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A ^{1}H NMR and molecular modelling investigation of diastereotopic methylene hydrogen atoms

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The ^{1}H NMR spectra of methyl 3-bromo-2-methylpropionate (1a) and the corresponding chloro compound (2a) show no long-range coupling between the methyl and methylene protons. In contrast, in the analogous dihalocompounds, methyl 2,3-dibromo-2-methylpropionate (1b) and methyl 2,3-dichloro-2-methylpropionate (2b), one of the methylene protons exhibits a large $^4J_{HH}$ coupling (0.8 Hz) to the methyl group, but the other proton shows no observable splitting. This can be explained quantitatively by calculations of the conformational preferences in these compounds combined with the known orientation dependence of the $^4J_{HH}$couplings. One conformer predominates in the dihalo compounds 1b and 2b, and this is responsible for the $^4J_{HH}$ coupling. In 1a and 2a all three conformers are populated and the $^4J_{HH}$ couplings average to zero. The technique is a potentially general method of unambiguously assigning diastereotopic methylene protons. Copyright © 2002 John Wiley & Sons, Ltd.

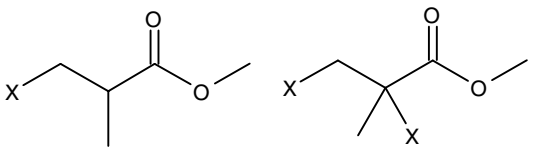
KEYWORDS: ^{1}H NMR spectroscopy; molecular modelling; diastereotopic hydrogen; halopropionates

INTRODUCTION

One of the most useful aspects of NMR spectroscopy is the interpretation of spin–spin splitting patterns in terms of the structural and configurational relationships among the magnetic nuclei of the molecules investigated.[1] Sanders and Hunter[2] in their guide for organic chemists, noted that many chemists still believe that the two protons of a methylene group in a flexible chain should always be equivalent. When the methylene protons are non-equivalent, restricted rotation is often invoked as the explanation. This response arises from the misconception that rapid rotation of a CH_2 group necessarily leads to equalizing of the two proton chemical shifts. This is of importance, as establishing the chemical equivalence or non-equivalence of such protons can be an important step in determining the structure of the compound by NMR.[3]

In principle, though not necessarily in practice, all diastereotopic methylene protons are non-equivalent, even when bond rotation is rapid on the NMR time scale.[2] Thus, in systems of the type A–CX_2–B, where A is a symmetric group and B a group that lacks a plane of symmetry, the X nuclei are internally diastereotopic and are therefore non-equivalent, though accidental equivalence may occur. The origin of such non-equivalence has usually been ascribed to differences in conformer population,[4a] but investigations with chiral moieties have shown that this is not the correct explanation.[4b] Waugh and Cotton[5] have noted that a symmetry argument alone, completely independent of any conformational isomerism, readily accounts for such non-equivalence. A striking example of this is the ^{1}H spectrum of the fluoroacetate derivative of α-methyl benzyl alcohol. The CH_2F moiety is an ABX system (δ_A 4.900, δ_B 4.783 ppm; J_{AB} 14.96, J_{AX} 47.09, J_{BX} 47.06 Hz).[6] This is observed even though there is a twofold barrier about the CH_2F–CO_2R bond with the populated conformations the cis and trans (F–C–C–O) forms with all the atoms involved coplanar.[7] Thus the non-equivalence of these protons is simply due to the fact that they are diastereotopic as a result of the chiral alcohol moiety of the ester.

Although many systems containing non-equivalent methylene hydrogen atoms have been reported,[8] there is no unambiguous method of assigning the diastereotopic protons in acyclic molecules. Here we present a method of distinguishing and assigning such protons based on molecular modelling plus the orientation dependence of the $^4J_{HH}$ coupling and illustrate the application of the method to some halopropionate esters. The molecules investigated are methyl 3-bromo-2-methylpropionate (**1a**), methyl 2,3-dibromo-2-methylpropionate (**1b**) and the corresponding chloro compounds (**2a**) and (**2b**).



