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Journal of Organic Chemistry

REACTIONS OF SUBSTITUTED METHYLTHIOBENZYLIDENE MELDRUM'S ACIDS WITH SECONDARY ALICYCLIC AMINES IN AQUEOUS DMSO. EVIDENCE FOR RATE LIMITING PROTON TRANSFER

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Table S1. Rate Constants for the Hydrolysis of **2-SMe-Z** by OH^- and Water in 50% DMSO-50% Water (v/v) at 20°C.[a]

Z	k_{OH} $M^{-1}\ s^{-1}$	$10^6 \times k_{H_2O}$ s^{-1}
CF_3	1.34 ± 0.05	4.58 ± 0.01
Br	0.92 ± 0.03	3.27 ± 0.01
H	0.69 ± 0.03	2.98 ± 0.03
CH_3	0.49 ± 0.03	2.42 ± 0.06
CH_3O	0.46 ± 0.03	2.33 ± 0.05

[a] μ = 0.5 M (KCl).

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Table S2. Reaction of **2-SMe-H** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, pH 10.93[a]: Dependence on Amine Concentration.

$[R_2NH]_{free}$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\ s^{-1}$
0.0004	2.31×10^{-4}	2.24×10^{-4}	0.509
0.0013	1.40×10^{-3}	1.39×10^{-3}	1.04
0.0022	2.96×10^{-3}	2.95×10^{-3}	1.32
0.0031	5.09×10^{-3}	5.08×10^{-3}	1.62
0.0045	8.97×10^{-3}	8.96×10^{-3}	2.00
0.0067	1.71×10^{-2}	1.71×10^{-2}	2.54
0.0090	2.55×10^{-2}	2.55×10^{-2}	2.84
0.0224	7.48×10^{-2}	7.48×10^{-2}	3.34
0.0448	1.59×10^{-1}	1.59×10^{-1}	3.55
0.0673	2.43×10^{-1}	2.43×10^{-1}	3.61
0.0897	3.24×10^{-1}	3.24×10^{-1}	3.61
0.112	4.15×10^{-1}	4.15×10^{-1}	3.70

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S3. Reaction of **2-SMe-H** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C,[a] [Piperidine] = 0.05 M: Dependence on [OH^-].

[OH^-] M	k_{obsd} s^{-1}	k_{obsd}(corr)[b] s^{-1}	k_A $M^{-1}\ s^{-1}$
5.01×10^{-7}	6.97×10^{-3}	6.97×10^{-3}	1.39
8.91×10^{-7}	7.12×10^{-3}	7.12×10^{-3}	1.42
1.58×10^{-6}	8.39×10^{-3}	8.39×10^{-3}	1.68
2.82×10^{-6}	9.20×10^{-3}	9.20×10^{-3}	1.84
5.01×10^{-6}	9.52×10^{-3}	9.51×10^{-3}	1.90
8.91×10^{-6}	1.02×10^{-2}	1.02×10^{-2}	2.03
1.58×10^{-5}	1.14×10^{-2}	1.14×10^{-2}	2.28
2.82×10^{-5}	1.42×10^{-2}	1.42×10^{-2}	2.84
5.01×10^{-5}	1.57×10^{-2}	1.57×10^{-2}	3.13
8.91×10^{-5}	1.95×10^{-2}	1.94×10^{-2}	3.89
1.58×10^{-4}	2.16×10^{-2}	2.14×10^{-2}	4.29
2.82×10^{-4}	2.08×10^{-2}	2.06×10^{-2}	4.12

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(\text{corr}) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S4. Reaction of **2-SMe-H** with Piperazine in 50% DMSO-50% Water (v/v) at 20°C, pH 9.90[a]: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\,s^{-1}$
0.002	6.02×10^{-4}	5.98×10^{-4}	0.300
0.003	1.04×10^{-3}	$1.04 \times 10^{-}$	0.346
0.004	1.51×10^{-3}	1.51×10^{-3}	0.377
0.005	2.39×10^{-3}	2.39×10^{-3}	0.477
0.0075	4.84×10^{-3}	4.84×10^{-3}	0.645
0.0112	9.62×10^{-3}	9.62×10^{-2}	0.855
0.015	1.49×10^{-2}	1.49×10^{-2}	0.993
0.025	2.93×10^{-2}	2.93×10^{-2}	1.17
0.035	4.22×10^{-2}	4.22×10^{-2}	1.21
0.050	6.35×10^{-2}	6.35×10^{-2}	1.27
0.075	9.46×10^{-2}	9.46×10^{-2}	1.26
0.100	1.30×10^{-1}	1.30×10^{-1}	1.30

