

ARTICLE

Predicting Rate Constants for Nucleophilic Reactions of Amines with Diarylcarbenium Ions Using an ONIOM Method

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The rate constants of the nucleophilic reactions between amines and benzhydrylium ions were calculated using first-principles theoretical methods. Solvation models including PCM, CPCM, and COSMORS, as well as different types of atomic radii including UA0, UAKS, UAHF, Bondi, and UFF, and several single-point energy calculation methods (B3LYP, B3P86, B3PW91, BHANDH, PBEPBE, BMK, M06, MP2, and ONIOM method) were examined. By comparing the correlation between experimental rate constants and the calculated values, the ONIOM(CCSD(T)/6-311++G(2df,2p):B3LYP/6-311++G(2df,2p))/B3LYP/6-31G(d)/PCM/UFF method was found to perform the best. This method was then employed to calculate the rate constants of the reactions between diverse amines and diarylcarbenium ions. The calculated rate constants for 65 reactions of amines with diarylcarbenium ions are in agreement with the experimental values, indicating that it is feasible to predict the rate constant of a reaction between an amine and a diarylcarbenium ion through *ab initio* calculation.

Key words: Amine, Diarylcarbenium ion, Nucleophilic reaction, Rate constant, N-layered integrated molecule orbit and molecule mechanics

I. INTRODUCTION

The nucleophilic attack of amines on electrophilic carbon systems has been widely used in organic synthesis. Figure 1 shows some common reactions as examples: (i) amines can react with alkyl halides via S_N2 nucleophilic substitution mechanism, (ii) primary amines can react with aldehydes to afford imines, (iii) secondary amines can react with ketones to afford enamines, (iv) amines can react with carboxylic acid derivatives (acid chlorides or acid anhydrides) to form the corresponding amides.

The rate constants of the reactions between various amines and electrophilic carbon systems have been widely investigated [1]. Of particular interest, in 2007 Mayr and coworkers have studied the kinetics of the reactions of a series of primary and secondary amines with diarylcarbenium ions in water [2]. Based on these rate constants the nucleophilicity parameters of the amines were obtained. Besides the experiment studies, it is also important to obtain the reactivities of the reactions between amines and electron acceptors through theoretical approaches. However, up to now, there is no general theoretical method that can economically and precisely calculate the rate constants for the reaction of amines

with electrophiles. In recent years, many new computational methods have been developed and successfully used in calculating various reactions [3], which makes it possible to develop theoretical methods to accurately calculate the rate constants. In this work, we will report an examination of various computational methods in calculating the rate constants for the reactions of amines with diarylcarbenium ions.

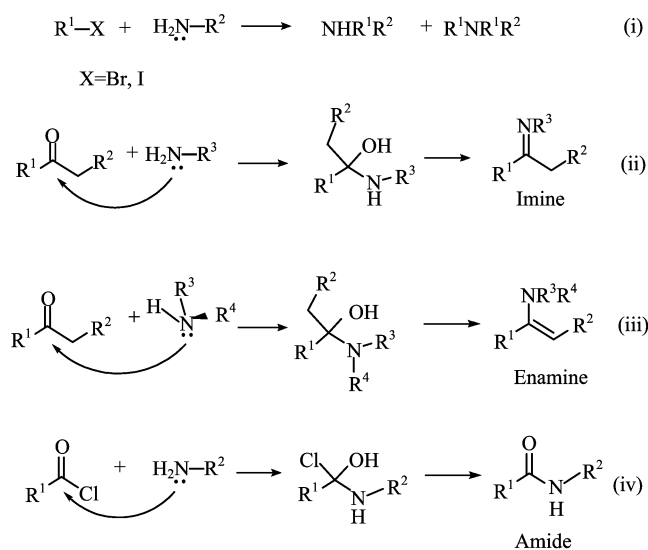


FIG. 1 Some common nucleophilic reactions between amines and electrophilic carbon systems.