1a, X = Br
2a, X = Cl

1b, X = Br
2b, X = Cl

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RESULTS AND DISCUSSION

The ^{1}H spectrum of **1a** in $CDCl_3$shows non-equivalent methylene hydrogen atoms at δ 3.58 and 3.47 [Fig. 1(a)]. Both are doublet of doublets (J_{HH} 10.0 and 6.7 Hz). In **1b** the two methylene hydrogen atoms are also non-equivalent [Fig. 1(b)], but one of them has a *geminal* coupling and a long-range coupling ($^4J_{HH} = 0.81$ Hz) with the methyl group, whereas the other hydrogen is a doublet ($^2J_{HH} = 9.80$ Hz). We suspected that this difference was due to differing conformational preferences in the two molecules and used modelling calculations to confirm this.

The conformer energies and populations were obtained from both *ab initio* and molecular mechanics (MM) calculations using the Gaussian 98 and PCMODEL programs respectively. The potential energy surfaces (PESs) for **1a** and **1b** obtained from Gaussian 98 are shown in Fig. 2, with the individual conformers in Fig. 3. There are three stable conformers for **1a** [Fig. 2(a)] with similar energies and populations. The calculated mole ratios are 0.14, 0.47 and 0.39 for conformers **I**, **II** and **III** respectively. The MM calculations agree with conformer energies of 1.3 kcal mol^{-1}, 0.0 kcal mol^{-1} and 0.5 kcal mol^{-1} for conformers **I**, **II** and **III** respectively. For **1b** there are also three possible conformers, but now conformer **IV** is far more stable than the other two. The conformer energies of 0.0 kcal mol^{-1}, 4.0 kcal mol^{-1} and 2.6 kcal mol^{-1} for **IV**, **V** and **VI** respectively show that conformer **IV** predominates in solution (>95%). Again, the MM calculations agree with conformer energies of 0.0 kcal mol^{-1}, 2.6 kcal mol^{-1} and 3.2 kcal mol^{-1} for **IV**, **V** and **VI** respectively. The much greater stability of conformer **IV** is clearly due to the anti Br–C–C–Br orientation, whilst in conformers **V** and **VI** the bromines are gauche to each other, thus increasing the steric repulsion. Note that in all the conformations shown the carbonyl group of the ester is cis to the central C–C bond and the ester methyl cis to the carbonyl.

In **1b** there is a coupling constant between one of the methylene hydrogen atoms with the methyl group. Abraham and coworkers[9,10] have described the orientation dependence of HH couplings over four saturated bonds as given by Eqn (1), where θ_1 and θ_2 are the C–C–C–H dihedral angles of the coupling path. Thus two dihedral angles of 180° lead to large coupling constants (1 to 2 Hz), due to favourable orbital overlap between the nuclei (the so-called *W* coupling).[10] For CH_3–C–C–H couplings, Eqn (1) reduces to Eqn (2).

