 © 1988 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 61, 2387—2391 (1988)

Reaction of 1,1,2,2-Tetrachloro-2,2aα,4α,8bα-tetrahydrocyclobuta-[c]quinolin-3(1H)-one with Nucleophiles; Reaction, Product Structure, and Mechanism[1)]

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(Received November 11, 1987)

2a-Substituted dichlorodihydrocyclobuta[c]quinolin-3(4H)-one (**3**) and trichlorovinyl-2-quinolone (**4**) were obtained from the cross photocycloadduct of 2-quinolone and tetrachloroethylene. The position of the substituent on **3** was determined from the NOE volumes in the NOESY spectrum in comparison with the AM1 geometries. The reaction of the photoadduct (**1**) with a base or nucleophile, yielding **3** and/or **4**, was interpreted to proceed via a cyclobutene intermediate formation followed by an S_N2' displacement or [2+2] cycloreversion.

The reactivity of a heterocyclic ring, such as a coumarin ring, shows enhanced reactivity when a cyclobutane ring is fused to that ring by photochemical cyclobutanation. We have reported high reactivities of coumarin dimers and their lactone-opened derivatives.[2,3)] In previous papers,[4)] we showed unique reaction behaviors of the photocycloadduct of coumarin with tetrachloroethylene, such as (a) ring contraction from a [4,6,6]- to a [4,5,6]-fused ring system through a lactone-opening, (b) cyclobutene formation, followed by an intramolecular S_N2' displacement, and (c) a [2+2] cycloreversion at the cyclobutene intermediate, yielding trichlorovinylcoumarin. These behaviors were ascribed to the strain in lactone ring induced by the adjacent cyclobutane ring.

As a part of a continuing study of compounds having a [4,6,6]-fused ring system, we investigated the reaction of 1,1,2,2-tetrachloro-2,2aα,4α,8bα-tetrahydrocyclobuta[c]quinolin-3(1H)-one (**1**), a cyclobutane-fused quinolone derivative. Contrary to our expectation, based on the reaction behavior of the cycloadduct from coumarin with tetrachloroethylene,[4)] **1** gave a new cyclobutene compound and trichlorovinyl-2-quinolone, but gave no ring-contracted product.

We report here the reaction of **1** with nucleophiles or bases, the structure of the product, and molecular orbital (MO) geometry calculations.

Experimental

Measurements. All melting points were measured on a MELTEMP micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer. NMR spectra were observed on a JEOL GX-400 spectrometer at 400 MHz. The chemical shifts for ^1H and ^{13}C NMR spectra are given in ppm in reference to the internal tetramethylsilane (TMS) signal.

2D (COSY and NOESY) spectra were recorded with a 3.1 s recycle time, 8 transitions correlated for each t_1 value, and accumulations of 512 spectra each consisting of 2048 data points.

Theoretical Calculations. Semiempirical AM1[5)] and MNDO[6)] calculations were performed on a HITAC M-680 or M-682 with the MOPAC package, version 3.1, of J. J. P. Stewart[7)] with complete geometry optimization.

Reactions. All the reagents and solvents were purified by methods described in the literature.[8)]

Photoirradiation was performed with an Eiko-sha EHB-WI(F)-500 high-pressure mercury lamp (500 W).

Unless specified otherwise, the reactions were carried out under an argon atmosphere. The extracts were washed with saturated aqueous sodium chloride and dried overnight over an appropriate deciccant. The deciccant was removed by filtration and the solvents were stripped off on a flash evaporator at a temperature below 10 °C. The conversions were determined from the ^1H NMR spectra of the reaction products dissolved in $CDCl_3$. Separations of the products were carried out by column chromatography using silica gel (Wako-gel C-200, 100—200 mesh).

1,1,2,2-Tetrachloro-2,2aα,4α,8bα-tetrahydrocyclobuta[c]-quinolin-3(1H)-one (1): 2-Quinolone (5.81 g, 40.0 mmol) and benzophenone (1.24 g, 6.8 mmol) were dissolved in a mixture of 1327.9 g (8.0 mol) of tetrachloroethylene and 1000 ml of dichloromethane. The solution was irradiated by a 500-W high-pressure mercury lamp through a Pyrex filter for 87 h. The reaction mixture was concentrated under reduced pressure and then passed through a silica-gel column (Wako C-200) with benzene as an eluent. Recrystallization from dichloromethane gave 5.64 g (43.9%) of pure **1**: Mp 285.0 °C (decomp).