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S5. Reaction of **2-SMe-H** with Piperazine in 50% DMSO-50% Water (v/v) at 20°C,[a] [Piperazine] = 0.008 M: Dependence on [OH^-].

[OH^-] M	k_{obsd} s^{-1}	k_{obsd}(corr)[b] s^{-1}	k_A $M^{-1}\ s^{-1}$
7.08×10^{-6}	8.29×10^{-3}	8.29×10^{-3}	1.04
1.12×10^{-5}	9.09×10^{-3}	9.08×10^{-3}	1.13
1.58×10^{-5}	9.76×10^{-3}	9.75×10^{-3}	1.22
2.00×10^{-4}	1.00×10^{-2}	9.86×10^{-3}	1.23
6.00×10^{-4}	1.12×10^{-2}	1.08×10^{-2}	1.35
8.00×10^{-4}	1.14×10^{-2}	1.08×10^{-2}	1.35
1.00×10^{-3}	1.20×10^{-2}	1.13×10^{-2}	1.41
3.00×10^{-3}	1.45×10^{-2}	1.25×10^{-2}	1.56
5.00×10^{-3}	1.62×10^{-2}	1.28×10^{-2}	1.60
1.00×10^{-2}	2.00×10^{-2}	1.31×10^{-2}	1.64
3.00×10^{-2}	3.40×10^{-2}	1.34×10^{-2}	1.67

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S6. Reaction of **2-SMe-H** with HEPA in 50% DMSO-50% Water (v/v) at 20°C,[a] pH 9.50: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\,s^{-1}$
0.0025	2.00×10^{-4}	1.97×10^{-4}	0.079
0.005	5.18×10^{-4}	5.15×10^{-4}	0.103
0.010	1.50×10^{-3}	1.50×10^{-3}	0.150
0.015	3.06×10^{-3}	3.06×10^{-3}	0.204
0.025	7.87×10^{-3}	7.87×10^{-3}	0.315
0.035	1.29×10^{-2}	1.29×10^{-2}	0.368
0.050	2.08×10^{-2}	2.08×10^{-2}	0.416
0.075	3.78×10^{-2}	3.78×10^{-2}	0.504
0.100	5.40×10^{-2}	5.40×10^{-2}	0.540
0.125	7.36×10^{-2}	7.36×10^{-2}	0.589
0.150	9.00×10^{-2}	9.00×10^{-2}	0.600
0.200	1.22×10^{-1}	1.22×10^{-1}	0.610

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S7. Reaction of **2-SMe-H** with HEPA in 50% DMSO-50% Water (v/v) at 20°C,[a] [HEPA] = 0.03 M: Dependence on [OH^-].

$[OH^-]$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\,s^{-1}$
0.0005	8.60×10^{-3}	8.26×10^{-3}	0.275
0.0007	1.33×10^{-2}	1.28×10^{-2}	0.427
0.0010	1.72×10^{-2}	1.65×10^{-2}	0.550
0.0030	2.76×10^{-2}	2.55×10^{-2}	0.851
0.0050	3.07×10^{-2}	2.73×10^{-2}	0.909
0.0070	3.49×10^{-2}	3.01×10^{-2}	1.00
0.0100	3.94×10^{-2}	3.25×10^{-2}	1.09
0.0200	5.03×10^{-2}	3.66×10^{-2}	1.22
0.0600	8.16×10^{-2}	4.04×10^{-2}	1.35
0.0800	9.57×10^{-2}	4.08×10^{-2}	1.36
0.0900	1.30×10^{-1}	4.13×10^{-2}	1.38
0.100	1.10×10^{-1}	4.18×10^{-2}	1.39