$$^4J_{HH} = \cos^2\theta_1 + \cos^2\theta_2 - 0.7 \quad (1)$$

$$^4J_{MeH} = \cos^2\theta - 0.2 \quad (2)$$

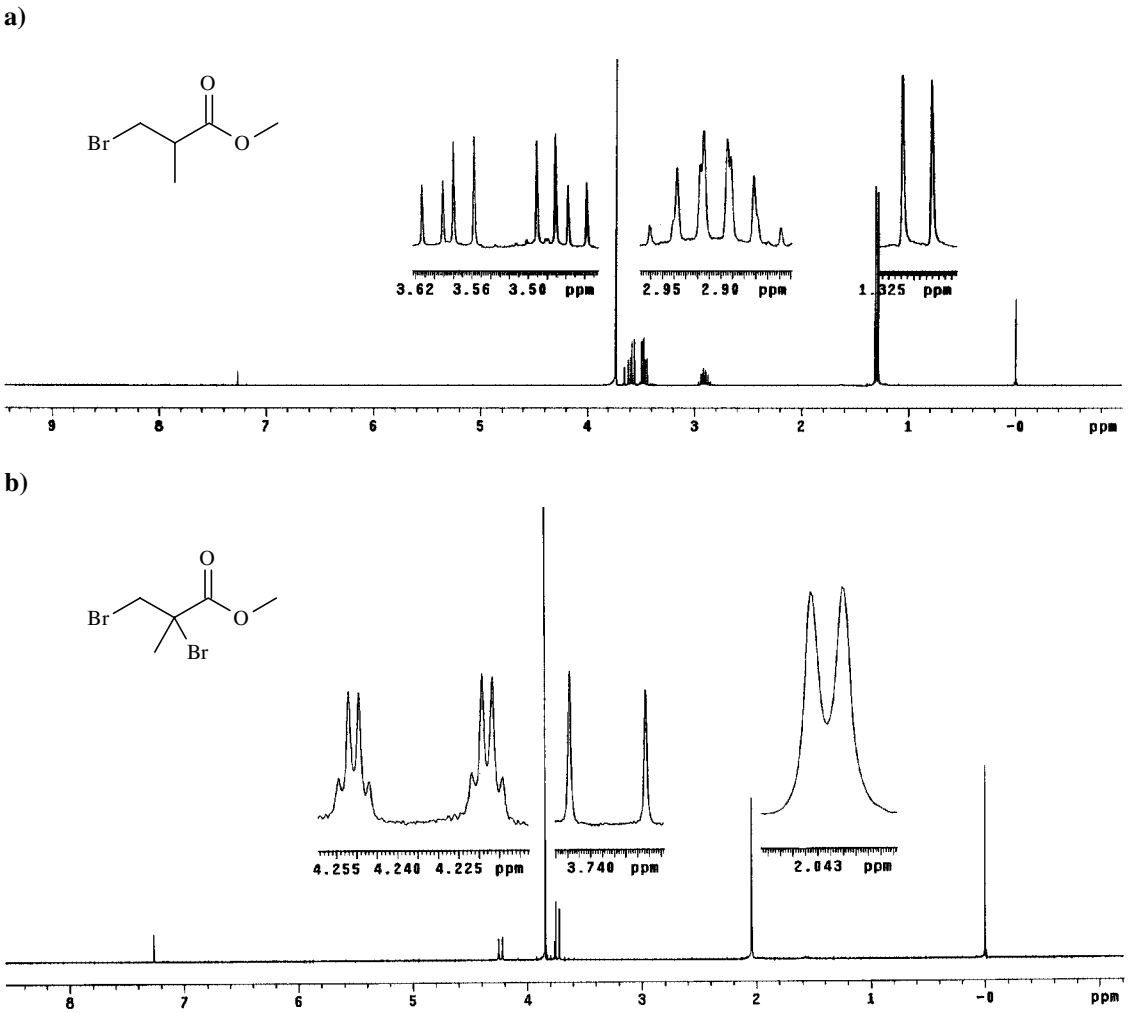

Figure 1. ^{1}H NMR spectrum in $CDCl_3$ at 300 MHz for: (a) **1a** and (b) **1b**.