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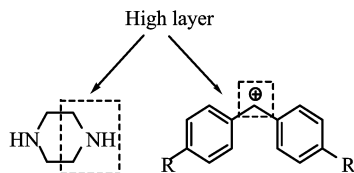


FIG. 2 An example for high layer in ONIOM method.

II. COMPUTATIONAL METHODS

All the calculations except for M06 calculation were conducted using Gaussian 03 packages [4]. The M06 calculation was conducted using NWChem programs [5]. The gas-phase geometries of all compounds were optimized using the (U)B3LYP/6-31G(d) method. The optimized structures were confirmed by the harmonic vibrational frequency calculation at the (U)B3LYP/6-31G(d) level to verify the minima and transition states. Several solvation models including PCM (polarizable continuum model) [6], CPCM (conductor-like polarizable continuum model) [7], and COSMORS (conductor like screening model for realistic solvents) [8], as well as different types of atomic radii including UAO, UAKS, UAHF, Bondi, and UFF, were examined. Single-point energies were then calculated with several DFT methods (B3LYP [9], B3P86 [10], B3PW91 [11], BHANDH [12], PBEPBE [13], BMK [14], M06 [15]) with 6-311++G(2df,2p) basis set, MP2 [16] method with 6-311+G(d,p), and ONIOM [17] method.

ONIOM (our own N-layered integrated molecule orbit and molecule mechanics) is an effective procedure to get as high as possible calculating accuracy with available computing cost. This method divides a molecule into two or three layers which are treated by methods with different accuracy. In a two-layer ONIOM system, the high layer, also named as small model system, is the region in which the bond formation and breaking occurs and therefore should be treated with high level method. The low layer is the whole molecule and typically treated with low level method. In our system, high layer is defined as attacking N atom and its link atoms in amines and the carbon cation center in diarylcarbenium ions. An example is shown in Fig.2. For high layer, CCSD(T)/6-311++G(2df,2p) method was used, whereas low layer which is the real system was treated by B3LYP/6-311++G(2df,2p).

The sum of Gibbs free-energy correction from frequency calculation, single-point energy, and solvation free energy is the Gibbs free energy in solution. All solution-phase free energies reported in the paper correspond to the reference state of 1 mol/L, 298.15 K.

III. RESULTS AND DISCUSSION

In order to evaluate the calculation methods, seven amines and four diarylcarbenium ions were chosen, which are shown as a01–a07 and d01–d04 in Fig.3.

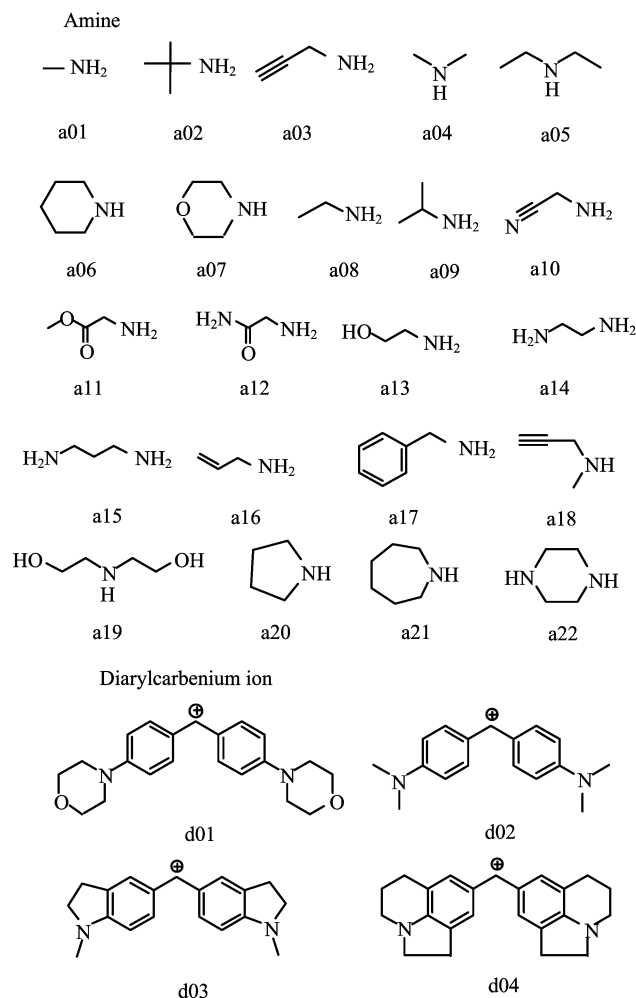


FIG. 3 Chemical structures of amines and diarylcarbenium ions used in this work.