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S8. Reaction of **2-SMe-H** with Morpholine in 50% DMSO-50% Water (v/v) at 20°C,[a] pH 8.70: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\ s^{-1}$
0.005	1.62×10^{-4}	1.59×10^{-4}	0.032
0.015	9.20×10^{-4}	9.17×10^{-4}	0.061
0.025	2.61×10^{-2}	$2.60 \times 10^{-}$	0.104
0.035	4.80×10^{-3}	4.80×10^{-3}	0.137
0.050	8.93×10^{-3}	8.39×10^{-3}	0.168
0.75	1.70×10^{-2}	1.70×10^{-2}	0.227
0.100	2.52×10^{-2}	2.52×10^{-2}	0.252
0.125	3.42×10^{-2}	3.42×10^{-2}	0.274
0.150	4.72×10^{-2}	4.72×10^{-2}	0.315
0.200	6.52×10^{-2}	6.52×10^{-2}	0.326

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S9. Reaction of **2-SMe-H** with Morpholine in 50% DMSO-50% Water (v/v) at 20°C,[a] [morpholine] = 0.03 M: Dependence on [OH^-].

[OH^-] M	k_{obsd} s^{-1}	k_{obsd}(corr)[b] s^{-1}	k_A M^{-1} s^{-1}
0.001	1.52×10^{-2}	1.45×10^{-2}	0.415
0.002	2.25×10^{-2}	2.11×10^{-2}	0.604
0.004	2.65×10^{-2}	2.38×10^{-2}	0.679
0.006	3.14×10^{-2}	2.73×10^{-2}	0.780
0.008	3.55×10^{-2}	3.00×10^{-2}	0.858
0.010	4.24×10^{-2}	3.56×10^{-2}	1.02
0.030	5.66×10^{-2}	3.61×10^{-2}	1.03
0.050	7.02×10^{-2}	3.66×10^{-2}	1.05
0.070	8.36×10^{-2}	3.59×10^{-2}	1.03
0.100	1.06×10^{-2}	3.78×10^{-2}	1.08

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(\text{corr}) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S10. Reaction of **2-SMe-CF$_3$** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, pH 11.02[a]: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	$k_{obsd} = k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\,s^{-1}$
0.0025	9.96×10^{-3}	3.98
0.0035	1.68×10^{-2}	4.80
0.0050	2.84×10^{-2}	5.68
0.0075	4.60×10^{-2}	6.13
0.010	7.11×10^{-2}	7.11
0.0125	9.65×10^{-2}	7.72
0.015	1.18×10^{-1}	7.89
0.0175	1.39×10^{-1}	7.94
0.025	2.04×10^{-1}	8.16

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S11. Reaction of **2-SMe-CF$_3$** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C,[a] [Piperidine] = 0.005 M: Dependence on [OH$^-$].

[OH$^-$] M	k_{obsd} s^{-1}	k_{obsd}(corr)[b] s^{-1}	k_A $M^{-1}\,s^{-1}$
5.01×10^{-7}	1.91×10^{-2}	1.91×10^{-2}	3.82
8.91×10^{-7}	2.08×10^{-2}	2.08×10^{-2}	4.16
1.58×10^{-6}	2.21×10^{-2}	2.21×10^{-2}	4.43
2.82×10^{-6}	2.27×10^{-2}	2.27×10^{-2}	4.54
5.01×10^{-6}	2.40×10^{-2}	2.40×10^{-2}	4.80
8.91×10^{-6}	2.70×10^{-2}	2.70×10^{-2}	5.40
1.58×10^{-6}	3.08×10^{-2}	3.08×10^{-2}	6.16
2.82×10^{-5}	3.60×10^{-2}	3.60×10^{-2}	7.19
5.01×10^{-5}	4.32×10^{-2}	4.31×10^{-2}	8.63
8.91×10^{-5}	4.66×10^{-2}	4.65×10^{-2}	9.30
1.58×10^{-4}	4.89×10^{-2}	4.87×10^{-2}	9.74
2.82×10^{-4}	5.00×10^{-2}	4.96×10^{-2}	9.92

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(\text{corr}) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S12. Reaction of **2-SMe-Br** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, pH 11.02[a]: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	$k_{obsd} = k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\ s^{-1}$
0.0025	5.70×10^{-3}	2.28
0.0035	1.04×10^{-2}	2.97
0.0050	1.94×10^{-2}	3.88
0.0075	3.80×10^{-2}	5.07
0.010	5.47×10^{-2}	5.47
0.0125	6.90×10^{-2}	5.52
0.015	8.95×10^{-2}	5.97
0.0250	0.154	6.16
0.050	0.305	6.10

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S13. Reaction of **2-SMe-Br** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, [Piperidine] = 0.005 M [a]: Dependence on [OH^-].