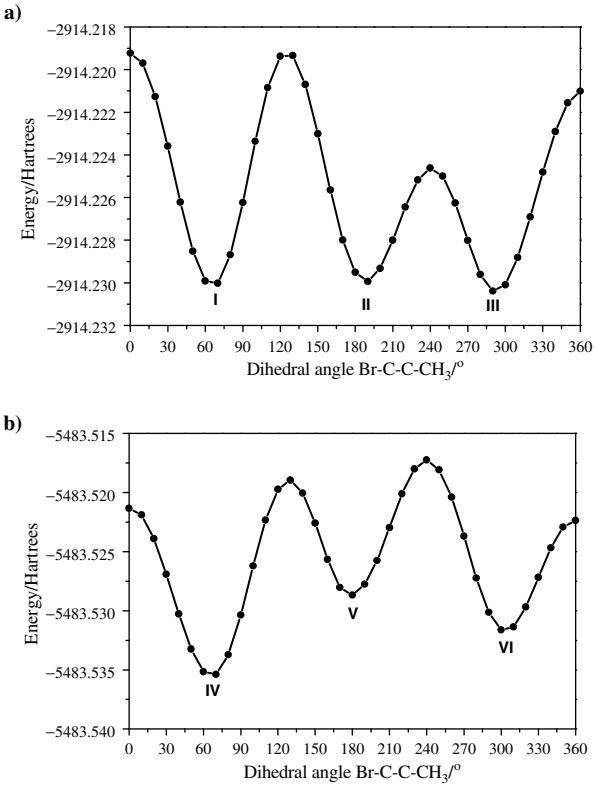

Figure 2. PESs at B3LYP/6-31g(d,p) level: (a) **1a** and (b) **1b**.

In the molecular fragment considered there are only staggered conformations thus the Me–C–C–H dihedral angle is *ca* 60 or 180° and the $^4J_{MeH}$ coupling is predicted to be *ca* 0.8 Hz ($\theta = 180°$) or 0.05 Hz ($\theta = 60°$). There are two possible conformations with antiperiplanar dihedral angles of 180° (H–C–C–CH_3) for **1b**: **IV** and **VI**.

NMR experiments in solvents of varying polarities (Table 1) were performed for **1a** and **1b**. The experimentally observed coupling is the weighted time-averaged value of the couplings in the individual conformers. The $^4J_{HH}$ coupling in **1b** changes only slightly with solvent polarity (0.81 Hz in $CDCl_3$ to 0.65 Hz in DMSO-d_6), indicating that there is no large change in the conformer populations with solvent.[11–13] Also, the calculated coupling constants for H_a and H_b with the methyl group in **IV** are H_a 0.8 Hz and H_b 0.07 Hz using the calculated dihedral angles of 175.0° for H_a and 58.5° for H_b. This confirms the existence of one predominant conformer (**IV**) for **1b** in both the vapour and solution, and also that the long-range coupling constant is due to the *antiperiplanar* (180°) orientation of the methyl group and H_a in conformer **IV**.

In **1a** the three stable conformers have almost the same energy and dipole moments, thus they have approximately equal populations in both the vapour and solution. If the populations were equal (1 : 1 : 1), the averaged coupling ($^4J_{MeH}$) between $H_{a,b}$ and the methyl from Eqn (2) is 0.3 Hz. This is just on the limit of resolution, and thus the observed spectrum does not show any long-range coupling.

Methyl 2-chloro-2-methylpropionate (**2a**) and methyl 2,3-dichloro-2-methylpropionate (**2b**) were also studied to see if the same behaviour was observed in the chloro derivatives. Chlorine is a smaller atom than bromine, and thus the conformer energy differences should also be smaller, which could stabilize the other conformations in the dichloro compound. The PES for **2a** and **2b** show the same behaviour as for the bromo compounds. The geometries and energies were optimized and the results are given in Fig. 3(c) and (d). The conformer mole fractions for **2a** are 0.15, 0.50 and 0.35 for **VII**, **VIII** and **IX** respectively. The corresponding MM conformer energies for **2a** are 1.4 kcal mol^{-1}, 0.0 kcal mol^{-1} and 0.4 kcal mol^{-1} for **VII**, **VIII** and **IX** respectively, and for **2b** 0.0 kcal mol^{-1}, 3.2 kcal mol^{-1} and 2.6 kcal mol^{-1} for **X**, **XI** and **XII** respectively. The conformer energies for **2a** are very similar to those of **1a**. In **2b** the energy differences are not so marked as in **2a**, but, even so, the calculations predict that conformer **X** with the anti Cl···Cl orientation is still predominant (>95%).

