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Designed Nucleophilic Attack Based on Molecular Electrostatic Potential

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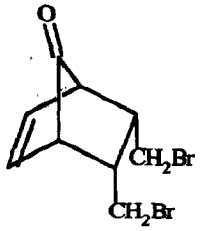
Abstract: We describe the computer-aided design of the steric preference in a nucleophilic attack on sterically unbiased carbonyl groups. To our knowledge, this is the first example for the successful application of the molecular electrostatic potential map to computer-assisted synthesis.

The origin of the π-face diastereoselectivity in nucleophilic addition to C=O and electrophilic addition to C=C double bonds has been subject of a continuous debate.[1] Various authors studied reduction of sterically unbiased ketones (such as 7-norbornanones,[2] 7-norbornenones,[3] benzonorbornanones[4] and adamantanones[5]) and the relative importance of electrostatic and orbital interactions. Predictions from both models were consistent with observed diastereoselectivities for most of the systems, however, for 7-norbornenones the face selectivity could not be rationalised.[6] The effect of donor substituents (Et and CH_2OCH_3) at C2 and C3 were predicted by an oversimplified charge model, while that of acceptor groups (CO_2Me, CN) was explained by hyperconjugation.

In this communication we report on the successful prediction of diastereoselectivity of 2,3-bis(substituted)-5,6-norbornen-7-one and its saturated analogue by molecular modelling, in particular, by application of the molecular electrostatic potential map (MEP). Our aim was to design substituents in the 2 and 3 positions that are quite distant from the attacked carbonyl group, yet influence selectivity. We constructed a geometric model for 2,3-bis(bromomethyl)-5,6-norbornen-7-one (**1**) based on a search from the Cambridge Structural Database[7] and on geometry optimisation with the semiempirical MNDO/AM1 molecular orbital method.[8]

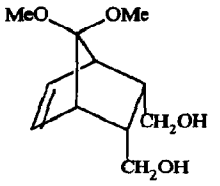


1

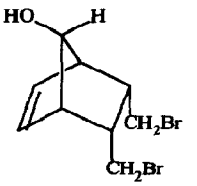
We found that the carbonyl group is planar with the bridgehead hydrogens eclipsed to the C=O bond, therefore the Felkin-Ahn torsional model[9] cannot be applied for the prediction of diastereoselectivity. Prediction was, however, possible on the basis of the MEP.

Orbital interactions were quantified by the Klopman-Salem equation[10] for which the LUMO energy of **1** and the HOMO energy of H^-, as calculated by MNDO/AM1, was 0.136 and -7.372 eV, respectively. Due to the large E_{HOMO}-E_{LUMO} difference the orbital term of the Klopman equation is overruled by the Coulombic one i.e. reduction of **1** should be charge-controlled. For such reactions the MEP gives information about preferred sites and directions of an attack.[11] Therefore we calculated it for the above geometric model of **1** (Figure 1). The negative MEP region around the bromine atoms is unfavourable for a nucleophilic attack from this side, the incident reaction channel is slightly reduced even if it is open in the middle, thus it is probable that formation of the *anti* product is preferred.

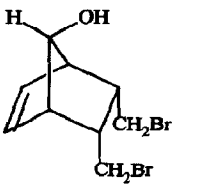
We checked our prediction by the reduction of **1** with $NaBH_4$. Its synthesis started from the Diels Alder adduct of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and maleic anhydride that was transformed to the corresponding dicarboxylic acid disodium salt and was dehalogenated by Na/NH_3 to give a dicarboxylic acid.[12] Treatment of the acid with $LiAlH_4$ gave the corresponding diol (**2**) that was converted to **1** with $SOBr_2$ with the concomitant deprotonation of the carbonyl group. Reduction of **1** with $NaBH_4$ led to the 76:24 mixture of diastereomers[13] (*anti*-**3a** and *syn*-**3b** respectively) which is in accordance with the diastereo-



2

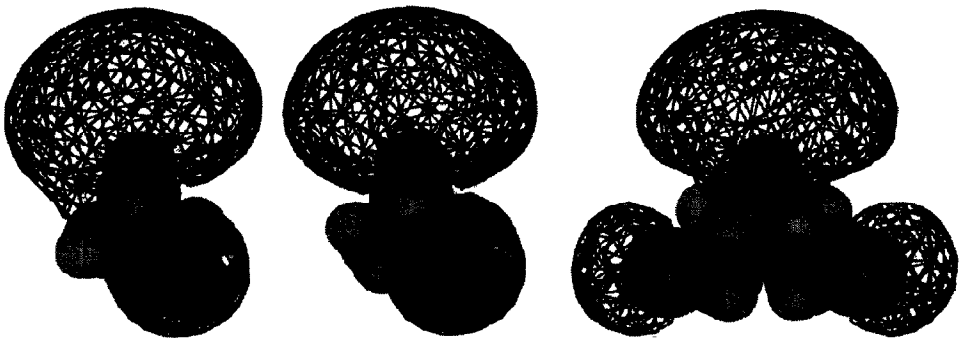


3a



3b

selectivity predicted on the basis of the MEP of **1** (Fig. 1). Let us notice that the π-electron system of the double bond on the *anti* side of **1** has a slight hindering effect on incoming nucleophiles that works against the observed selectivity.[11a] This is also seen on Fig. 1a, the upper negative region of the MEP is slightly asymmetric.