$[OH^-]$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$ [b] s^{-1}	k_A $M^{-1}\ s^{-1}$
5.01×10^{-7}	1.26×10^{-2}	1.26×10^{-2}	2.52
8.91×10^{-7}	1.31×10^{-2}	1.31×10^{-2}	2.62
1.58×10^{-6}	1.36×10^{-2}	1.36×10^{-2}	2.72
2.82×10^{-6}	1.43×10^{-2}	1.43×10^{-2}	2.86
5.01×10^{-6}	1.66×10^{-2}	1.66×10^{-2}	3.32
8.91×10^{-6}	1.95×10^{-2}	1.95×10^{-2}	3.90
1.58×10^{-5}	2.16×10^{-2}	2.16×10^{-2}	4.32
2.82×10^{-5}	2.53×10^{-2}	2.53×10^{-2}	5.06
5.01×10^{-5}	3.00×10^{-2}	3.00×10^{-2}	5.99
8.91×10^{-5}	3.57×10^{-2}	3.56×10^{-2}	7.13
1.58×10^{-4}	3.70×10^{-2}	3.69×10^{-2}	7.38
2.82×10^{-4}	3.72×10^{-2}	3.70×10^{-2}	7.40

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S14. Reaction of **2-SMe-Me** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, pH 11.02[a]: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	$k_{obsd} = k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\ s^{-1}$
0.0025	2.43×10^{-3}	0.97
0.0035	4.22×10^{-3}	1.21
0.0050	8.30×10^{-3}	1.66
0.010	2.19×10^{-2}	2.19
0.015	3.73×10^{-2}	2.49
0.025	6.57×10^{-2}	2.63
0.035	9.32×10^{-2}	2.66
0.050	1.44×10^{-1}	2.89
0.100	2.88×10^{-1}	2.88

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

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Table S15. Reaction of **2-SMe-Me** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, [Piperidine] = 0.005 M [a]: Dependence on [OH^-].

$[OH^-]$ M	k_{obsd} s^{-1}	$k_{obsd}(corr)$ [b] s^{-1}	k_A $M^{-1}s^{-1}$
5.01×10^{-7}	6.35×10^{-3}	6.35×10^{-3}	1.27
8.91×10^{-7}	6.50×10^{-3}	6.50×10^{-3}	1.30
1.58×10^{-6}	6.66×10^{-3}	6.66×10^{-3}	1.33
2.82×10^{-6}	6.82×10^{-3}	6.82×10^{-3}	1.36
5.01×10^{-6}	7.20×10^{-3}	7.20×10^{-3}	1.44
8.91×10^{-6}	7.80×10^{-3}	7.79×10^{-3}	1.56
1.58×10^{-5}	8.46×10^{-3}	8.45×10^{-3}	1.69
2.82×10^{-5}	9.90×10^{-3}	9.07×10^{-3}	1.82
5.01×10^{-5}	1.15×10^{-2}	1.14×10^{-2}	2.29
8.91×10^{-5}	1.38×10^{-2}	1.37×10^{-2}	2.74
1.58×10^{-4}	1.45×10^{-2}	1.44×10^{-2}	2.88
2.82×10^{-4}	1.50×10^{-2}	1.49×10^{-2}	2.97

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

C. F. Bernasconi, M. Ali, K. Nguyen, V. Ruddat, and Z. Rappoport, "Reactions of Substituted Methylthiobenzylidene Meldrum's Acids with Secondary Alicyclic Amines in Aqueous DMSO. Evidence for Rate Limiting Proton Transfer."