Thus, as expected, the NMR data for the chloro compounds (Table 1) show very similar behaviour to the bromo compounds. In **2b** the long-range coupling constant ($^4J_{MeH}$) is 0.56 Hz in $CDCl_3$ and 0.45 Hz in acetone. From Eqn (2) the calculated coupling constants for H_a and H_b with the methyl group in conformer **X** are 0.8 Hz ($\theta = 175.8°$) for H_a and 0.16 Hz ($\theta = 53.0°$) for H_b. This confirms that conformer **X** predominates in solution as well as in the vapour.

In **2a** the three stable conformers have almost the same energy and dipole moments. Thus, the same analysis as for **1a** is valid, to give the averaged $^4J_{MeH}$ coupling equal to 0.33 Hz.

These results show that small changes in the molecular structure can affect the conformer populations, and thus

Table 1. Proton chemical shifts (δ, ppm) and coupling constants (Hz) for methyl 3-bromo-2-methylpropionate (**1a**), methyl 2,3-dibromo-2-methylpropionate (**1b**) and the corresponding chloro compounds (**2a**) and (**2b**)

Compound	H_a	H_b	H_c	Me	$^2J_{ab}$	$^3J_{ac}$	$^3J_{bc}$	$^3J_{(Me.Hc)}$	$^4J_{(Me.Ha)}$
1a $CDCl_3$	3.59	3.47	2.91	1.30	10.02	6.67	5.90	6.99	–
1a DMSO	3.67	3.61	2.98	1.17	9.95	5.04	6.39	6.99	–
1b $CDCl_3$	4.21	3.73	–	2.04	9.80	–	–	–	0.81
1b Ac-d_6	4.24	4.00	–	2.02	9.87	–	–	–	0.73
1b DMSO	4.20	4.13	–	1.96	9.88	–	–	–	0.65
2a $CDCl_3$	3.73	3.61	2.85	1.28	10.88	6.64	5.95	7.10	–
2a DMSO	3.79	3.75	2.94	1.16	10.83	5.18	6.34	7.04	–
2b $CDCl_3$	4.09	3.75	–	1.86	10.93	–	–	–	0.56
2b DMSO	4.13	3.99	–	1.83	11.13	–	–	–	0.45