1,2-Dichloro-2aα-methoxy-2aα,8bα-dihydrocyclobuta[c]-quinolin-3(4H)-one (3a): To a stirred methanol solution (20 ml) of **1** (31.0 mg, 0.10 mmol), 1 M NaCl (1.0 ml) (1 M =1 mol dm^{-3}) was added at room temperature. After stirring for 16 h at room temperature, the reaction mixture was poured into 1 M HCl (20 ml). The resultant solution was concentrated until the methanol was removed; then, the products were extracted three times with $CHCl_3$ (20 ml each). All extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to leave a white solid. The residue was dissolved in $CDCl_3$. Based on the integrated intensities of the ^1H NMR lines of the residues, the content of **3a** was calculated to be 89% and that of **4** to be 11%.

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Evaporation of $CDCl_3$ followed by recrystallization from CH_2Cl_2–hexane gave **3a** as white needles (15.1 mg, 56%): Mp 183 °C (decomp); IR (KBr) 1680, 1640, 1100, and 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.51 (3H, s, methoxyl protons), 4.21 (1H, s, cyclobutene ring proton), 7.00—7.14 (2H, m, aromatic protons), 7.23—7.32 (2H, m, aromatic protons), and 9.51 (1H, s, NH proton); ^{13}C NMR ($CDCl_3$) δ=53.2 (d), 54.3 (q), 80.7 (s), 116.6 (d), 118.3 (s), 123.9 (d), 126.2 (s), 128.5 (d), 129.3 (d), 131.9 (s), 135.3 (s), and 166.0 (s). Found: C, 53.24; H, 3.39; N, 5.18%. Calcd for $C_{12}H_9Cl_2NO_2$: C, 53.36; H, 3.36; N, 5.19%.

1,2-Dichloro-2aα-ethoxy-2aα,8bα-dihydrocyclobuta[*c*]-quinolin-3(4*H*)-one (3b): To a stirred ethanol solution (60 ml) of **1** (31.0 mg, 0.10 mmol), 1 M NaOH (1.0 ml) was added at room temperature. After stirring for 16 h at room temperature, the reaction mixture was poured into 1 M HCl (20 ml). The solution was concentrated until the ethanol was removed; then, the products were extracted three times with CH_2Cl_2 (20 ml each). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$ to give white needles of **3b** (49.6 mg, 35%):Mp 190 °C (decomp); ^1H NMR ($CDCl_3$) δ=1.30 (3H, t, ethoxyl methyl protons), 3.70 (2H, m, ethoxyl methylene protons), 4.01 (1H, s, cyclobutene ring proton), 6.80—7.30 (4H, m, aromatic protons), and 9.72 (1H, s, NH proton); ^{13}C NMR ($CDCl_3$) δ=15.3 (q), 54.2 (d), 63.0 (t), 80.0 (s), 116.8 (d), 118.4 (s), 123.8 (d), 126.5 (s), 128.4 (d), 129.2 (d), 131.6 (s), 135.4 (s), and 166.7 (s). Found: *m/z* 283.0161. Calcd for $C_{13}H_{11}Cl_2NO_2$:M, 283.0167, (rel intensity, M:M+2:M+4=8.8:5.7:1.0).

1,2-Dichloro-2aα-butylamino-2aα,8bα-dihydrocyclobuta[*c*]-quinolin-3(4*H*)-one (3c): To a stirred acetone solution (50 ml) of **1** (155.0 mg, 0.50 mmol), butylamine (365.7 mg, 5 mmol) was added at room temperature. After stirring for 7 h at room temperature, the solution was concentrated to give a black solid. The residue was washed by hexane (50 ml), dissolved in 1 M NaOH (30 ml). The products were extracted three times with CH_2Cl_2 (50 ml each). The extracts were combined, dried ($MgSO_4$), and concentrated to leave colorless glass, which was washed with hexane to give **3c** (140.2 mg, 90%): Glass; ^1H NMR ($CDCl_3$) δ=0.90 (3H, t, *J*=7.5 Hz, $CH_2CH_2CH_2\underline{CH_3}$), 1.32—1.43 (2H, m, $CH_2CH_2\underline{CH_2}$-CH_3), 1.49—1.57 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$), 2.58—2.66 (2H, m, $\underline{CH_2}CH_2CH_2CH_3$), 4.20 (1H, s, cyclobutene ring proton), 6.68 (1H, br s, amine proton), 6.89—7.18 (2H, m, aromatic protons), 7.20—7.29 (2H, m, aromatic protons), and 9.12 (1H, s, amide proton). Found: *m/z* 310.0638. Calcd for $C_{15}H_{16}Cl_2NO_2$:M, 310.0640, (rel intensity, M:M+2:M+4=9.0:6.2:1.0).

