47 \pm 0.57;\ \Delta_{\mathrm{aromatization}}\\
&= -5.09 \pm 0.64;\ \mathrm{BDE}_0 = 94.8 \pm 1.0
\end{aligned}$$

The error bar for each parameter in Eqn (5) is calculated by assuming that the standard deviation of the 'recommended' BDEs in Table 2 equals 2 kcal mol^{-1}. The detailed procedure for calculating the error bars is as follows. (1) For each theoretical BDE value ξ_i kcal mol^{-1} (i runs for all the bonds considered in this study), we assume that the probability of finding the real value (x) follows the Gaussian distribution (or normal distribution), i.e.

$$P(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{-(x-\xi_i)^2}{(2\sigma^2)}}$$

Here $\sigma = 2.0$ kcal mol^{-1} is the standard deviation of the calculation. (2) Using a program we can automatically generate the 'real' value for each bond by computer, so that the probability of generating a particular real value follows the Gaussian distribution equation. (3) Using the method in step 2, we can generate 'real' values for all the bonds. Using these 'real' values, we can optimize a set of parameters for Eqn (5). (4) We go back to step 2, regenerate a group of 'real' values and regenerate a set of parameters for Eqn (5). (5) When the above procedure is repeated 10 000 times, we obtain 10 000 sets of parameters for Eqn (5). Using these 10 000 sets of parameters, we can calculate the error bar for each parameter.

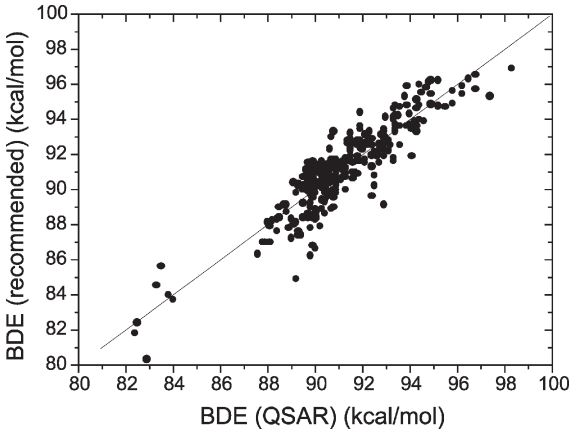


Figure 11. Correlation between the BDEs calculated using Eqn (5) and the recommended BDEs listed in Tables 1 and 2

The correlation between the BDEs calculated using Eqn (5) and the recommended BDEs listed in Tables 1 and 2 is shown in Fig. 11. The mean error of Eqn (5) is $0.0\,\mathrm{kcal\,mol^{-1}}$ and the standard deviation is $1.1\,\mathrm{kcal\,mol^{-1}}$. Therefore, Eqn (5) is a fairly successful QSAR model for the benzylic C—H BDEs of diverse heterocyclic compounds.

Analysis of the optimized parameters also reveals some valuable information about the effects of the heterocycles on the benzylic C—H BDEs. First, $\Delta_{\mathrm{N}} = +3.47 \pm 0.57\,\mathrm{kcal\,mol^{-1}}$, which is in agreement with the fact that *N*-methyl groups have systematically higher C—H BDEs than *C*-methyl groups. Second, $\Delta_{\mathrm{aromatization}} = -5.09 \pm 0.64\,\mathrm{kcal\,mol^{-1}}$. Hence the aromatization effect reduces the C—H BDEs significantly. Third, for NH, O and S groups, the coefficient for an even distance is more negative than that for an odd distance. This is consistent with the previous finding that a methyl group at the α-position relative to the NH, O and S groups usually has a lower BDE than that at the β-position, because the α-methyl group has an even distance ($D = 2$ bonds) and the β-methyl group has an odd distance ($D = 3$ bonds). Fourth, the coefficients for the N group are positive ($\delta_{\mathrm{N}}^{\mathrm{odd}} = +0.34 \pm 0.19$; $\delta_{\mathrm{N}}^{\mathrm{even}} = +2.09 \pm 0.85$), indicating that this group tends to increase the C—H BDE. Also, the coefficient for an even distance is more positive than that for an odd distance. This is consistent with the previous finding that a methyl group at the β-position relative to N has a lower C—H BDE than that at the α-position. Finally, $\gamma_{\mathrm{odd}} = +0.71 \pm 0.17$; $\gamma_{\mathrm{even}} = +0.58 \pm 0.06$. These two values indicate that the effect of the heteroatoms diminishes as the methyl–heteroatom distance increases.