These amines, including primary aliphatic amines, secondary aliphatic amines, and alicyclic amines, were considered to be representative. The rate constants of most reactions between the amines and the diarylcarbenium ions have already been measured [2] and were used to evaluate the computational methods.

For the reaction between the amines and diarylcarbenium ions, the energy barrier could be calculated using standard transition state theory [18]. A representative example of optimized structures of the reactants and transition state in the reaction of bis(4-(dimethylamino)phenyl)carbenium ion and piperidine is shown in Fig.4. Compared with the reactants, in the transition state the C1–C2, C1–C3, N1–C4, and N1–C5 bonds are all slightly elongated while the C2–C1–C3 bond angle is lessened, and the C1–N1 distance is 2.114 Å as opposed to 1.47 Å for a standard sp^3 - sp^3 C–N bond length.

Then the free energy barriers was converted to rate

TABLE II Performances of different single-point calculation methods for calculating the second-order rate constants for the benchmark reactions (unit in $(\text{s mol/L})^{-1}$).

Entry	Method	Correlation equation	Correlation coefficient	rmse
1	B3LYP/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.498\lg k_{\text{calc}}+5.19$	0.860	0.70
2	B3P86/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.531\lg k_{\text{calc}}+3.58$	0.890	0.63
3	B3PW91/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.520\lg k_{\text{calc}}+4.47$	0.867	0.69
4	BHANDH/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.556\lg k_{\text{calc}}-0.70$	0.895	0.62
5	PBEPBE/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.511\lg k_{\text{calc}}+3.39$	0.888	0.64
6	BMK/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.549\lg k_{\text{calc}}+3.26$	0.910	0.57
7	M06/6-311++G(2df,2p)	$\lg k_{\text{exp}}=0.535\lg k_{\text{calc}}+2.00$	0.911	0.57
8	MP2/6-311+G(d,p)	$\lg k_{\text{exp}}=0.452\lg k_{\text{calc}}-1.32$	0.840	0.75
9	ONIOM(CCSD(T)/6-311++G(2df, 2p): B3LYP/6-311++G(2df,2p))	$\lg k_{\text{exp}}=0.516\lg k_{\text{calc}}+5.20$	0.932	0.50

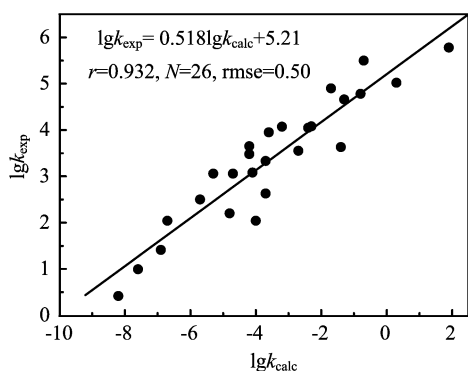


FIG. 5 Correlation between experimental rate constants and the ONIOM calculated values for the benchmark reactions.