3-(Trichlorovinyl)-2-quinolone (4): Triethylamine (4.5 g, 45.0 mmol) was added to a stirred benzene solution (300 ml) of **1** (311.0 mg, 1.0 mmol) at room temperature. After stirring at room temperature for 15 min, the reaction mixture was poured into water (50 ml). The products were extracted three times with $CHCl_3$ (50 ml each). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to leave a white solid. Recrystallization from acetone gave **4** as parallelepiped: Mp 276—278 °C; IR (KBr) 1660, 1570, and 1430 cm^{-1}; ^1H NMR (DMSO-d_6) δ=7.21—7.37 (2H, m, aromatic protons), 7.55—7.76 (2H, m, aromatic protons), and 8.27 (1H, s, olefinic proton). Found: C, 47.92; H, 2.20; N, 5.09%. Calcd for $C_{11}H_6Cl_3NO$: C, 48.13; H, 2.20; N, 5.10%.

Results and Discussion

Reaction of 1 with a Nucleophile and/or a Base. Cross adduct **1** was obtained from 2-quinolone and tetrachloroethylene under irradiation with a 500-W high-pressure mercury lamp. The yield of **1** based on 2-quinolone was 43.9%. Our procedure gives a higher yield than the method described by Evanega and Fabiny.[9]

Upon treatment of **1** with a nucleophile and/or a base, we obtained two products, a cyclobutene compound **3** and trichlorovinyl-2-quinolone (**4**), in place of the expected compound having a [4,5,6]-fused ring system.[4] The ratio of **3** to **4** in the products was influenced by the nucleophile used. The results of the reaction are summarized in Table 1. For the reaction of **1** with NaOH in methanol, the yields of **3** and **4** based on **1** were 70 and 7%, respectively. When NaOMe was used as a nucleophile, the conversion and yield were almost the same as those for the reaction of **1** with NaOH in methanol. Using NaH or Et_3N as a base in aprotic solvent benzene we obtained **4** exclusively, which is similar to the results of the reaction of the coumarin–tetrachloroethylene photoadduct with a non-nucleophilic base.[4] From the reaction of **1** with NaOH in aqueous acetone, **4** was also formed quantitatively. When butylamine was used in aprotic solvent acetone, **3** was obtained

Table 1. Reactions of **1** with Various Bases (See Experimental Section for Detailed Reaction Conditions)

Base	Equiv. to **1**	Solvent	Time/h	Conv. (Yield)/%[a]	
				3	**4**
NaOH	10	MeOH	16	89(70)	11(7)
NaOMe	900	MeOH	14	86(70)	14(5)
$NaHCO_3$	23	MeOH	23	40(32)	60(50)
NaOH	10	EtOH	7	40(35)	60(51)
NaOH	1900	Acetone (aq.)	16	0	100(85)
NaH	15	Benzene	5	0	100(90)
NEt_3	45	Benzene	7	0	100(92)
$BuNH_2$	10	Acetone	7	100(97)	0

a) Based on **1**.

exclusively. Thus the fraction of the cyclobutene compound **3** in the products was different, depending on the nucleophile employed. The highest ratio and yield of **3** in the products was observed for butylamine nucleophile. When methoxide and ethoxide anions were used, the ratio of **3** was lower than that observed for butylamine. Methoxide anion gave a higher ratio of **3** than the ethoxide anion. No product attacked by an OH^- anion at the carbon α to the carbonyl carbon, nor at β, was obtained when **1** was treated with an alkaline solution in alcohols.