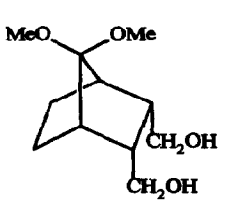


a) **b)** **c)**

Figure 1. -1 kcal/mol MEP contour as calculated from atomic monopoles after Gasteiger and Marsili.[14] Graphics provided by the SYBYL software.[15] (a) Side view for **1**, (b) side view for **5**, (c) front view for **5**. Carbon: black, oxygen: grey, hydrogen: small light grey, bromine: large light grey spheres.

The computer model of **1** indicates a slight steric hindrance by *exo* hydrogens on the *syn* side of the molecule. Therefore we also studied 2,3-bis(bromomethyl)-norbornan-7-on (**5**), a saturated and symmetric derivative of **1** in order to separate this effect neglected in everyday stereochemistry. We hydrogenated **2** and converted the product (**4**) to a dibromide (**5**). We reduced **5** by $NaBH_4$ in methanol to get the mixture of diastereomeric *anti*-**6a** and *syn*-**6b** alcohols and to observe a stereoselectivity in a ratio of 55:45,[13] much smaller

than for 1. The low selectivity may be due to the widely open reaction channel reduced only slightly by the



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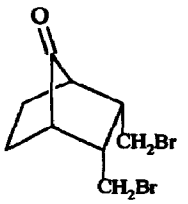
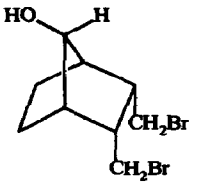
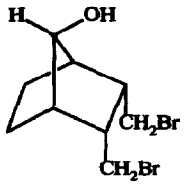


5



6a



6b

negative MEP regions (cf. Fig. 1c). However, it still stresses the importance of non-steric, non-inductive, electrostatic control of nucleophilic substitution reactions by distant groups.