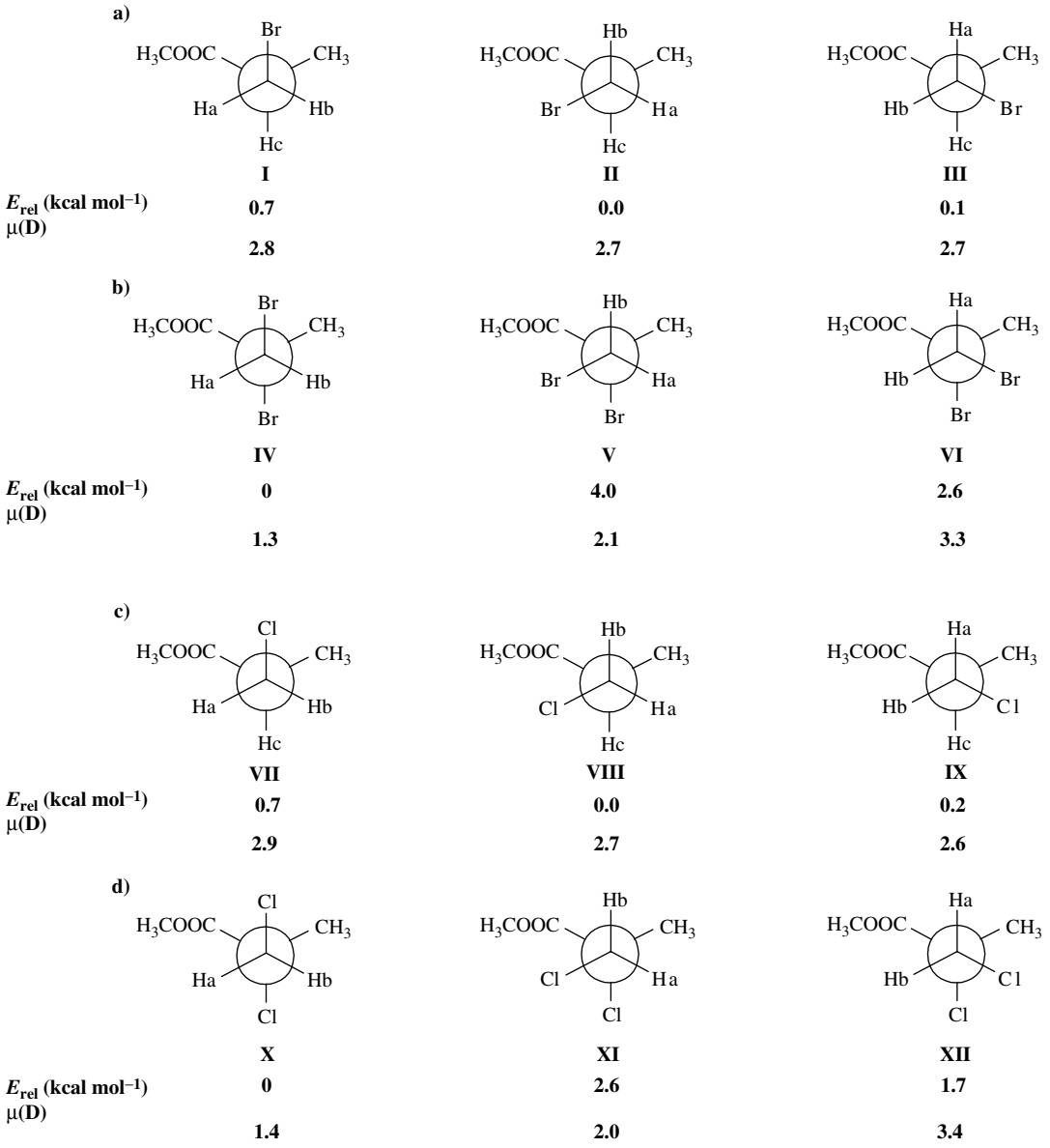

Figure 3. Energies and dipole moments for stable rotamers at B3LYP/6-311++g(2df,2p) level: (a) **1a**; (b) **1b**; (c) **2a**; (d) **2b**.

the NMR spectrum. The joint application of theoretical calculations and NMR theory gives a complete explanation of the behaviour of the long-range coupling constant in this system and also provides a definitive assignment of the diastereotopic protons.

EXPERIMENTAL

Spectra

The solvents ($CDCl_3$, acetone-d_6 and DMSO-d_6) were obtained commercially (Aldrich), stored over molecular sieves and used without further purification. ^{1}H NMR spectra were obtained on a Varian Gemini spectrometer operating at 300.06 MHz for ^{1}H and 75.45 MHz for ^{13}C. Spectra were of *ca* 20 mg cm^{-3} solutions, with a probe temperature of *ca* 20 °C , referenced to Me_4Si. Typical conditions were: 48 transients, spectral width 2500 Hz with 32k data points and zero filled to 128k to give a digital resolution of 0.04 Hz.

Theoretical calculations

The calculations used both the MM PCMODEL program[14] and the *ab initio* Gaussian 98 program.[15] In the latter the DFT/B3LYP method was used with the 6-31G(d,p) basis set for the potential surface scan, and the energies and geometries for the stable rotamers were optimized with the 6-311++G(2df,2p) basis set.

Syntheses

Methyl 3-bromo-2-methylpropionate

A solution of 18.7 g (0.187 mol) of washed and dried methyl methacrylate in 100 ml of anhydrous diethyl ether was placed in a 250 ml three-neck flask equipped with glass inlet tube for hydrogen bromide and magnetic stirring. The flask with its contents was placed in an ice bath, and 16.6 g (0.206 mol) of anhydrous hydrogen bromide was passed into the solution. After the hydrogen bromide had been added, the flask was stoppered and allowed to stand overnight at room temperature. After that, the reaction mixture was washed with water (4 × 50 ml) and dried with $MgSO_4$. The solvent was removed, and the desired product was vacuum distilled through a Vigreux column to give pure methyl 3-bromo-2-methylpropionate (b.p. 84 °C/37 mmHg) yield 5.0 g (15.0%).[16] ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, Me_4Si): δ 3.75 (s, 3H, OCH_3), 3.59 (dd, 1H, $^2J_{HH}$ = 10.02,