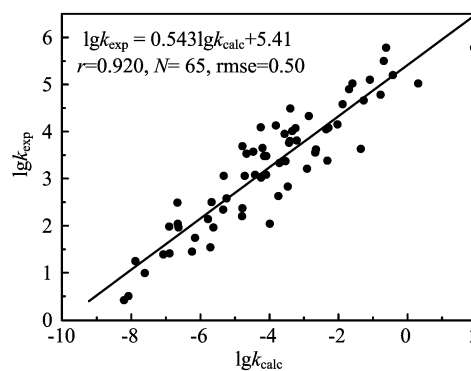


FIG. 6 Correlation between experimental rate constants and the calculated values for the reactions of amines with diarylcarbenium ions.

methods. However, MP2 method with higher basis set is too resource-demanding so that we deem that the MP2 method is not suitable for calculating this system. Among the seven DFT methods, BMK and M06 method developed by Truhlar's group in recent years both have relatively good performance. For M06 the correlation coefficient is 0.911 and rmse is 0.57. Other than global DFT calculation, we hope higher level and more accurate method such as coupled cluster method could be used for calculation. Unfortunately, coupled cluster method is so expensive that it could be only used to calculate the system less than 8 non-hydrogen atoms. Consequently, ONIOM method was used. It is very gratifying that the ONIOM method performs even better than M06, suggesting that it is necessary to improve the calculation accuracy for the reaction center. The correlation coefficient is up to 0.932 and the rmse is down to 0.50. Figure 5 shows the correlation between experimental rate constants and the ONIOM calculated values for the benchmark reactions.

It is suggested that the ONIOM(CCSD(T)/6-311++G(2df,2p):B3LYP/6-311++G(2df,2p))/B3LYP/6-31G(d)/PCM/UFF method is a appropriate method to calculate the rate constants for the reaction of amines

with diarylcarbenium ions. Subsequently, the method was used to calculate the rate constants of the reactions between more amines (Fig.3) and diarylcarbenium ions. The calculated parameters compared with experimental values are shown in Table III.

Figure 6 illustrates the correlation between experimental rate constants and the ONIOM calculated values for the reactions of amines with diarylcarbenium ions. There is a good correlation between experimental rate constants and the calculated values for the 65 reactions of amines with diarylcarbenium ions. The correlation equation is $\lg k_{\text{exp}}=0.543\lg k_{\text{calc}}+5.41$ with a correlation coefficient of 0.920 and rmse of 0.50. Using this correlation equation, the credible rate constant of a reaction between an amine and a diarylcarbenium ion could be obtained through calculation.

IV. CONCLUSION

The rate constants of the reactions between amines and benzhydrylium ions were calculated by first-principles theoretical methods for the first time. Solvation models including PCM, CPCM, and COSMORS, as well as different types of atomic radii

TABLE III Experimental rate constants k ((s mol/L)⁻¹), $\lg k$, theoretical free energy barriers ΔG^\ddagger (kJ/mol) and $\lg k$ for the reactions of amines with diarylcarbenium ions. Calculation was performed using ONIOM(CCSD(T)/6-311++G(2df,2p):B3LYP/6-311++G(2df, 2p)//B3LYP/6-31G(d)/PCM/UFF.