Experimental Procedure

1: *endo*-5,6-Bis-bromomethyl-bicyclo[2.2.1]hept-2-ene-7-one. To the solution of **2** (0.6 g, 3 mmol) in 40 ml CH_2Cl_2 1.35 g (6.5 mmol) $SOBr_2$ was added, the mixture was stirred for 3 h and poured into ice. The organic layer was separated, dried over $MgSO_4$ and evaporated to give **1** as a pale yellow oil (0.63 g, 78%). - ^{1}H-NMR ($CDCl_3$): 3.00 (m, 2H, 2,3-H), 3.12 (m, 2H, 1,4-H), 3.54 [dd, ^2J(H,H)=9.5 Hz, ^3J(H,H)=3.5 Hz, 2H, CH_2Br], 3.82 [dd, ^2J(H,H)=9.5 Hz, ^3J(H,H)=7.3 Hz, 2H, CH_2Br], 6.49 [t, J(H,H)=2.4 Hz, 2H, 5,6-H]. **2:** *endo*-(3-Hydroxymethyl-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2-yl)-methanol. A solution of 7,7-dimethoxybicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid[12] (0.5 g, 2.2 mmol) in 10 ml of tetrahydrofuran (THF) was added to a suspension of $LiAlH_4$ (0.25 g, 6.6 mmol) in 15 ml of THF. The mixture was stirred for 36 h at room temperature, then hydrolysed with 5 ml 20% H_2SO_4. Insoluble salts were filtered off, the filtrate was dried over $MgSO_4$ and evaporated to give **2** as an oil (0.42 g, 95%). - ^{1}H-NMR ($CDCl_3$): 2.75 (m, 2H, 2,3-H), 2.86 (m, 2H, 1,4-H), 3.12, 3.24 (s, 3H, OCH_3), 3. 48 [dd, ^2J(H,H)=11.4 Hz, ^3J(H,H)=10.1 Hz, 2H, CH_2-O], 3.62 [dd, ^2J(H,H)=11.4 Hz, ^3J(H,H)=3.8 Hz, 2H, CH_2-O], 6.07 [t, J(H,H)=2.4 Hz, 2H, 5,6-H]. **3a** and **3b:** *anti*- and *syn-endo*-5,6-Bis-bromomethylbicyclo[2.2.1]hept-2-ene-7-ol. To a stirred solution of 120 mg **1** (0.4 mmol) in 10 ml of abs. MeOH 50 mg $NaBH_4$ (1.2 mmol) was added at 0 °C. The mixture was stirred for 1 h, 5 drops of AcOH were added and the solution evaporated. The residue was dissolved in CH_2Cl_2 washed with water, dried over $MgSO_4$ and evaporated to give a 76:24 mixture (110 mg, 90%). - ^{1}H-NMR ($CDCl_3$): 2.70 (m, 2H, *anti*-1,4-H), 2.85 (m, 2H, *syn*-2,3-H), 2.93 (m, 2H, *syn*-1,4-H), 3.11 (m, 2H, *anti*-2,3-H), 3.44 [dd, ^2J(H,H) =9.0 Hz, ^3J(H,H)=2.8 Hz, 2H, *syn*-CH_2Br], 3.58 [dd, ^2J(H,H)=9.0 Hz, ^3J(H,H)=2.5 Hz, 2H, *anti*-CH_2Br], 3.6 (br.s, 2x1H, *syn* and *anti* 7-OH), 3.67 [2xdd, ^2J(H,H)=9.0 Hz, ^3J(H,H)=7.2 Hz, 2x2H, *syn*- and *anti*-CH_2Br], 3.80 (br.s, 1H, *anti*-7-H), 3.92 (br.s, 1H, *syn*-7-H), 6.12 [t, J(H,H)=2.4 Hz, 2H, *anti*-5,6-H], 6.23 [t, J(H,H) =2.4 Hz, 2H, *syn*-5,6-H]. **4:** *endo*-(3-Hydroxymethyl-7,7-dimethoxybicyclo[2.2.1]hept-2-yl)-methanol. 690 mg (3.5 mmol) of **2** was hydrogenated over 10% Pd-C in EtOAc to give 690 mg **4** (95%). - ^{1}H-NMR ($CDCl_3$): 1.36, 1.59 (m, 2x2H, 5,6-H2), 2.09 (m, 2H, 1,4-H), 2.51 (m, 2H, 2,3-H), 3.25, 3.30 (2xs, 2x3H, OCH_3), 3.62 [dd, ^2J(H,H)=11.4 Hz, ^3J(H,H)=3.5 Hz, 2H, CH_2-O], 4.01 [dd, ^2J(H,H)=11.4 Hz, ^3J(H,H)=10.1 Hz, 2H, CH_2-O]. **5:** *endo*-2,3-Bis-bromomethyl-7,7-dimethoxy-bicyclo[2.2.1]-heptan-7-one. 700 mg (3.5 mmol) of **5** was converted to dibromide as described for **1** (620 mg, 63%). - ^{1}H-NMR ($CDCl_3$): 1.68, 1.87 (2xm, 2x2H, 5,6-H_2), 2.03 (m, 2H, 1,4-H), 2.73 (m, 2H, 2,3-H), 3.59 [dd, ^2J(H,H)=10.3 Hz, ^3J(H,H)=6.5 Hz, 2H, CH_2Br], 4.07 [dd, ^2J(H,H)=10.3 Hz, ^3J(H,H)<1 Hz, 2H, CH_2Br]. **6a** and **6b:** *anti*- and *syn-endo*-2,3-Bis-bromomethyl-7,7-dimethoxy-bicyclo[2.2.1]heptan-7-ol. 300 mg (1.1 mmol) of **5** was reduced with $NaBH_4$ as

described for **1** to give 290 mg of a 45:55 mixture of diastereomeric alcohols **6a** and **6b** (92%). - ^{1}H-NMR ($CDCl_3$): 1.35, 1.63 (m, 2x2H, *syn*-5,6-H_2), 1.55, 1.63 (2xm, 2x2H, *anti*-5,6,-H_2), 2.01 (m, 2H, *syn*-1,4-H), 2.08 (m, 2H, *anti*-1,4-H), 2.50 (m, 2H, *anti*-2,3-H), 2.90 (m, 2H, *syn*-2,3-H), 3.25 (br.s, 2x1H, *syn* and *anti* 7-OH), 3.37 [dd, ^2J(H,H)=9.9 Hz, ^3J(H,H)=6.6 Hz, 2H, *anti*-CH_2Br], 3.51 [dd, ^2J(H,H)=9.6 Hz, ^3J(H,H)=6.5 Hz, 2H, *syn*-CH_2Br], 3.92 [dd, ^2J(H,H)=9.9 Hz, ^3J(H,H)<1 Hz, 2H, *anti*-CH_2Br], 3.92 [dd, ^2J(H,H)= 9.6 Hz, ^3J(H,H)<1 Hz, 2H, *syn*-CH_2Br], 4.12 (br.s, 1H, *anti*-7-H), 4.33 (br.s, 1H, *syn*-7-H).

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13. The *anti-syn* ratio was assessed by the intensity ratio of NMR signals of olefinic protons and by HPLC analysis of the crude reaction mixture. The relative deshielding of the H-5, H-6 olefinic protons in **2b** was $\Delta\delta$ = 0.11 ppm as compared to **2a** and the deshielding of H-2, H-3 *exo* protons in **2a** was $\Delta\delta$ = 0.18 ppm as compared to **2b**.[3a] Similarly, in **5a** the deshielding of H-5, H-6 *exo* protons is $\Delta\delta$ = 0.24 ppm as compared to **5b** while for the H-2, H-3 *exo* protons in **5b** $\Delta\delta$ is 0.17 ppm as compared to **5a**. NMR spectra were recorded on a Varian VXR-400 spectrometer with TMS internal standard at 400 MHz.
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