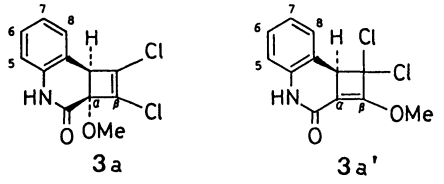


Fig 1. The candidate structures, **3a** and **3a'**, for the cyclobutene product **3** (Nu = OMe).

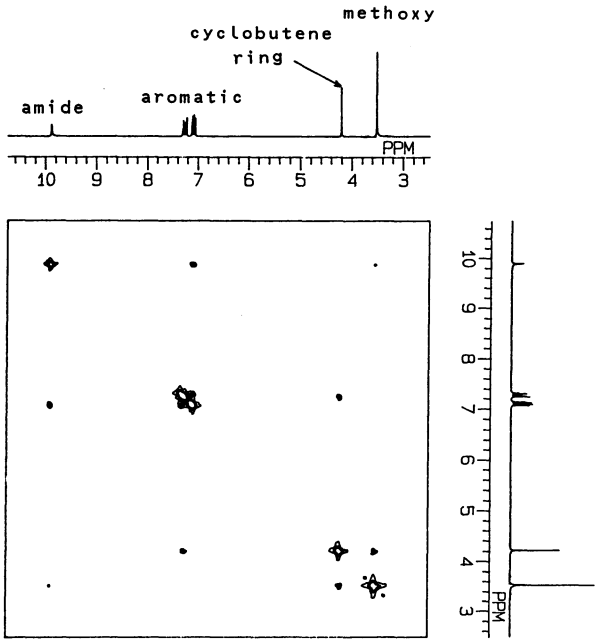


Fig 2. 400 MHz proton NOESY NMR spectrum of **3** in $CDCl_3$ at 27 °C. Data matrix by 1024 points with a frequency range of 5000 Hz in both dimensions was zero-filled to 2048.

Structure of the Cyclobutene Compound. For the cyclobutene compound **3** (Nu=OMe) two possible structures can be considered (Fig. 1). One is compound **3a** having a methoxyl group on the α carbon with respect to the carbonyl carbon formed as a result of the S_N2' replacement reaction. The other is **3a'**, where the chlorine atom at the β position to the carbonyl carbon is substituted by the methoxyl group via a 1,4-addition reaction. To determine which is the structure of the cyclobutene product, **3a** or **3a'**, we studied the Nuclear Overhauser Effect (NOE) by 2D NMR spectroscopy[10] and compared the results with the fully optimized geometries predicted by the AM1[5] and MNDO[6] MO calculations. Under the condition that the NMR T_1 values of the compared nuclei are almost the same, the NOE value becomes approximately proportional to $1/R^6$ for the correlated nuclei couple separated by a distance R.[11] The relative values of NOE can be determined from the volume of the cross-peak in the NOESY spectrum and, hence, candidate geometries predicted by MO calculations can be checked by the observed cross-peak volumes.

The NOESY contour plot observed for compound **3** ($Nu=OCH_3$) is shown in Fig. 2. In the COSY spectrum, no off-diagonal peak due to proton–proton J coupling was observed, except for those among aromatic protons. Thus, the correlation between the peaks at 3.5 ppm (methoxyl protons) and 4.2 ppm (cyclobutene ring proton) in the NOESY spectrum indicates that the geometrical distance between these protons is very short (less than 4 Å). The cross peak between 4.2 ppm (cyclobutene ring proton) and 7.2 ppm (one of the aromatic protons) indicates that these protons are also closely located. Furthermore, a correlation was observed between one of the aromatic protons and the amide proton (9.93 ppm). NOE values for these three correlations were determined from the cross-peak volumes in the NOESY spectrum and are given in Table 2, where the volumes of the cross peaks are given in relative to those between the cyclobutene proton and one of the aromatic protons (a proton at C8 in Fig. 1). Since the aromatic protons

Table 2. Observed Relative NOE Volumes of the Product **3** ($Nu = OCH_3$), and Expected Distance R and Relative $1/R^6$ for **3a** and **3a'**