Table S16. Reaction of **2-MeS-OMe** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, pH 11.02[a]: Dependence on Amine Concentration.

$[[R_2NH]_{free}$ M	$k_{obsd} = k_{obsd}(corr)$[b] s^{-1}	k_A $M^{-1}\,s^{-1}$
0.0025	2.20×10^{-3}	0.88
0.0035	3.53×10^{-3}	1.01
0.0050	5.58×10^{-3}	1.11
0.010	1.35×10^{-2}	1.35
0.015	2.20×10^{-2}	1.47
0.025	4.59×10^{-2}	1.84
0.035	7.14×10^{-2}	2.04
0.050	1.06×10^{-1}	2.11
0.100	2.12×10^{-1}	2.12
0.150	3.20×10^{-1}	2.13

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(corr) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

C. F. Bernasconi, M. Ali, K. Nguyen, V. Ruddat, and Z. Rappoport, "Reactions of Substituted Methylthiobenzylidene Meldrum's Acids with Secondary Alicyclic Amines in Aqueous DMSO. Evidence for Rate Limiting Proton Transfer."

Table S17. Reaction of **2-MeS-OMe** with Piperidine in 50% DMSO-50% Water (v/v) at 20°C, [Piperidine] = 0.005 M [a]: Dependence on [OH^-].

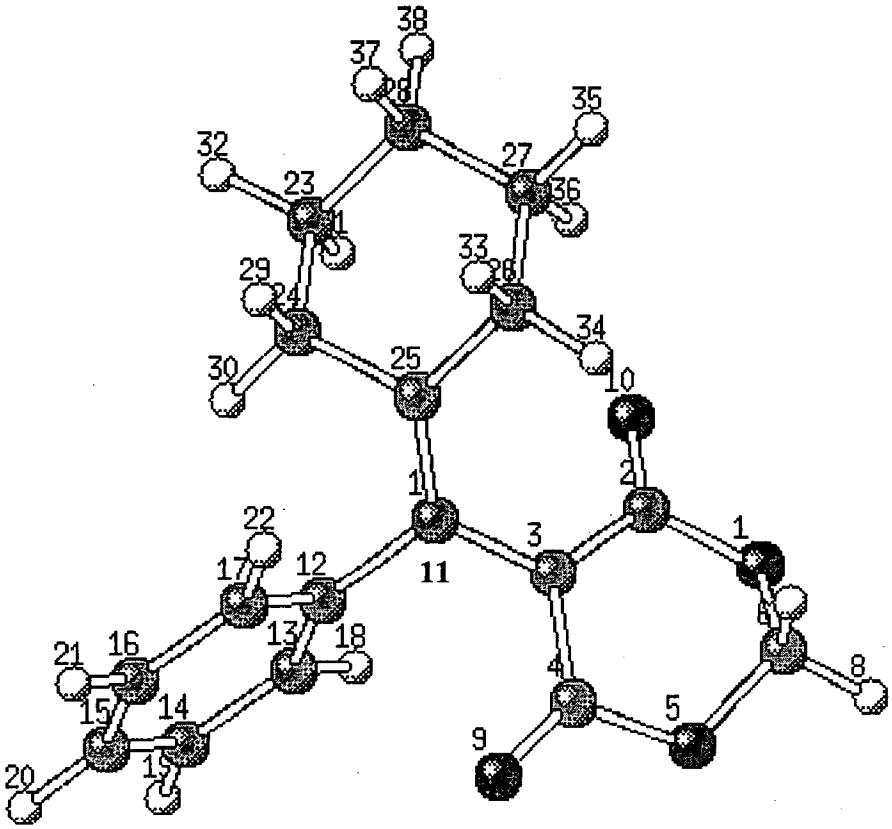
[OH^-] M	k_{obsd} s^{-1}	k_{obsd}(corr) [b] s^{-1}	k_A M^{-1} s^{-1}
5.01×10^{-7}	4.28×10^{-3}	4.28×10^{-3}	0.856
8.91×10^{-7}	4.75×10^{-3}	4.75×10^{-3}	0.950
1.58×10^{-6}	4.66×10^{-3}	4.66×10^{-3}	0.932
2.82×10^{-6}	4.68×10^{-3}	4.68×10^{-3}	0.936
5.01×10^{-6}	4.80×10^{-3}	4.80×10^{-3}	0.960
8.91×10^{-6}	5.08×10^{-3}	5.08×10^{-3}	1.02
1.58×10^{-5}	5.50×10^{-3}	5.49×10^{-3}	1.10
2.82×10^{-5}	6.64×10^{-3}	6.62×10^{-3}	1.33
5.01×10^{-5}	7.90×10^{-3}	7.87×10^{-3}	1.58
8.91×10^{-5}	9.96×10^{-3}	9.92×10^{-3}	1.99
1.58×10^{-4}	1.25×10^{-2}	1.24×10^{-2}	2.49
2.82×10^{-4}	1.26×10^{-2}	1.25×10^{-3}	2.50