$^3J_{HH}$ = 6.67, CH_2), 3.47 (dd, 1H, $^2J_{HH}$ = 10.02, $^3J_{HH}$ = 5.90, CH_2), 2.91 (ddd, 1H, $^3J_{HH}$ = 5.90, $^3J_{HH}$ = 6.67, $^3J_{HH}$ = 6.99, CH), 1.31 (d, 3H, $^3J_{HH}$ = 6.99, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si): 173.8 (C═O), 52.1 (CH_2Br), 42.1 (OCH_3), 34.0 (CH), 16.3 (CH_3).

Methyl 2,3-dibromo-2-methylpropionate
Methyl methacrylate 14.0 g (0.14 mol) in diethyl ether (60 ml) were placed in a 100 ml three-neck flask equipped with a condenser, addition funnel and magnetic stirrer. Bromine 22.4 g (0.14 mol) was added dropwise over a period of 60 min. The reaction mixture was washed with water (4 × 50 ml) and dried with $MgSO_4$. The solvent was removed, and the desired product was vacuum distilled through a Vigreux column to give pure methyl 3,2-dibromo-2-methylpropionate (b.p. 86 °C/10 mmHg) yield 13.0 g (49.0%).[16] ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, Me_4Si): δ 4.24 (dq, 1H, $^2J_{HH}$ = 9.80, $^4J_{HH}$ = 0.81, CH_2), 3.84 (s, 3H, OCH_3), 3.73 (d, 1H, $^2J_{HH}$ = 9.80, CH_2), 2.04 (d, 3H, $^4J_{HH}$ = 0.81, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si): 169.2 (C═O), 55.2 (CBr), 53.5 (CH_2Br), 38.1 (OCH_3), 26.4 (CH_3).

Methyl 3-chloro-2-methylpropionate
The monochloro compound was prepared similarly to the corresponding monobromo by using HCl instead of HBr. The compound distilled at 66 °C/30 mmHg yielded 4.8 g (18.8%) from 18.7 g (0.187 mol) of methyl methacrylate. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, Me_4Si): δ 3.73 (s, 3H, OCH_3), 3.73 (dd, 1H, $^2J_{HH}$ = 10.88, $^3J_{HH}$ = 6.64, CH_2), 3.60 (dd, 1 H, $^2J_{HH}$ = 10.88, $^3J_{HH}$ = 5.95, CH_2), 2.86 (ddd, 1 H, $^3J_{HH}$ = 5.95, $^3J_{HH}$ = 6.64, $^3J_{HH}$ = 7.10, CH), 1.29 (d, 3H, $^3J_{HH}$ = 7.10, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si): 173.5 (C═O), 52.0 (CH_2Br), 45.8 (OCH_3), 42.1 (CH), 15.1 (CH_3).

Methyl 2,3-dichloro-2-methylpropionate
The dichloro compound was prepared similarly to the corresponding dibromo compound by using Cl_2. The compound distilled at 67 °C/5 mmHg yielded 12.5 g (39.3%) from 18.7 g (0.187 mol) of methyl methacrylate. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, Me_4Si): δ 4.09 (dq, 1H, $^2J_{HH}$ = 10.93, $^4J_{HH}$ = 0.56, CH_2), 3.84 (s, 3H, OCH_3), 3.75 (d, 1H, $^2J_{HH}$ = 10.93, CH_2), 1.86 (d, 3H, $^4J_{HH}$ = 0.56, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si): 169.1 (C═O), 65.4 (CH_2Cl), 53.5 (CCl), 50.1 (OCH_3), 24.9 (CH_3).

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