Proton pair	Relative NOE volume	Relative $1/R^6$ (Distance/Å)[a] **3a**	**3a'**
H(cyclobutene)-H(Aro)[b]	1.0	1.0 (2.589)[c]	1.0 (2.979)[c]
H(cyclobutene)-H(OMe)	2.0	1.9 (2.418 / 3.936 / 3.461)	0.3 (4.967 / 6.626 / 5.532)
H(NH)-H(Aro)[b]	1.3	1.6 (2.392)[d]	3.6 (2.411)[d]

a) Calculated for the AM1 optimized geometries. b) Aro stands for one of the aromatic protons. c) Aromatic proton is assumed on the C8 in the phenyl ring (Fig. 1). d) Aromatic proton is assumed on the C5 in the phenyl ring (Fig. 1).

give a complex multiplet structure, as shown in the one-dimensional spectrum, the cross-peak volumes involving aromatic protons were determined after the line assignments as an ABCD 4-spin system had been performed with the aid of the LAOCN3 program.[12] Table 2 also shows the relative values of $1/R^6$, together with the proton–proton distance R, calculated for the geometries predicted from AM1 MO calculations. A good correlation between each NOE volume and the corresponding relative $1/R^6$ value is found for the candidate structure **3a**. It follows that the methoxyl group is situated at the α position with respect to the carbonyl carbon. Product **3** is, therefore, confirmed to be 1,2-dichloro-2aα-methoxy-2aα,8bα-dihydrocyclobuta-[*c*]quinolin-3(4*H*)-one (**3a**) (Fig. 3).

Reaction Mechanism. In the case of the [4,6,6] lactone-fused ring system studied before,[4] the first step of the reaction with a nucleophile is the lactone-ring-opening reaction. The second and third steps are a dehydrochlorination and an intramolecular S_N2' displacement to form the [4,5,6] fused ring system.[4] On the contrary, a lactam-ring-opening at **1** dose not occur under the mild conditions employed in this study, since the amide linkage in the lactam ring is known to be far stronger than the ester linkage in the corresponding lactone ring. Thus, the first step should be dehydrochlorination to yield the unstable intermediate **2**, although we did not try to isolate **2**.

For a reaction from **2** to the cyclobutene product **3** (i.e. **3a** or **3a'**), we calculated the heats of formation of these two candidates by the MNDO and AM1 MO methods. The heat of formation of **3a** (−0.6 kcal mol^{-1} from AM1, and −23.3 kcal mol^{-1} from MNDO) was slightly higher than that of 1,4-adduct **3a'**

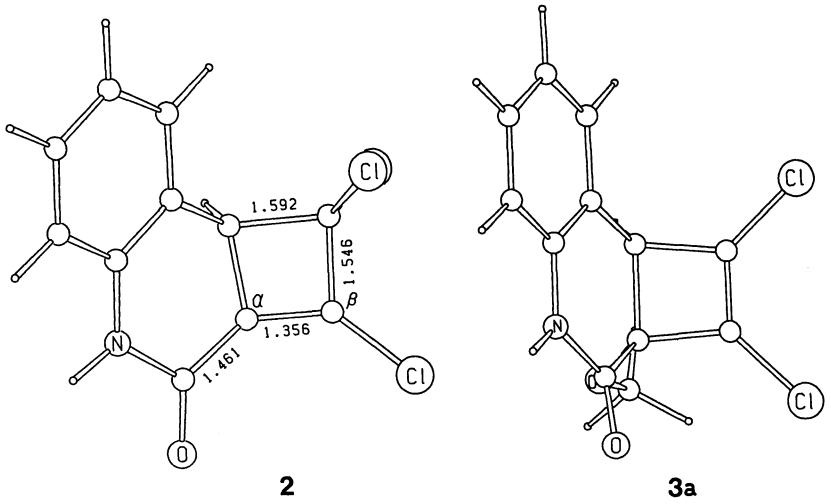
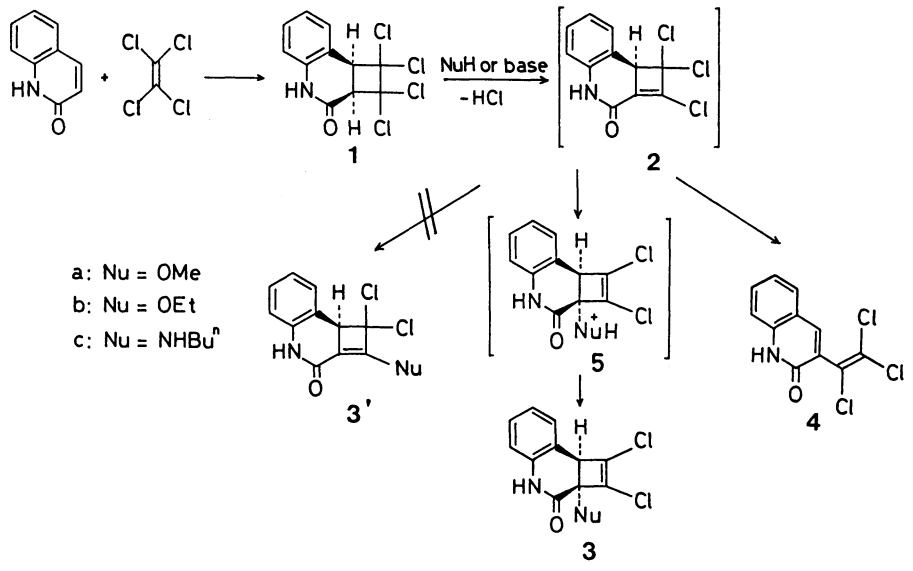