[a] $\mu = 0.5$ (KCl). [b] $k_{obsd}(\text{corr}) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-]$.

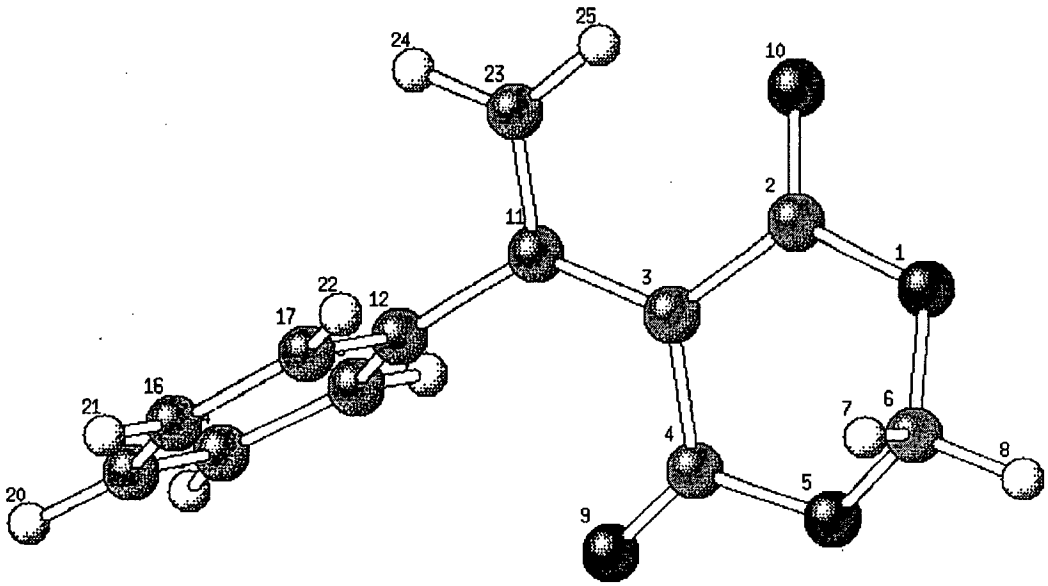
B3LYP/6-311G(d) optimization
Geometry:

(a)

R(C11-C12)= 1.492 Å ; R(C11-C3)= 1.416 Å; R(C11-N25) = 1.344 Å
∠ C12C11C3C4 = -27.5 ; ∠ N25C11C3C2 =-39.5 ; ∠ C12C11N25C3 =179.9
∠ C26C25C11C3 = -23.3 ∠ C24C25C11C12 = -19.0
Charges:
C11 +0.38 e ; N25 -0.39e; C3 -0.45e; C12 0.0
The whole Meldrum Moiety -0.59e
The whole piperidine +0.15e
The phenyl group +0.06



(b)



Geometry:
R(C11-C3) = 1.400; R(C11-N23) =1.336 ; R(C11-C12) 1.4966
∠ H25N23C11C3 = 5.0; ∠ C2C3C11N23 = -0.4; ∠ C17C12C11C3 = 107.1

Charges:

C11 +0.38e
C3 -0.44e
N23 -0.68e

Charge on: the whole Meldrum Moiety:	-0.58e
NH2	+0.1e
Phenyl	+0.1e
Occupancy on the π(C11-C3)	1.72e
Occupancy in the N23 lone pair orbital	1.6e