CONCLUSIONS

We have calculated the C—H bond dissociation energies of methyl groups attached to a large number of heterocyclic compounds using the carefully calibrated B3LYP method. These C—H bond dissociation energies are important for evaluating the metabolic stability of methyl groups in heterocyclic compounds that may be used as drug candidates. In addition to the compilation of a large number of new, important and reliable data, we also made the following interesting findings.

1. The C—H BDEs of methyl groups attached diverse heterocycles can vary dramatically from ca 80 to ca $100\,\mathrm{kcal\,mol^{-1}}$. Therefore, the benzylic positions of different heterocycles may have remarkably different metabolic stabilities, ranging by about 10^{12}-fold.
2. The heteroatoms in the aromatic rings can vary the benzylic BDEs either by delocalizing the spin or by changing the charge carried by the radical center. Generally, more delocalization of the spin reduces the C—H BDEs, whereas an increase in the charge on the radical center amplifies the C—H BDEs.
3. *N*-Methyl groups have systematically higher C—H BDEs than *C*-methyl groups.
4. NH, O and S groups have similar effects on the benzylic C—H BDEs. A methyl group at the α-position relative to NH, O and S groups usually has a lower BDE than that at the β-position. On the other hand, the N group has a different effect on the benzylic C—H BDEs; a methyl group at the β-position relative to N has a lower C—H BDE than that at the α-position.
5. There is a special aromatization effect associated with 1-methyl-2*H*-isoindole, 1-methylisobenzofuran, 1-methylbenzo[*c*]thiophene and related compounds. This aromatization effect dramatically decreases the benzylic C—H BDEs.
6. An interesting QSAR model has been developed that can successfully predict the benzylic C—H BDEs of diverse heterocyclic compounds. It also quantitatively reveals the structure–activity relationships as discussed above.

Acknowledgement

We thank the NSFC (No. 20332020) for financial support.

REFERENCES

1. (a) Bhaduri AP. *Synlett* 1990; 557–564; (b) Kidwai M, Venkataramanan R, Mohan R, Sapra P. *Curr. Med. Chem.* 2002; **9**: 1209–1228; (c) Santagada V, Perissutti E, Caliendo G. *Curr. Med. Chem.* 2002; **9**: 1251–1283; (d) Brase S, Gil C, Knepper K. *Bioorg. Med. Chem.* 2002; **10**: 2415–2437; (e) Li Z-F, Luo F-Y. *Chin. J. Org. Chem.* 2002; **22**: 233–238; (f) Orru RVA, de Greef M. *Synthesis* 2003; 1471–1499; (g) Zheng H, Huang W, Lou R, Weng L. *Acta Pharm. Sini.* 2003; **38**: 75–78; (h) Yang DQ, Lu F, Guo W. *Chin. J. Org. Chem.* 2004; **24**: 366–373.
2. (a) Nefzi A, Ostresh JM, Houghten RA. *Chem. Rev.* 1997; **97**: 449–472; (b) Yu A-M, Yang H-Z, Zhang Z-P. *Chin. J. Org. Chem.* 1998; **18**: 275–281; (c) Ganesan A. *Drug Discov. Today* 2002; **7**:

47–55; (d) Zhu J. *Eur. J. Org. Chem.* 2003, 1133–1144; (e) Kundu B. *Curr. Opin. Drug Discov. Dev.* 2003; **6**: 815–823; (f) Xu Y, Guo Q-X. *Heterocycles* 2004; **63**: 903–974.
3. (a) Yu H, Adedoyin A. *Drug Discov. Today* 2003; **8**: 852–861; (b) Kubinyi H. *Nature Rev. Drug. Discov.* 2003; **2**: 665–668; (c) Roberts SA. *Curr. Opin. Drug. Discov. Dev.* 2003; **6**: 66–80; (d) Wilson AGE, White AC, Mueller RA. *Curr. Opin. Drug Discov. Dev.* 2003; **6**: 123–128; (e) Yang X, Yang X. *Prog. Chem.* 2002; **14**: 273–278; (f) Li AP. *Drug Discov. Today* 2001; **6**: 357–366; (g) Tarbit MH, Berman J. *Curr. Opin. Chem. Biol.* 1998; **2**: 411–416.
4. (a) Hou TJ, Xu XJ. *Curr. Pharm. Des.* 2004; **10**: 1011–1033; (b) Stouch TR, Kenyon JR, Johnson SR, Chen X-Q, Doweyko A, Li Y. *J. Comput.-Aided Mol. Des.* 2003; **17**: 83–92; (c) van de Waterbeemd H, Gifford E. *Nature Rev. Drug Discov.* 2003; **2**: 192–204; (d) Ekins S. *Biochem. Soc. Trans.* 2003; **31**: 611–614; (e) Langowski J, Long A. *Adv. Drug Deliv. Rev.* 2002; **54**: 407–415; (f) Grass GM, Sinko PJ. *Adv. Drug. Deliv. Rev.* 2002; **54**: 433–451.
5. Williams DA, Lemke TL. *Foye's Principles of Medicinal Chemistry* (5th edn). Lippincott Williams and Wilkins: Philadelphia, PA, 2002.
6. (a) Omura T. *Biochem. Biophys. Res. Commun.* 1999; **266**: 690–698; (b) Wang H, Peng R. *Acta Pharm. Sin.* 1999; **34**: 877–882; (c) Peter GF. *Arch. Biochem. Biophys.* 2002; **409**: 59–83; (d) Danielson PB. *Curr. Drug Metab.* 2002; **3**: 561–597; (e) Lewis DFV. *Pharmacogenomics* 2003; **4**: 387–395; (f) Yang XF, Wang NP, Lu WH, Zeng FD. *Acta Pharm. Sini.* 2003; **24**: 1033–1038; (g) Guo LQ, Yamazoe Y. *Acta Pharm. Sini.* 2004; **25**: 129–136.
7. (a) Jones JP, Korzekwa KR. *Methods Enzymol.* 1996; **272**: 326–335; (b) Lewin JL, Cramer CJ. *Mol. Pharm.* 2004; **1**: 128–135.
8. (a) Hansch C, Kurup A, Garg R, Gao H. *Chem. Rev.* 2001; **101**: 619–672; (b) Cherkasov AR, Jonsson M, Galkin VI, Cherkasov RA. *Usp. Khim.* 2001; **70**: 3–27; (c) Lin BL, Fu Y, Liu L, Guo QX. *Chin. Chem. Lett.* 2003; **14**: 1073–1076.
9. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA. *Gaussian 03, Revision A.1*. Gaussian: Pittsburgh, PA, 2003.
10. (a) McMillen DF, Golden DM. *Annu. Rev. Phys. Chem.* 1982; **33**: 493–532; (b) Blanksby SJ, Ellison GB. *Acc. Chem. Res.* 2003; **36**: 255–263.
11. Feng Y, Liu L, Wang J-T, Huang H, Guo Q-X. *J. Chem. Inf. Comput. Sci.* 2003; **43**: 2005–2013.
12. Tsang W. In *Energetics of Organic Free Radicals*, Simoes JAM, Greenberg A, Liebman JF (eds). Blackie Academic: New York, 1996, 22.
13. (a) Zhang YH, Wang DX, Ji GZ, Jiang XK. *Acta Chim. Sini.* 1989; **47**: 253–257; (b) Jiang X-K. *Acc. Chem. Res.* 1997; **30**: 283–289; (c) Shi J-L, Zhou C-M, Zhao X, Xu J-Y, Jiang X-K. *Chin. J. Chem.* 2001; **19**: 154–157; (d) He HY, Lin C, Zhao CX, Jiang XK. *Chin. Chem. Lett.* 2001; **12**: 1097–1100.
14. Song K-S, Liu L, Guo Q-X. *J. Org. Chem.* 2003; **68**: 4604–4607.
15. Reed AE, Curtiss LA, Weinhold E. *Chem. Rev.* 1988; **88**: 899–926.