Amine	Diarylcarbenium	ΔG^\ddagger	$\lg k_{\text{calc}}$	$\lg k_{\text{exp}}$	k_{exp}	Amine	Diarylcarbenium	ΔG^\ddagger	$\lg k_{\text{calc}}$	$\lg k_{\text{exp}}$	k_{exp}
a01	d02	79.4	-1.35	3.63	4.25×10^3	a11	d02	96.6	-4.41	3.08	1.21×10^3
	d03	92.8	-3.74	2.63	4.24×10^2	a12	d01	90.3	-3.34	4.01	1.03×10^4
	d04	94.1	-3.99	2.04	1.11×10^2		d02	95.7	-4.24	3.02	1.05×10^3
a02	d01	92.4	-3.71	3.33	2.14×10^3		d03	109.1	-6.63	1.96	92.2
	d02	98.6	-4.79	2.20	160		d04	111.2	-7.07	1.39	24.5
	d03	114.5	-7.60	1.00	9.90	a13	d01	83.2	-2.03	4.15	1.40×10^4
	d04	117.9	-8.21	0.42	2.61		d02	88.2	-2.91	3.21	1.64×10^3
a03	d01	89.9	-3.25	4.07	1.17×10^4		d04	103.7	-5.71	1.54	35.0
	d02	94.9	-4.10	3.08	1.20×10^3		d01	82.3	-1.88	4.58	3.78×10^4
	d03	109.1	-6.65	2.04	109		d02	86.5	-2.65	3.62	4.19×10^3
	d04	110.4	-6.89	1.41	25.7		d03	101.2	-5.24	2.58	378
a04	d01	61.0	1.93	5.78	6.10×10^5		d04	103.2	-5.62	1.96	90.3
	d02	69.8	0.31	5.02	1.05×10^5	a15	d02	91.1	-3.43	3.76	5.80×10^3
	d03	84.4	-2.29	4.08	1.20×10^4		d04	104.1	-5.78	2.14	138
	d04	86.5	-2.67	3.55	3.52×10^3	a16	d02	91.5	-3.53	3.37	2.35×10^3
a05	d01	81.1	-1.69	4.90	7.92×10^4		d04	106.2	-6.15	1.74	55.3
	d02	84.9	-2.36	4.05	1.12×10^4	a17	d01	90.7	-3.39	4.49	3.13×10^4
	d03	101.6	-5.32	3.06	1.16×10^3		d02	94.5	-4.09	3.48	3.04×10^3
	d04	103.7	-5.67	2.50	316		d03	109.1	-6.66	2.49	306
a06	d02	76.1	-0.78	4.78	6.09×10^4		d04	110.4	-6.90	1.98	94.6
	d03	91.5	-3.56	3.95	9.01×10^3	a18	d02	89.9	-3.21	3.81	6.47×10^3
	d04	94.9	-4.15	3.48	3.05×10^3	a19	d02	98.6	-4.78	3.69	4.88×10^3
a07	d01	75.7	-0.69	5.50	3.16×10^5	a20	d02	80.7	-1.59	5.02	1.06×10^5
	d02	79.0	-1.27	4.66	4.61×10^4		d03	95.7	-4.25	4.09	1.22×10^4
	d03	95.3	-4.20	3.65	4.51×10^3		d04	97.8	-4.66	3.53	3.41×10^3
	d04	98.2	-4.72	3.06	1.14×10^3	a21	d02	74.0	-0.42	5.20	1.60×10^5
a08	d02	84.9	-2.32	3.38	2.39×10^3		d03	87.8	-2.86	4.33	2.13×10^4
	d03	98.6	-4.78	2.37	236		d04	90.7	-3.41	3.80	6.37×10^3
						a22	d01	75.2	-0.62	5.78	6.10×10^5
a09	d02	91.1	-3.47	2.83	670		d02	77.7	-1.09	5.10	1.27×10^5
	d04	106.6	-6.24	1.45	27.9		d03	93.2	-3.81	4.13	1.36×10^4
a10	d02	101.6	-5.34	2.34	219		d04	97.0	-4.47	3.57	3.74×10^3
	d03	115.8	-7.88	1.25	17.9						
	d04	117.0	-8.08	0.51	3.20						

including UA0, UAKS, UAHF, Bondi, and UFF, and several single-point energy calculation methods (B3LYP, B3P86, B3PW91, BHANDH, PBEPBE, BMK, M06, MP2, and ONIOM method) were employed to calculate the second-order rate constants for the reaction of amines with benzhydrylium ions. By examining the correlation between experimental rate constants and the calculated values, ONIOM(CCSD(T)/6-311++G(2df,2p):B3LYP/6-311++G(2df,2p)//B3LYP/6-31G(d)/PCM/UFF was found to perform best in calculating the rate constants for the reaction of amines with benzhydrylium ions. This method was then employed to calculate the rate constants of the reactions between more amines and di-

arylcarbenium ions. The calculated rate constants for 65 reactions of amines with diarylcarbenium ions are in agreement with the experimental values, indicating that it is feasible to predict the rate constant of a reaction between an amine and a diarylcarbenium ion through calculation. Further study of the application of this method to other nucleophilic reactions is undergoing in our laboratory and will be reported in due course.

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