Fig 3. ORTEP[13] perspective view of **2** and **3a**, determined by the AM1 MO calculations.



Scheme 1.

(-3.4 kcal mol^{-1} from AM1, and -26.9 kcal mol^{-1} from MNDO), suggesting that **3a** was thermodynamically less stable than **3a'**. Since **3a'** was not detected experimentally, as discussed in the previous section, the reaction of **2** with a nucleophile is not a thermodynamically equilibrium reaction. The lactam ring of **2** at the AM1 geometry (Fig. 3) is folded in against the cyclobutene ring by 51 ° while the benzene ring is on the same plane with the lactam ring. All these geometrical features indicate that the carbonyl group and the cyclobutene double bond are not well conjugated, which is also suggested from the calculated π-π overlap population. In these situations, a 1,4-addition of the attacking methoxide anion to the β position with respect to the carbonyl carbon should be improbable. Thus, molecular orbital calculations again support the conclusion from the NOE measurements described in the previous section that the cyclobutene product is **3a.**

Based on the information given above, the following reaction mechanism can be drawn (Scheme 1). In the first step of the reaction from **1,** dehydrochlorination leading to **2,** i.e. cyclobutene formation, takes place. In the second step, two possible routes can be considered. One is an S_N2' displacement by an attack of a nucleophile at the α carbon with respect to the carbonyl carbon in the cyclobutene intermediate **2,** resulting in another cyclobutene compound **3** by way of the assumed intermediate **5.** The other is the [2+2] cycloreversion of **2,** yielding trichlorovinyl-2-quinolone **4.** Since **2** should be very unstable due to the high steric strain expected for the AM1 geometry, the succeeding competitive reactions, i.e. a nucleophilic substitution reaction or the cycloreversion of the cyclobutene ring, may take place immediately when **2** is produced.

We wish to thank Mr. Hiroshi Tsuchiya, Mr. Mikio Kaihara, and Dr. Hiroaki Mametsuka (Advanced Technology Research Center, Nippon Kokan K. K) for the measurement of high mass spectra.

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7) A HITAC version converted from the Vax version MOPAC supplied from J. J. P. Stewart, Frank J. Seiler Research Laboratory, U.S. Air Force Academy, Colorado Springs, Colorado, U.S.A.

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11) The volume of a cross peak a_{AB} in the NOESY spectrum can be related to the distance R_{AB} between two correlated atoms A and B as,[10b]

$$a_{AB} = f(\tau_m) \cdot \sigma$$

$$\sigma = \frac{1}{10} \cdot \frac{\gamma^4 \hbar^2}{R_{AB}^6} \cdot \left[\frac{6\tau_c}{1 + 16\pi^2 \nu^2 \tau_c^2} - \tau_c \right]$$

where τ_m is the mixing time, $f(\tau_m)$ a function of the τ_m, σ the cross-relaxation rate, γ the gyro-magnetic ratio, ν the observed frequency, and τ_c the correlation time which is inversely proportional to the relaxation time T_1.

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